

Holly J. Pederson, MD

Director, Medical Breast Services, Cleveland Clinic Breast Center, Cleveland Clinic, Cleveland, OH; Department of General Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH; Former Member of the National Comprehensive Cancer Center Committees for Breast Cancer Risk Reduction and Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Zahraa Al-Hilli, MD

Department of General Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Allison W. Kurian, MD

Departments of Medicine and of Epidemiology & Population Health, Stanford University, Stanford, CA

Reducing the risk of breast cancer

ABSTRACT

Breast cancer remains the most common female malignancy in the United States. Reducing this cancer burden involves identification of high-risk individuals and personalized risk management. Because coronary artery disease remains the primary cause of death for women, any intervention to reduce breast cancer risk must be weighed against comorbidities and interventions affecting cardiovascular risk reduction. For select women at increased risk for breast cancer, preventive medication can greatly decrease risk and is vastly underutilized. Women's health clinicians are poised to evaluate risk, promote breast cancer risk reduction, and manage overall health.

KEY POINTS

Patients with atypical hyperplasia (ductal or lobular) or lobular carcinoma in situ greatly benefit from risk-reducing medication.

Benefits of risk-reducing medication likely outweigh risks if the 5-year risk estimate is 3% or greater with the Gail model, or if the 10-year risk is 5% or greater with the Tyrer-Cuzick model.

Carriers of genetic or likely pathogenic variants who are predisposed to estrogen-receptor–positive breast cancers should consider preventive medication.

Cardiovascular risk and risk reduction as it relates to hormonal manipulation must weigh into decision-making.

Obesity management and alcohol reduction are critical in all patients.

ONE IN 8 WOMEN (13%) will develop breast cancer in her lifetime, at a median age of 62.¹ We aim to help practitioners identify patients at risk, understand options for risk reduction, and determine when the benefits of risk-reducing medications outweigh the risks. High-risk individuals include those with hereditary cancer syndromes, adverse genomic profiles, personal or family history of breast cancer, or benign high-risk lesions, and cancer survivors who underwent therapeutic irradiation as part of prior treatment before age 30.²⁻⁴ In some scenarios, absolute risks are well defined, and in others, risk modeling can support decision-making.^{2,3}

The pillars of breast cancer risk management include enhanced surveillance with contrast-enhanced magnetic resonance imaging (MRI), risk-reducing endocrine therapy, and risk-reducing surgery.³ Enhanced surveillance is recommended for patients meeting certain criteria. A discussion of risk-reducing surgery is advised for those with pathogenic variants (PVs) or likely pathogenic variants (LPVs) in highly penetrant genes (*BRCA1*, *BRCA2*, *PALB2*, *CDH1*, *TP53*, *STK11*, and *PTEN*) and is considered for those with a compelling family history or a history of therapeutic thoracic radiation before age 30.⁵ Discussing preventive medication in patients predisposed to estrogen-receptor–positive (ER+) breast cancers is clinically indicated, and a solid understanding of risk assessment and risk reduction is critical for the primary care provider to decrease morbidity and mortality. Four medications are recommended for breast cancer prevention: tamoxifen, raloxifene, exemestane, and anastrozole.⁶

We review here the approach to risk assessment, specific agents used in risk reduction, patient selection, and timing of therapy within a framework for personalized risk management.

TABLE 1
Guidelines to evaluate for hereditary breast cancer

- Age 50 or younger
- Ovarian cancer (at any age)
- Triple-negative breast cancer (at any age)
- Male breast cancer (at any age)
- Multiple primary breast cancers
- Pancreatic cancer
- Metastatic prostate cancer
- Three or more diagnoses of breast cancer in the patient or a close blood relative
- Two or more close (first-degree) relatives with breast or prostate cancer at any age
- To aid in treatment decisions using poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors in patients with metastatic or very-high-risk breast cancer
- Lobular breast cancer with a personal or family history of diffuse gastric cancer
- Ashkenazi Jewish ancestry
- Finding of a mutation in somatic tumor testing
- A patient without a cancer diagnosis but with a first-, second-, or third-degree relative meeting the above criteria: Exceptions: 1) If patient is eligible for PARP inhibitors; 2) If patient meets testing criteria based only on pancreatic cancer or metastatic prostate cancer, the affected relative must be a first-degree relative

Based on information in references 5, 7, and 8.

IDENTIFYING THOSE AT HEREDITARY RISK

Identified germline PVs or LPVs in genes associated with hereditary breast cancer account for 5% to 10% of breast cancer cases.¹ The National Comprehensive Cancer Network (NCCN), the United States Preventive Services Task Force (USPSTF), and other organizations recommend that primary care providers assess family history to identify those at hereditary risk, ideally by age 30 (Table 1).^{5,7,8} It is most important to identify patients with increased hereditary risk as breast cancers occur more frequently and at a much younger age.⁹ Historically, few patients met early eligibility criteria for genetic testing. Over time, however, guidelines have broadened, reflecting emerging evidence that germline PVs and LPVs are more common than previously believed. In a study of more than 4,100 patients in 2 large obstetrics-gynecology practices, 23.8% met criteria for genetic testing.¹⁰ Another recent study of underserved patients at an urban academic medical center also found that 24.4% of patients met USPSTF criteria for genetic counseling.¹¹ It is not uncommon for patients needing genetic counseling to present to a generalist's practice.

Genetic testing refers to clinical-grade next-generation multigene panel sequencing of highly penetrant

and moderately penetrant genes causal in hereditary breast cancer.⁴ These genes are inherited in an autosomal dominant fashion: only 1 copy of the malfunctioning gene need be inherited to exhibit the syndrome. As testing becomes more common, practitioners must understand how to interpret results. And as data have matured, estimates of risk and recommendations for management of carriers of PVs or LPVs in breast cancer predisposition genes have been refined by national cancer organizations such as NCCN.⁵

For example, a negative result must be interpreted based on what is known in the patient's family. If the patient is a "true negative" for a known highly penetrant PV, that person returns to a population-level risk estimate (eg, that of average women). True negatives for moderate-risk genes, uninformative negatives (a negative result in a patient or family member of that patient), and patients with "variants of uncertain significance" (considered to be clinically negative) default to the use of mathematical risk modeling for risk estimation and management.

Multifactorial risk models have been developed to inform practitioners about eligibility for enhanced surveillance with contrast-enhanced MRI and to guide discussions with patients about preventive medication.² The development of breast cancer in families with moderate-risk genes and in families where there is "clustering" but no identified genetic mutation may be influenced by other factors that modulate an individual's risk, so a negative test for a moderately penetrant familial variant does not negate possible risk.^{2,12}

Common genetic variants called single nucleotide polymorphisms, in combination, may explain up to 18% of familial clustering.^{1,13} The polygenic risk score (a weighted sum of these breast cancer-associated single nucleotide polymorphisms) may further refine risk estimates in both carriers and noncarriers of PVs or LPVs. This genomic contribution to risk assessment will be further discussed.

PREVENTIVE MEDICATION IN GENE CARRIERS

For patients with PVs or LPVs in breast cancer predisposition genes, there are evidence-based risk-management guidelines.⁵ Risk-reducing salpingo-oophorectomy (RRSO) is recommended in *BRCA1* carriers between ages 35 and 40 and in *BRCA2* carriers between ages 40 and 45.⁵ Consequences of early surgical menopause include an increased risk of cardiovascular disease, accelerated bone loss, dementia, and increased overall mortality.¹⁴ Additionally, many women suffer from severe vasomotor symptoms, sleep

TABLE 2
An overview of tumor pathology in hereditary breast cancer

Gene with pathogenic variant	Estrogen-receptor-positive tumor	Estrogen-receptor-negative tumor	Triple-negative tumor
<i>BRCA1</i>	Increasingly positive after age 50	+++ particularly before age 50	+++ particularly before age 50
<i>BRCA2</i>	++	Over-representation, ^a but still primarily estrogen-receptor-positive	Over-representation, ^a but still primarily estrogen-receptor-positive
<i>PALB2</i>	++	Over-representation, ^a but still primarily estrogen-receptor-positive	Over-representation, ^a but still primarily estrogen-receptor-positive
<i>ATM</i>	+++		
<i>CHEK2</i>	+++		
<i>CDH1</i>	+++		
<i>TP53</i>	+++		
<i>BARD1</i>		+++	+++
<i>RAD51C</i>		+++	+++
<i>RAD51D</i>		+++	+++

^aEstrogen receptor tumors are more common than in the general population but are still not the predominant type of tumor pathology.

+ = relative prevalence

disturbance, fatigue, anxiety, depression, urogenital changes, and sexual dysfunction.¹⁴ Thus, systemic hormone therapy is recommended unless otherwise contraindicated for *BRCA1/2* PV and LPV carriers undergoing early RRSO until the age when natural menopause would have occurred (approximately age 50), and generally precludes the use of preventive agents.^{15–17} Studies suggest that undergoing RRSO before age 50 is associated with a decrease in breast cancer risk, all-cause mortality, and breast cancer mortality, particularly in those with *BRCA2* PVs or LPVs. This breast cancer risk reduction is not mitigated by postmenopausal hormonal therapy.^{15,18}

Cardiovascular risk

While previous American Heart Association guidelines noted that early menopause increases cardiovascular disease risk, it is now recognized that coronary heart disease risk accelerates in average-risk women during the menopause transition and after menopause.¹⁹ Literature suggests that menopausal hormone therapy in women ages 50 to 59 is associated with improved cardiovascular morbidity and all-cause mortality (in healthy average-risk women).^{19,20} Additionally, the Women's Health Initiative studied the

administration of conjugated equine estrogen, with more than 20 years of follow up (in average risk women randomized to estrogen or placebo), and showed that use of conjugated equine estrogen in postmenopausal women with prior hysterectomy was significantly associated with a lower risk of breast cancer incidence and mortality.²¹ Although this finding cannot be extrapolated to “previvors” (unaffected gene carriers) with early surgical menopause, the data are provocative and should be discussed with patients at the time that hormone use would typically be discontinued.

Preventive endocrine therapy

Germline PV and LPV carriers predisposed to ER+ breast cancers may benefit from preventive endocrine therapy. In a study of more than 50,000 breast cancer patients, tumor pathology was associated with known breast cancer predisposition genes.^{22–26} ER+ tumors are commonly seen in patients with pathogenic or likely pathogenic variants in *BRCA1* (after age 50), *BRCA2*, *PALB2*, *ATM*, *CHEK2*, *CDH1*, and *TP53*. Estrogen-receptor-negative (ER–) or triple-negative breast cancers are more common in patients with PVs and LPVs in *BRCA1* under age 50 and in patients with *BARD1*, *RAD51C*, and *RAD51D* (Table 2).

Follow-up studies will determine the effectiveness of preventive endocrine therapy in patients with hereditary cancer syndromes, but the medication will most likely be effective in patients prone to ER+ disease, given the mechanism of action of these medications. Data from the Breast Cancer Prevention Trial of the National Surgical Adjuvant Breast and Bowel Project suggested that tamoxifen reduced breast cancer risk by 62% in *BRCA2* carriers (risk ratio [RR] 0.38; 95% confidence interval [CI] 0.06–1.56) but not in *BRCA1* carriers (RR 1.67; 95% CI 0.32–10.07).²⁷ However, these were very small numbers, and results did not meet statistical significance. Of the 288 women who developed breast cancer among the more than 13,000 in the study, only 8 had *BRCA1* PVs or LPVs, and 11 had *BRCA2* PVs or LPVs.²⁷ There are no published data in other gene PV and LPV carrier groups.

The most important factors influencing risk in patients without germline PVs or LPVs are family history, atypical benign breast lesions, and extreme breast density

RISK MODELING

In noncarriers of PVs or LPVs, in patients with variants of uncertain significance, or in untested patients with a family history or other risk factors, risk can be estimated using models. Short-term thresholds have been suggested at which the benefits of preventive therapy likely outweigh the risks; risks for coronary artery disease and venous thromboembolism must also be considered.³

The most important factors influencing risk are family history, atypical benign breast lesions, and extreme breast density. Breast density is a term that describes the relative amounts of glandular and fibrous connective tissue vs fatty tissue seen on a mammogram.^{28,29} Women with heterogeneously dense tissue (approximately 40% of women) and women with extremely dense tissue (approximately 7% of women) are considered to be mammographically “dense.”²⁹ Women with extremely dense breast tissue are at increased risk of breast cancer, and detection is more difficult with mammography alone.³⁰

Tyrer-Cuzick, CanRisk, and Gail models

Some risk models (eg, Tyrer-Cuzick, CanRisk) incorporate first-, second-, and third-degree relatives, family size, and genetic testing in their risk estimation.

^{31,32} Breast density, postmenopausal hormone use, lobular carcinoma in situ (LCIS), and polygenic risk score are also incorporated into the Tyrer-Cuzick and CanRisk models. The Tyrer-Cuzick model uses the *BRCA* status of tested family members, and the CanRisk model has recently been updated to incorporate the effects of *PALB2*, *CHEK2*, and *ATM* PVs and LPVs as well. It also incorporates lifestyle factors and disease pathology and predicts both breast and ovarian cancer risk.^{31,32}

The modified Gail model, also known as the Breast Cancer Risk Assessment model (<http://bcrisk-tool.cancer.gov>) is clinically the most commonly used model, validated in women age 35 and older. It involves 8 questions and provides estimates of 5-year and lifetime risk. However, it does not apply to women with a history of LCIS, incorporates only first-degree relatives, and does not take into account age at diagnosis, paternal history, anthropomorphic or lifestyle factors, genetic testing, or breast density. If a woman has an estimated 5-year risk of developing breast cancer of at least 1.66% using the Gail model, risk-reducing medication might be discussed, though the threshold at which the benefits outweigh the risk is felt to be 3% or greater.^{6,33–35}

The Tyrer-Cuzick model (<http://www.ems-trials.org/riskevaluator/>) takes more time to complete but is manageable in a busy clinic and provides estimates of short-term and lifetime risk. The CanRisk model (<http://www.canrisk.org>) is comprehensive but would likely need to be done outside of a routine clinical visit.

An international validation study with long-term follow-up comparing the models showed that models that include a multigenerational family history have better ability to predict risk.³⁶ The USPSTF suggests that if the 5-year estimated risk using the Gail model is 3% or greater, the benefit of preventive medication likely outweighs the risks in the absence of contraindications.⁷ The American Society of Clinical Oncology recommends a threshold of 5% or greater using the 10-year risk estimate from the Tyrer-Cuzick model.³⁷

MAMMOGRAPHIC DENSITY, BENIGN ATYPICAL LESIONS, AND THERAPEUTIC CHEST IRRADIATION

Density

Although breast density is an important independent risk factor for breast cancer,³⁸ no recommendations currently exist for the use of preventive medication based solely on density. Discussion of

TABLE 3
Medications used for breast cancer risk reduction: A brief summary of clinical trials

Trial	N	Eligibility	HR ^a	HR ^b	NNT
NSABP P-1 5-year trial Tamoxifen 20 mg vs placebo ³³	13,388	Pre- and post-menopausal; Gail model-estimated 5-year risk $\geq 1.66\%$	0.51	0.14 for AH; 0.44 for LCIS	22
IBIS-1 5-year trial Tamoxifen 20 mg vs placebo ⁴⁸	7,154	Pre- and post-menopausal; 50% on hormone-replacement therapy	0.75; with long-term follow-up 0.71	Not stated	Not stated
STAR P-2 5-year trial Tamoxifen 20 mg vs raloxifene 60 mg ^{34,50}	19,747	Postmenopausal	Equal at 5 years; with long-term follow-up; raloxifene = 0.62	Equal	Not stated (about 22)
MAP.3 3-year trial Exemestane 25 mg, exemestane 25 mg plus celecoxib, vs placebo ⁴⁶	4,560	Postmenopausal	0.35	0.36 (for AH/LCIS combined)	26 at 5 years
IBIS II 5-year trial Anastrozole 1 mg vs placebo ⁴⁷	3,864	Postmenopausal	0.47	0.31 (for AH/LCIS combined)	29 ^c
Low-dose tamoxifen 3-year trial Tamoxifen 5 mg vs placebo ⁴⁹	500	Pre- and post-menopausal; included patients with ductal carcinoma in situ	0.48	Not stated	22

^aFor reduction in invasive breast cancer.

^bFor reduction in invasive breast cancer in patients with AH and LCIS.

^cTo prevent 1 cancer in 7 years of follow-up, 36 women would need to be treated.

AH = atypical hyperplasia; HR = hazard ratio; IBIS = International Breast Cancer Intervention Study; LCIS = lobular carcinoma in situ; MAP = Mammary Prevention trial; NNT = number needed to treat; NSABP = National Surgical Adjuvant Breast and Bowel Project; STAR = Study of Tamoxifen and Raloxifene

supplemental imaging is warranted, particularly in high-risk patients.

Atypical lesions

In women with benign atypical biopsy lesions and in women with LCIS, preventive therapy is highly recommended. Atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH) confers an approximately 30% risk of breast cancer at 25 years of follow up.^{39–41} LCIS is associated with a risk of approximately 2% per year.⁴² The risk increases if ADH, ALH, or

LCIS is detected in younger women and if more tissue is involved (measured as the number of terminal duct lobular units involved).³⁹

Chest irradiation

Therapeutic thoracic radiation in a patient under age 30 (eg, to treat Hodgkin lymphoma) results in a breast cancer risk exceeding 35% by age 50⁴³ and may be associated with a higher mortality risk.⁴⁴ A study examining low-dose tamoxifen (5 mg daily for 2 years) demonstrated reduction in established biomarkers of

risk (mammographic density and serum insulin-like growth factor-1 levels) in these patients.⁴⁵

■ PREVENTIVE AGENTS

Table 3^{33,34,46–50} summarizes trials of 4 medications used for breast cancer risk reduction: tamoxifen, raloxifene, exemestane, and anastrozole. In breast cancer treatment trials,^{33,34,46–52} tamoxifen and the aromatase inhibitors prevented not only breast cancer recurrence, but also contralateral disease. Raloxifene had been shown in osteoporosis trials to reduce breast cancer risk.⁵² Thus, these agents were selected for randomized trials of primary reduction of breast cancer risk. The following section will review the medications, results of relevant clinical trials, and side effects. The clinical trials were all randomized and double-blind, and all except the Study of Tamoxifen and Raloxifene were placebo-controlled.⁵⁰ Although breast cancer rates decreased overall with the use of these medications,^{33,34,46,47} no decrease in mortality has been demonstrated to date.

The protective effects of risk-reducing agents persist at least 10 years after stopping the medication

Selective estrogen receptor modulators: Tamoxifen and raloxifene

Selective estrogen receptor modulators (SERMs) are a class of drug that acts on the estrogen receptor with action that varies by tissue, selectively inhibiting or stimulating estrogen-like action. Contraindications to SERMs include a history of deep vein thrombosis or pulmonary embolism, thrombotic stroke, retinal vein thrombosis, transient ischemic attack, or known inherited clotting predisposition. They should not be used while pregnant or breastfeeding or with concurrent use of warfarin or estrogen.⁵³ Other considerations include the presence of independent risk factors for thromboembolic disease (advancing age, obesity, smoking),⁵⁴ migraine with aura (due to concern for stroke),⁵⁵ and use of an unreliable birth control method along with use of tamoxifen.⁵³ Given the increased risk of thromboembolic disease with SERMs, it is imperative that women be assessed for personal and familial risks for this potential complication.

Tamoxifen was approved in 1998 by the US Food and Drug Administration (FDA) for breast cancer risk

reduction following results of the National Surgical Adjuvant Breast and Bowel Project P-1 study.³³ The study showed an approximate 50% reduction in invasive and noninvasive breast cancer in premenopausal and postmenopausal women, and a greater reduction in women with atypical hyperplasia or LCIS.³³

The study randomized 13,388 women at increased risk of breast cancer to receive tamoxifen 20 mg daily for 5 years or placebo.³³ Women were considered at increased risk of breast cancer if they were age 60 or older, were age 35 to 59 with a 5-year risk of 1.66% or higher (using the Gail model), or had a history of LCIS.³³ A reduction in rate of fractures of the hip, radius (Colles fracture), and spine was observed in the tamoxifen arm, and no effect was noted on the rate of ischemic heart disease. There was an increased risk of endometrial cancer (5.4 per 1,000 women in the placebo group, and 13 per 1,000 women in the tamoxifen group at 66 months).³³

There were 18 pulmonary emboli in the tamoxifen group vs 6 in the placebo group (RR 3.01; 95% CI 1.15–9.27).³³ The average annual rate of deep vein thrombosis was 1.34 vs 0.84 per 1,000 women in the tamoxifen vs placebo-treated groups (RR 1.60; 95% CI 0.91–2.86), which reached statistical significance only in women age 50 and older.³³

The rate of cataract formation in women who were cataract-free at randomization was 21.72 per 1,000 in the placebo group and 24.82 per 1,000 in the tamoxifen group (RR 1.14; 95% CI 1.01–1.29).³³

In healthy premenopausal women, there was no statistically significantly increased risk of serious side effects with tamoxifen, and it was generally well tolerated.³³ Vasomotor symptoms were common in both the tamoxifen and control groups but more common in the tamoxifen group, and the drug was associated with vaginal discharge.³³ Benefits have been shown to persist for at least 10 years after stopping the medication.⁴⁸

The recommended duration of tamoxifen therapy for risk reduction is 5 years.^{6,7,37} Another option for patients with ADH, ALH, or LCIS is “low-dose” tamoxifen.³⁷ A 2019 study from Italy cited a 50% risk reduction with the use of 5 mg daily for 3 years in this population.⁴⁹ As 5-mg tablets are not available in the United States, an alternate regimen is 10 mg every other day. The efficacy of low-dose tamoxifen seems to be greater, however, in postmenopausal women.⁵⁵

Raloxifene (also FDA-approved for osteoporosis prevention) was FDA-approved for breast cancer risk reduction in September 2007 after the publication of results from the National Surgical Adjuvant Breast

and Bowel Project Study of Tamoxifen and Raloxifene P-2 trial.^{34,56} The Study of Tamoxifen and Raloxifene randomized 19,747 postmenopausal women with a mean age of 58.5 and a mean Gail model-estimated 5-year breast cancer risk of 4.03% to either tamoxifen 20 mg or raloxifene 60 mg daily for 5 years.³⁴ There were 36 cases of uterine cancer with tamoxifen and 23 with raloxifene (RR 0.62; 95% CI 0.35–1.08), and cumulative uterine cancer incidence rates through 7 years were 14.7 per 1,000 for tamoxifen and 8.1 per 1,000 for raloxifene ($P = .07$). Thromboembolic events were less common with raloxifene (RR 0.70; 95% CI 0.54–0.91), and no differences were found for ischemic heart disease or stroke. There were also fewer cataracts (RR 0.79; 95% CI 0.68–0.92). Osteoporotic fractures and death were similar in the 2 groups. Tamoxifen and raloxifene had equivalent effects in reducing the risk of invasive breast cancer in all examined subgroups, including women with a history of atypical hyperplasia and LCIS, who had the highest annual rates of developing breast cancer. Tolerance was similar.³⁴

At a mean follow-up of 81 months, raloxifene retained 76% of the effectiveness of tamoxifen (with a 38% reduction in breast cancer risk) with less endometrial cancer risk (RR = 0.55; 95% CI 0.36–0.83; $P = .003$).⁵⁰ The superiority of tamoxifen in reducing risk comes with significant costs in postmenopausal women: more endometrial cancers, hysterectomies for benign disease, thromboembolic events, and cataracts, particularly for women over age 65, who have a higher risk of adverse events with tamoxifen.⁵⁷

Aromatase inhibitors: Exemestane and anastrozole

Aromatase catalyzes the aromatization of androgen precursors such as testosterone, producing estrogen. Aromatase inhibitors are taken to block the production of estrogen. While neither exemestane nor anastrozole is FDA-approved for breast cancer risk reduction, both are recommended by NCCN, USPSTF, and the American Society of Clinical Oncology.^{6,7,37} Aromatase inhibitors can reduce bone density, necessitating monitoring.

Exemestane. In the study by Goss et al of exemestane for breast cancer prevention in postmenopausal women,⁴⁶ 4,560 postmenopausal women with a median age of 62.5 and a median Gail-estimated 5-year risk of 2.3% were randomly assigned to daily exemestane 25 mg, exemestane 25 mg plus celecoxib, or placebo.⁴⁶ At a median follow-up of 35 months, there was a 65% relative reduction in the annual incidence of breast cancer with exemestane. There were no significant

differences between the 2 treatment groups in terms of skeletal fractures, cardiovascular events, other cancers, or treatment-related deaths. No serious toxic effects and only minimal changes in health-related quality of life were noted. Exemestane also reduced the risk of ductal carcinoma in situ, LCIS, ADH, and ALH, suggesting possible further reductions in invasive cancers during long-term follow-up.⁴⁶

Anastrozole. In the International Breast Cancer Intervention Study II trial,⁴⁷ 3,864 postmenopausal women ages 40 to 70 from 18 countries were randomized to receive anastrozole 1 mg daily or placebo for 5 years.⁴⁷ There was a 53% reduction in breast cancer with the use of anastrozole (hazard ratio 0.47; 95% CI 0.32–0.68; $P < .0001$). Musculoskeletal adverse events (including carpal tunnel syndrome and joint stiffness) and vasomotor symptoms were reported in more women in the anastrozole group ($P < .0001$). Dry eyes, vaginal dryness, and hypertension were also significantly increased. Overall adherence was 75%, and after a median follow-up of 131 months, a 49% reduction in risk persisted, with no excess fractures, other cancers, cardiovascular disease, or death.⁵⁸

■ OBESITY AND BREAST CANCER

Obesity and physical inactivity have been shown to have a major impact on outcomes in both breast cancer and cardiovascular disease, and all patients should be counseled on diet and lifestyle, including alcohol in moderation or not at all.^{59,60}

The mechanisms by which obesity increases breast cancer risk are complex, but achieving and maintaining ideal body weight appears to be critical

Defined as a body mass index of at least 30 kg/m², obesity has a major impact across the breast cancer continuum, including an increased risk of postmenopausal and triple-negative breast cancers, delay in diagnosis, increased complications from surgery and radiation, and decreased survival.⁵⁹ The high prevalence of obesity is a major public health concern for all Americans and disproportionately affects Black women, with a recent study showing more than 55% obesity.⁶⁰

In the Women's Health Initiative Dietary Modification randomized trial (N = 48,835),²¹ triple-negative breast cancer cases were significantly reduced

in the low-fat diet arm (defined as 24.3% of energy). Body weight was also significantly reduced, and there was a significant reduction in deaths from breast cancer ($P = .02$).²¹ The mechanisms by which obesity increases breast cancer risk are complex, and it is not yet known whether the low-fat diet or weight loss resulted in mortality reduction, but the importance of achieving and maintaining ideal body weight appears to be critical.

■ IMPACT OF THE POLYGENIC RISK SCORE

The polygenic risk score has been shown to improve the discriminatory accuracy of risk modeling in validation cohorts,⁶¹ and it has also been shown to sub-stratify risk in carriers of genetic PVs and LPVs and in high-risk noncarriers.⁶² Clinically, it was recently shown to influence the uptake of risk-reducing medication in a cohort of women at high risk for breast cancer.⁶³ The polygenic risk score has strong potential to refine clinical breast cancer risk assessment and to assist in prevention counseling of women at increased risk. More study is needed.

■ KEYS TO SUCCESSFUL RISK MANAGEMENT

A comprehensive approach to breast cancer risk management includes personalized risk assessment with consideration of comorbidities and patient goals.

■ REFERENCES

1. Labrèche F, Goldberg MS, Hashim D, Weiderpass E. Breast Cancer. In: Anttila S, Boffetta P (eds). Occupational cancers. Springer, Cham; 2020.
2. Vegunta S, Bhatt AA, Choudhery SA, Pruthi S, Kaur AS. Identifying women with increased risk of breast cancer and implementing risk-reducing strategies and supplemental imaging. *Breast Cancer* 2022; 29(1):19–29. doi:10.1007/s12282-021-01298-x
3. Pederson HJ, Kurian AW, Al Hilli Z. What are the considerations in patient selection and timing of risk-reducing mastectomy? *Cleve Clin J Med* 2022; 89:442–444. doi:10.3949/ccjm.89a.21114
4. Tung N, Battelli C, Allen B, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer* 2015; 121(1):25–33. doi:10.1002/cncr.29010
5. National Comprehensive Cancer Network. Genetic/familial high-risk breast assessment: breast, ovarian, and pancreatic, version 1.2023, published online September 7, 2022. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed October 18, 2022.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Risk Reduction Version 1.2022, published online January 31, 2022, by NCCN.org. https://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf. Accessed October 18, 2022.
7. US Preventive Services Task Force, Owens DK, Davidson KW, et al. Medication use to reduce risk of breast cancer: US Preventive Services Task Force recommendation statement. *JAMA* 2019;

Patient selection, clear communication of risks and benefits, and appropriate timing are the keys to successful management as noted in these take-home points.

- Informed practitioners are needed to care for specified high-risk patients and to educate patients about the risks and benefits of risk modification.
- Prevention strategies should involve identification of patients at risk for hereditary breast cancer, as early intervention is critical.
- Preventive medication is extremely effective in patients with benign atypical lesions.
- Short-term risk thresholds can inform discussions regarding risk-reducing medication.
- The epidemic of obesity, inactivity, and alcohol consumption must be addressed in the United States to reduce burden of disease.^{60,64}
- The polygenic risk score can be used to further sub-stratify risk estimates, aiding women in clinical decision-making.^{61–63}
- Potential cardioprotective effects of hormonal therapy in early postmenopause must be considered in shared decision-making with patients, as well as noting cardiovascular and venous thromboembolic risk factors.

■ DISCLOSURES

Dr. Pederson has disclosed consulting for Myriad Genetics. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

- 322(9):857–867. doi:10.1001/jama.2019.11885
8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology – Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. Version 1.2023 published online September 7, 2022 by NCCN.org. <https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1503>. Accessed October 18, 2022.
9. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* 2017; 317(23):2402–2416. doi:10.1001/jama.2017.7112
10. DeFrancesco MS, Waldman RN, Pearlstone MM, et al. Hereditary cancer risk assessment and genetic testing in the community-practice setting. *Obstet Gynecol* 2018; 132(5):1121–1129. doi:10.1097/AOG.0000000000002916
11. Parente DJ. BRCA-related cancer genetic counseling is indicated in many women seeking primary care. *J Am Board Fam Med* 2020; 33(6):885–893. doi:10.3122/jabfm.2020.06.190461
12. Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol* 2016; 13(9):581–588. doi:10.1038/nrclinonc.2016.90
13. Michailidou K, Lindström S, Dennis J, et al. Association analysis identifies 65 new breast cancer risk loci. *Nature* 2017; 551(7678):92–94. doi:10.1038/nature24284
14. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. *Climacteric* 2015; 18(4):483–491. doi:10.3109/13697137.2015.1020484
15. Gordhandas S, Norquist BM, Pennington KP, Yung RL, Laya MB,

- Swisher EM. Hormone replacement therapy after risk reducing salpingo-oophorectomy in patients with BRCA1 or BRCA2 mutations; a systematic review of risks and benefits. *Gynecol Oncol* 2019; 153(1):192–200. doi:10.1016/j.ygyno.2018.12.014
16. Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. *J Clin Oncol* 2005; 23(31):7804–7810. doi:10.1200/JCO.2004.00.8151
17. Faubion SS, Crandall CJ, Davis L, et al; The 2022 hormone therapy position statement of The North American Menopause Society advisory panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022; 29(7):767–794. doi:10.1097/GME.0000000000002028
18. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 2010; 304(9):967–975. doi:10.1001/jama.2010.1237
19. El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. *Circulation* 2020; 142(25):e506–e532. doi:10.1161/CIR.0000000000000912
20. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013; 310(13):1353–1368. doi:10.1001/jama.2013.278040
21. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials. *JAMA* 2020; 324(4):369–380. doi:10.1001/jama.2020.9482
22. Hu C, Polley EC, Yadav S, et al. The contribution of germline predisposition gene mutations to clinical subtypes of invasive breast cancer from a clinical genetic testing cohort. *J Natl Cancer Inst* 2020; 112(12):1231–1241. doi:10.1093/jnci/djaa023
23. Hu C, Hart SN, Gnanaolivu R, et al. A population-based study of genes previously implicated in breast cancer. *N Engl J Med* 2021; 384(5):440–451. doi:10.1056/NEJMoa2005936
24. Tung N, Wang Y, Collins LC, et al. Estrogen receptor positive breast cancers in BRCA1 mutation carriers: clinical risk factors and pathologic features. *Breast Cancer Res* 2010; 12(1):R12. doi:10.1186/bcr2478
25. Schmidt MK, Hogervorst F, van Hien R, et al. Age- and tumor subtype-specific breast cancer risk estimates for CHEK2*1100delC carriers. *J Clin Oncol* 2016; 34(23):2750–2760. doi:10.1200/JCO.2016.66.5844
26. Hall MJ, Bernhisel R, Hughes E, et al. Germline pathogenic variants in the ataxia telangiectasia mutated (ATM) gene are associated with high and moderate risks for multiple cancers. *Cancer Prev Res (Phila)* 2021; 14(4):433–440. doi:10.1158/1940-6207.CAPR-20-0448
27. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA* 2001; 286(18):2251–2256. doi:10.1001/jama.286.18.2251
28. American College of Radiology; D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA, et al (eds). *ACR BI-RADS Atlas—Mammography: Breast Imaging Reporting and Data System*, 5th ed. Reston, VA: American College of Radiology; 2013:1–175.
29. Sprague BL, Kerlikowske K, Bowles EJA, et al. Trends in clinical breast density assessment from the Breast Cancer Surveillance Consortium. *J Natl Cancer Inst* 2019; 111(6):629–632. doi:10.1093/jnci/djy210
30. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med* 2007; 356(3):227–236. doi:10.1056/NEJMoa062790
31. Brentnall AR, Cuzick J. Risk models for breast cancer and their validation. *Stat Sci* 2020; 35(1):14–30. doi:10.1214/19-ST5729
32. Carver T, Hartley S, Lee A, et al. CanRisk tool-A Web interface for the prediction of breast and ovarian cancer risk and the likelihood of carrying genetic pathogenic variants. *Cancer Epidemiol Biomarkers Prev* 2021; 30(3):469–473. doi:10.1158/1055-9965.EPI-20-1319
33. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; 90(18):1371–1388. doi:10.1093/jnci/90.18.1371
34. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006; 295(23):2727–2741. doi:10.1001/jama.295.23.joc60074
35. Moyer VA. Medications to decrease the risk for breast cancer in women: recommendations from the U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2013; 159(10):698–708. doi:10.7326/0003-4819-159-10-201311190-00717
36. Terry MB, Liao Y, Whittemore AS, et al. 10-year performance of four models of breast cancer risk: a validation study. *Lancet Oncol* 2019; 20(4):504–517. doi:10.1016/S1470-2045(18)30902-1
37. Visvanathan K, Fabian CJ, Bantug E, et al. Use of endocrine therapy for breast cancer risk reduction: ASCO clinical practice guideline update. *J Clin Oncol* 2019; 37(33):3152–3165. doi:10.1200/JCO.19.01472
38. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006; 15(6):1159–1169. doi:10.1158/1055-9965.EPI-06-0034
39. Hartmann LC, Degnim AC, Dupont WD. Atypical hyperplasia of the breast. *N Engl J Med* 2015; 373(13):1271–1272. doi:10.1056/NEJMc1501046
40. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast — risk assessment and management options. *N Engl J Med* 2015; 373(1):78–89. doi:10.1056/NEJMs1407164
41. Hartmann LC, Radisky DC, Frost MH, et al. Understanding the premalignant potential of atypical hyperplasia through its natural history: a longitudinal cohort study. *Cancer Prev Res (Phila)* 2014; 7(2):211–217. doi:10.1158/1940-6207.CAPR-13-0222
42. King TA, Pilewskie M, Muhsen S, et al. Lobular carcinoma in situ: a 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk. *J Clin Oncol* 2015; 33(33):3945–3952. doi:10.1200/JCO.2015.61.4743
43. Moskowitz CS, Chou JF, Wolden SL, et al. Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol* 2014; 32(21):2217–2223. doi:10.1200/JCO.2013.54.4601
44. Moskowitz CS, Chou JF, Neglia JP, et al. Mortality after breast cancer among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2019; 37(24):2120–2130. doi:10.1200/JCO.18.02219
45. Bhatia S, Palomares MR, Hageman L, et al. A randomized phase IIb study of low-dose tamoxifen in chest-irradiated cancer survivors at risk for breast cancer. *Clin Cancer Res* 2021; 27(4):967–974. doi:10.1158/1078-0432.CCR-20-3609
46. Goss PE, Ingle JN, Alés-Martínez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med* 2011; 364(25):2381–2391. doi:10.1056/NEJMoa11035073507
47. Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet* 2014; 383(9922):1041–1048. doi:10.1016/S0140-6736(13)62292-8
48. Cuzick J, Forbes JF, Sestak I, et al. Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 2007; 99(4):272–282. doi:10.1093/jnci/djk049
49. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized placebo controlled trial of low-dose tamoxifen to prevent local and contralateral recurrence in breast intraepithelial neoplasia. *J Clin Oncol* 2019; 37(19):1629–1637. doi:10.1200/JCO.18.01779

50. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of tamoxifen and raloxifene (STAR) P-2 trial: preventing breast cancer. *Cancer Prev Res (Phila)* 2010; 3(6):696–706. doi:10.1158/1940-6207.CAPR-10-0076
51. Bens A, Langballe R, Bernstein JL, Cronin-Fenton D, Friis S, Mellekjær L. Preventive drug therapy and contralateral breast cancer: summary of the evidence of clinical trials and observational studies. *Acta Oncol* 2019; 58(11):1581–1593. doi:10.1080/0284186X.2019.1643915
52. Lee WL, Chao HT, Cheng M-H, Wang P-H. Rationale for using raloxifene to prevent both osteoporosis and breast cancer in postmenopausal women. *Maturitas* 2008; 60(2):92–107. doi:10.1016/j.maturitas.2008.04.009
53. Buonomo B, Brunello A, Noli S, et al. Tamoxifen exposure during pregnancy: a systematic review and three more cases. *Breast Care (Basel)* 2020;15(2):148–156. doi:10.1159/000501473
54. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis* 2016; 41(1):3–14. doi:10.1007/s11239-015-1311-6
55. DeCensi A, Puntoni M, Johansson H, et al. Effect modifiers of low-dose tamoxifen in a randomized trial in breast noninvasive disease. *Clin Cancer Res* 2021; 27(13):3576–3583. doi:10.1158/1078-0432.CCR-20-4213
56. US Food and Drug Administration. Drug approval package: Evista (raloxifene hydrochloride) tablets, 60 mg. September 13, 2007. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022042_evista_toc.cfm. Accessed October 18, 2022.
57. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst* 1999; 91(21):1829–1846. doi:10.1093/jnci/91.21.1829
58. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. *Lancet* 2020; 395(10218):117–122. doi:10.1016/S0140-6736(19)32955-1
59. Lee K, Kruper L, Dieli-Conwright CM, Mortimer JE. The impact of obesity on breast cancer diagnosis and treatment. *Curr Oncol Rep* 2019; 21(5):41. doi:10.1007/s11912-019-0787-1
60. Stierman B, Afful J, Carroll MD, et al. US Department of Health and Human Services. Centers for Disease Control and Prevention. National Health Statistics Reports. National Health and Nutrition Examination Survey 2017–March 2020 Prepandemic Data Files—Development of Files and Prevalence Estimates for Selected Health Outcomes. June 14, 2021. <https://stacks.cdc.gov/view/cdc/106273>. Accessed October 18, 2022.
61. Hughes E, Tshiaba P, Wagner S, et al. Integrating clinical and polygenic factors to predict breast cancer risk in women undergoing genetic testing. *JCO Precis Oncol* 2021; 5:PO.20.00246. doi:10.1200/PO.20.00246
62. Gallagher S, Hughes E, Wagner S, et al. Association of a polygenic risk score with breast cancer among women carriers of high- and moderate-risk breast cancer genes. *JAMA Netw Open* 2020; 3(7):e208501. doi:10.1001/jamanetworkopen.2020.8501
63. Kim JO, Schaid DJ, Vachon CM, et al. Impact of personalized genetic breast cancer risk estimation with polygenic risk scores on preventive endocrine therapy intention and uptake. *Cancer Prev Res (Phila)* 2021; 14(2):175–184. doi:10.1158/1940-6207.CAPR-20-0154
64. LoConte NK, Brewster AM, Kaur JS, Merrill JK, Alberg AJ. Alcohol and Cancer: a statement of the American Society of Clinical Oncology. *J Clin Oncol* 2018; 36(1):83–93. doi:10.1200/JCO.2017.76.1155

Address: Holly J. Pederson, MD, Department of Breast Services, A80, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; pedersh@ccf.org