



PCE Practicing Clinicians EXCHANGE™

Created for Nurse Practitioners and Physician Assistants

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PCE Primary Care Issues and Insights for Nurse Practitioners and Physician Assistants

Breast Cancer: Risk Assessment and Prevention Strategies

Therese B. Bevers, MD, FAAFP, Senior Editor

During the past several years, there has been a steady decline in the number of women diagnosed with breast cancer. Although this decline has been attributed to a decrease in the use of hormones, another possible contributing factor may be the use of chemopreventive agents. Clearly, interventions now are available that help can reduce a woman's chance of developing breast cancer. The concept of individualized breast cancer risk reduction and screening strategies is now a part of the paradigm of the management of breast cancer. It is essential that clinicians in the primary care setting recognize women at increased risk so that specific screening activities can be encouraged, appropriate risk reduction interventions offered, and/or referrals made to specialists for breast cancer risk assessment and counseling.

Needs Assessment

Nurse practitioners (NPs) and physician assistants (PAs) have a unique opportunity to save women's lives by discussing ways patients may improve their chances of preventing breast cancer. Preventive measures include aggressive screening, lifestyle changes, chemoprevention, and prophylactic surgery.¹ Lifestyle modifications are effective,² but not as effective as prophylactic surgery, which is unacceptable to many women, or pharmacologic therapy in high-risk women.¹ Despite its benefits, chemoprevention is not used widely.³ NPs and PAs must understand the efficacy and side effect profiles of chemoprevention, as well as methods to assess breast cancer risk.

1. Brown PH. Choosing agents for clinical risk reduction. In: Govindan R, ed. *American Society of Clinical Oncology Educational Book*. Alexandria, Va: American Society of Clinical Oncology; 2007:149-154.

2. Available at: <http://mayoclinic.com/health/breast-cancer-prevention/W000091>. Accessed April 29, 2008.

3. Evans D, Lalloo F, Shenton A. Uptake of screening and prevention in women at very high risk of breast cancer. *Lancet*. 2001;358:889-890.

Target Audience

NPs, PAs, and Physicians

Learning Objectives

After completing this activity, participants should be better able to:

1. Assess women for breast cancer risk reduction.
2. Counsel women on appropriate lifestyle alterations aimed at lowering breast cancer risk.
3. Explain the rationale and current clinical trial results of pharmacologic interventions for breast cancer risk reduction.

How to Receive Credit

Participants wishing to earn CME/CE credit must:

1. Read the newsletter.
2. Relate the content material to the learning objectives.
3. Complete the Self-Assessment Questions and Evaluation Form online at: www.practicingclinicians.com/bcnewsletter. Successful completion of the self-assessment is required to earn CME/CE credit. Successful completion is defined as a cumulative score of at least 70%.

Estimated time to complete this activity is 1 hour.

Release date: April 30, 2008

Expiration date: Required materials must be submitted before April 30, 2009.

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CME credit will be awarded provided this activity is used and completed according to instructions and a score of 70% or better is achieved. A certificate of credit will be sent within six weeks of receipt of the test answers to those who successfully complete the examination.

This program has been approved for 1.16 contact hours of continuing education by the American Academy of Nurse Practitioners. Program ID 0804190.

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Breast Cancer: Facts and Stats

Breast cancer is the most frequently diagnosed cancer in women. An estimated 182,460 invasive and 67,770 in situ breast cancers will be diagnosed in 2008.¹ In 2003, the number of women diagnosed with breast cancer decreased dramatically² (see *Decreases in the Incidence of Breast Cancer*, page 4). In addition, the number of women dying of breast cancer has been decreasing steadily in recent years.¹

Several risk factors for breast cancer have been identified (Table 1).³ Of the estimated 13% of American women who will develop breast cancer,⁴ the overwhelming majority of occurrences (~70%) are considered “sporadic.” Another 15% to 20% of breast cancers occur in women with a family history of the disease but no readily identifiable inheritance pattern (familial). Approximately 5% to 10% of women

diagnosed with breast cancer do have a hereditary form of the disease.¹

Inherited alterations of BRCA1 and BRCA2 genes are involved in 80% to 90% of hereditary breast and ovarian cancers. An alteration in the BRCA1 or BRCA2 gene greatly increases a woman’s risk of developing these cancers (Table 2).^{4,5}

Primary care clinicians play an important role in the assessment of a patient’s breast cancer risk and the discussion and, if necessary, management of prevention strategies.

Breast Cancer Risk Assessment Steps

Step 1. Identify Individuals With an Inherited Predisposition for Breast Cancer

Step 1 in the breast cancer risk assessment process is identifying individuals with a family history suggestive of a possible inherited predisposition for breast cancer (Table 3).⁶ This can be determined by taking a family history that includes information about the types of cancer, the ages at which cancer diagnoses were made, and the vital status of 3 generations of relatives within a family. It is important to ask patients about both their paternal and maternal lines, as both can pass on breast cancer genes. Family ethnicities are also a factor; for example, the incidence of specific BRCA1/2 mutations is increased among individuals of Ashkenazi Jewish

descent, and should be recorded.³ Patients with a family history suggestive of an inherited disorder predisposing them to breast cancer should then be referred to genetic counseling.

Genetic counselors will determine the probability of an inherited mutation. If genetic testing, which is a blood test,

is recommended, the risks, benefits, and limitations of genetic testing should be discussed before a woman makes the decision to undergo such testing. Women who do undergo genetic testing and carry a BRCA gene mutation must be advised of the importance of this information for themselves and for blood relatives.

Genetic counselors can help women who have a genetic predisposition for breast cancer to understand the options, including prophylactic mastectomy and/or oophorectomy, and explain the kind of surveillance and testing they and their families should receive. It is important to note that not all women who inherit an altered gene will develop breast or ovarian cancer, nor will all the children of people who have a gene mutation inherit that alteration or develop a cancer.

Step 2. Determine Risk for Noncarriers Using Population-Based Risk Assessment Tools

Step 2 in the process of assessing breast cancer risk is to calculate the risk for individuals who are not carriers of a breast cancer mutation. The Gail model is

Breast Cancer Risk Assessment

- Step 1. Identify individuals with an inherited predisposition for breast cancer
- Step 2. Determine risk for noncarriers using population-based risk assessment tools

Table 1.

Breast Cancer Risk Factors

- ▶ Female gender
- ▶ Increasing age
- ▶ Early menarche
- ▶ Late menopause
- ▶ Nulliparity
- ▶ Older age at first live birth
- ▶ Family history of breast cancer
- ▶ Personal history of proliferative benign breast disease
- ▶ History of radiation exposure
- ▶ BRCA1/2, p53, or PTEN gene mutations
- ▶ Current or prior estrogen and progesterone hormone replacement therapy
- ▶ High body mass index
- ▶ Alcohol consumption
- ▶ Increased breast density

National Comprehensive Cancer Network.³

Table 2.

Lifetime Breast Cancer Risk and Median Age of Onset

	Lifetime Risk	Median Age of Onset
General population	11%	61 years
BRCA1	65%	43 years
BRCA2	45%	41 years

Antoniou A et al.⁵

Table 3.

Family History Patterns Suggesting Referral for BRCA Testing

- ▶ 2 first-degree relatives with breast cancer, 1 <50 years of age
- ▶ ≥3 first- or second-degree relatives with breast cancer, regardless of age at diagnosis
- ▶ Combination of both breast and ovarian cancer among first- and second-degree relatives
- ▶ First-degree relative with bilateral breast cancer
- ▶ ≥2 first- or second-degree relatives with ovarian cancer, regardless of age at diagnosis
- ▶ Breast cancer in a male relative
- ▶ Jewish heritage
- ▶ First- or second-degree relative with both breast and ovarian cancers
- ▶ Second-degree relative on same side of the family with breast or ovarian cancer

US Preventive Services Task Force.⁶

Commentary

Individualizing Risk Reduction Robin L. Coyne, MSN, FNP-BC

Breast cancer risk reduction has evolved well beyond annual mammography screening. Since the late 1990s chemopreventive agents have given women options to reduce the risk of breast cancer. One size, however, no longer fits all. In the clinical setting we strive to individualize breast cancer risk reduction by assessing risk factors more precisely and counseling accordingly.

The risk assessment process begins with a complete family history. Women reporting breast cancer throughout several generations, particularly in premenopausal relatives, are referred to genetic counseling. In women without a suggested genetic predisposition for breast cancer, the Gail risk assessment model (available at: www.nci.nih.gov/bcrisktool) can be used to estimate the risk (inset). Women with a <1.7% 5-year risk for breast cancer are advised to obtain an annual mammogram and clinical breast examination. Those with a ≥1.7% 5-year risk may be eligible for

chemoprevention with either tamoxifen or raloxifene. Tamoxifen and raloxifene reduce the risk for estrogen-receptive positive (ER+) breast cancer by approximately 69%.

Primary care clinicians should counsel patients who are eligible for chemoprevention on the risks and benefits of these

agents. The patient must be given ample opportunity to ask questions, understand the information, and consult with other clinical specialists as needed. The goal is to educate women regarding their risk and allow them to make an informed decision regarding risk reduction strategies.

Gail Model Risk Assessment Questions

1. Does the woman have a medical history of any breast cancer or DCIS or LCIS? (The model does not calculate risk for women with DCIS or LCIS. The intent of this question is to identify and exclude these women from having their risk calculated by the Gail model.)
2. What is the woman's age? This tool only calculates risk for women ≥35 years of age.
3. What was the woman's age at the time of her first menstrual period?
4. What was the woman's age at the time of her first live birth?
5. How many of the woman's first-degree relatives – mother, sisters, daughters – had breast cancer?
6. Has the woman ever had a breast biopsy?
 - 6a. How many breast biopsies (positive or negative) has the woman had?
 - 6b. Has the woman had at least one breast biopsy with atypical hyperplasia?
7. What is the woman's race/ethnicity?

National Cancer Institute. Breast cancer risk assessment tool. Available at: www.cancer.gov/bcrisktool/. Accessed April 3, 2008.

a simple, on-line risk assessment model, which can be found at: www.nci.nih.gov/bcrisktool^{7,8} (see *Commentary: Individualizing Risk Reduction*). The 5-year and lifetime risk for invasive breast cancer can be calculated from this model. A ≥1.7% risk of developing invasive breast cancer during the next 5 years is considered an elevated risk.

This risk assessment tool has limitations, however, and may underestimate actual risk due to the simplifications it uses.⁸ The Gail risk assessment model:

- ▶ Calculates risk only in women ≥35 years of age
- ▶ Used studies of breast cancer in white women, thus the risk in African American women may be underestimated
- ▶ Breast cancer risk in women from certain ethnic groups, such as recent immigrants from Japan or China, may be overestimated
- ▶ The CARE model, which is based on data from the Women's Contraceptive and Reproductive Experiences (CARE) study, is now available to determine more

accurately the breast cancer risk in African American women.⁹ (The CARE model can be accessed at: dceg.cancer.gov/tools/riskassessment/care.)

- ▶ Is not applicable in women who have had invasive breast cancer, ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS)
- ▶ Does not take into account hormone replacement therapy
- ▶ Does not calculate the risk association of breast cancer with thoracic radiation¹⁰

Nevertheless, the current tool is useful clinically because it provides an easy way to estimate a woman's risk of developing breast cancer.

Breast Cancer Risk Reduction Interventions

Once a woman's breast cancer risk has been determined, appropriate risk reduction interventions should be discussed and chosen based on her specific risk category. Because all women are at risk for breast cancer to some degree, all female patients should be

counseled to follow a healthy lifestyle (see *Lifestyle Changes to Reduce Breast Cancer Risk*, page 5).

Women at highest risk, such as those who carry breast cancer risk-associated genes, should be counseled about the risk reduction of prophylactic mastectomy or prophylactic oophorectomy. Women at increased risk also should be counseled about chemoprevention using approved pharmacologic intervention.

Prophylactic Surgical Interventions

For women with a genetic predisposition for breast cancer, prophylactic mastectomy and prophylactic oophorectomy are options. Prophylactic mastectomy is highly effective, reducing the risk of breast cancer by at least 90%.¹¹ Bilateral risk reduction mastectomy (RRM) is a less common option for women with a history of LCIS.³ Women should be educated to the fact that bilateral RRM does not eliminate the risk of breast cancer. A mastectomy cannot remove all breast tissue, which is widely distributed over the entire chest wall and axilla.

The surgical risks and benefits of prophylactic mastectomy must be discussed with women who are contemplating this intervention. The irreversibility of the surgery, breast reconstruction options, and the impact of surgery on body image and sexuality should be addressed. Chemoprevention is not indicated for patients who have had a bilateral mastectomy because the risk reduction from surgery is high (see *Chemoprevention*).

Prophylactic bilateral oophorectomy reduces the risk of breast cancer in BRCA1 and BRCA2 carriers by approximately 50%.¹² If performed after age 40, the reduction in risk is not dramatic.^{13,14} The benefit is greater in women with BRCA1 mutations.¹³ Women with BRCA1/2 mutations are also at increased risk for ovarian cancer. Prophylactic oophorectomy also reduces the risk of ovarian cancer in carriers of BRCA1/2 mutations by 80% to 95%.¹²

Because ovarian cancer is often detected at a late stage and carries a poor prognosis, bilateral risk reduction salpingo-oophorectomy (RRSO) should be considered. However, the protection conferred by RRSO against gynecologic, as well as breast, cancers may differ between carriers of BRCA1 and BRCA2 mutations.¹⁵

Primary care providers generally assess breast cancer risk primarily using family history, potentially missing women at increased risk based on other criteria. Although providers tailor screening and refer women at high risk to specialists, they infrequently discuss chemoprevention or genetic testing.

— Sabatino SA, McCarthy EP, Phillips RS, Burns RB. *Cancer Detect Prev.* 2007;31:375-383.

Women who are contemplating removal of their ovaries should be counseled that it does not eliminate cancer risk. In addition, it causes

premature menopause, which is often abrupt in onset, and is associated with systemic effects, such as hot flashes and increased risk of osteoporosis.

Chemoprevention

Two drugs are approved for the prevention of breast cancer in women at elevated risk (ie, those with $\geq 1.7\%$ risk of developing breast cancer within 5 years). In 1998, tamoxifen was the first drug approved for breast cancer risk reduction. Recently, raloxifene, a drug initially approved to prevent and treat osteoporosis in postmenopausal women, was approved for risk reduction of invasive breast cancers in postmenopausal women with or without osteoporosis. Both tamoxifen and raloxifene have been found effective in reducing the risk of ER+ invasive breast cancer. Tamoxifen is also indicated for reducing the risk of DCIS.

Decreases in the Incidence of Breast Cancer

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries data showed that the age-adjusted incidence rate of breast cancer in women in the United States decreased sharply (6.7%) in 2003, compared with the rate in 2002. As shown in the top of the figure, the drop was seen only in women ≥ 50 years and was more evident in ER+ compared with ER- breast cancers. This sharp decline coincides with the decreased use of hormone replacement therapy after the Women's Health Initiative reported a significant increase in breast cancer risk with the use of estrogen-progestin combination therapy. The decrease in the incidence of breast cancer was unrelated to a decrease in mammography screenings or the number of breast biopsies performed. Following the initial decrease, the incidence of breast cancer appears to have reached a plateau.

Sources:

Chlebowski RT, Hendrix SL, Langer RD, et al, for the WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in health postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA.* 2003;289:3243-3253.

Kerlikowske K, Miglioretti DL, Buist DS, et al. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. *J Natl Cancer Inst.* 2007;99:1335-1339.

Levin DC, Rao VM, Frangos AJ, et al. Current practice patterns and recent trends in breast biopsy among radiologists and surgeons. *J Am Coll Radiol.* 2006;3:707-709.

Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med.* 2007;356:1670-1674.

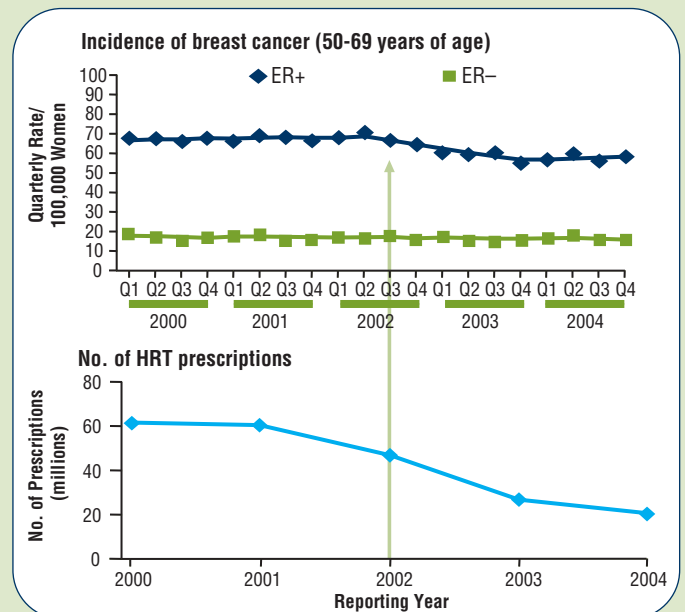


Figure. Quarterly incidence of breast cancer in women between 50 and 69 years of age (top) according to ER status, and the number of HRT prescriptions (2000-2004). HRT = hormone replacement therapy. Adapted from Ravdin PM et al.

Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-333.

When discussing the option of chemoprevention, consideration should be given to any comorbidities the patient may have that would point either for or against the use of chemoprevention or a particular agent. The side effect profiles of the agents and the patient preference also should be considered.

Modeling suggests approximately 2.5 million American women aged 35-70 could benefit from chemopreventive therapy.

– Freedman AN, Graubard BI, Rao SR, et al. *J Natl Cancer Inst.* 2003;95:526-532.

One of the challenges facing breast cancer researchers is the lack of an effective chemopreventive agent against ER– breast cancer. It is important to remind patients undergoing chemopreventive therapy that they must continue routine breast cancer screening.¹⁶ The use of chemoprevention in women with inherited mutations of BRCA1 and BRCA2 is less certain¹⁷ (see *Commentary: Barriers to Chemoprevention*).

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) that is used primarily to treat early and advanced ER+ breast

Commentary

Barriers to Chemoprevention Therese B. Bevers, MD, FAAFP

Despite the proven benefits of breast cancer chemoprevention, a recent literature review suggests that adoption of chemoprevention in the primary care setting has been low. There have been several explanations for this lack of use, including the time and effort needed to assess risk and engage in shared decision making; lack of familiarity with the results of chemoprevention studies; discomfort prescribing (and, on the part of patients taking) a drug, such as tamoxifen, which is also used for cancer treatment; and fear of side effects. A recent survey found that

chemoprevention with tamoxifen was being used infrequently even among women who were deemed at high risk for breast cancer following breast lumpectomy and who were being seen in a family practice setting. Nearly half the women surveyed said fear of adverse events was the primary cause of their decision not to start chemoprevention. Almost one third of patients said the family physician's recommendation not to use tamoxifen had the most influence on their use of chemoprevention. Fully one third of women who were at high risk for breast cancer incorrectly perceived themselves as being at low risk for breast cancer.

Sources:

Kinsinger LS, Kahwati LC, Hamilton R. Putting it all together: How do primary care physicians interpret and use the results of prevention trials? Presented at: Frontiers in Cancer Prevention Research; November 12-15, 2006; Boston, Mass.

Taylor R, Taguchi K. Tamoxifen for breast cancer chemoprevention: low uptake by high-risk women after evaluation of a breast lump. *Ann Fam Med.* 2005;3:242-247.

cancer. Tamoxifen has different effects on different tissues. It inhibits estrogen activity in the breast, but has estrogen-like activity in the uterus, which can result in endometrial hyperplasia and an increased risk for endometrial cancer. In postmenopausal women, this estrogen activity can increase bone mineral density.^{18,19}

The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1: Breast Cancer Prevention Trial (BCPT)

was the first randomized clinical trial to demonstrate that chemoprevention can reduce the incidence of breast cancer.²⁰ In that trial, which took place from 1992 through 1997, 13,388 women at increased risk for breast cancer were randomized to receive tamoxifen 20 mg/d for 5 years or placebo for 5 years. Results of the BCPT showed that tamoxifen significantly decreased the risk of invasive and noninvasive breast

Lifestyle Changes to Reduce Breast Cancer Risk

All women—whether they are at an increased risk of developing breast cancer or not—should be encouraged to lead a healthful lifestyle. Clinical studies have shown that these steps can reduce breast cancer risk, but the exact benefit of these lifestyle changes is difficult to quantify.

Encourage your female patients to:

- Maintain a healthy weight, with a body mass index <25 kg/m²
- Eat a diet high in fruits, vegetables, and whole grains and low in processed red meat
 - The precise association between high-fat diets and breast cancer risk is unclear

- Because high-fat content foods are high in calories, a diet that limits these foods will help reduce the risk of becoming overweight or obese
- Exercise regularly (at least moderate activity for 45 to 60 minutes at least 5 days a week)
 - The E3N cohort study, a large prospective study of French women, aged 40 to 65 years, found a linear decrease in breast cancer risk with increasing amounts of moderate and vigorous recreational activities
- Limit alcohol intake
 - Women who consume 2 to 5 drinks daily have an increased risk (~1.5×) of breast cancer compared with women who do not consume alcohol

Sources:

American Cancer Society. What are the risk factors for breast cancer? Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_2X_What_are_the_risk_factors_for_breast_cancer_5.asp. Accessed April 3, 2008.

National Cancer Institute. Breast cancer. Available at: www.cancer.gov/cancertopics/types/breast. Accessed April 3, 2008.
Tehard B, Friedenreich CM, Oppert JM, Clavel-Chapelon F. Effect of physical activity on women at increased risk of breast cancer: results from the E3N cohort study. *Cancer Epidemiol Biomarkers Prev.* 2006;15:57-64.

cancer in women ≥35 years of age with a high risk of breast cancer (Table 4).²⁰ In addition, tamoxifen was associated with a nonstatistically significant decrease of 19% in the incidence of bone fractures; it had no effect on the risk of ischemic heart disease. The BCPT also demonstrated the risks of tamoxifen (see *Commentary: Managing Side Effects of Chemopreventive Agents*).

Several European studies also evaluated tamoxifen for breast cancer chemoprevention, but the reduction in breast cancer risk was not as great as that seen in the American NSABP BCPT study.²¹ In a report of the long-term results of tamoxifen prophylaxis from the International Breast Cancer Intervention Study (IBIS-1), the 96-month follow-up found that the risk-reducing effect of tamoxifen appears to persist for at least 10 years; most of its side effects do not continue after the 5-year treatment period.²²

Raloxifene

Raloxifene is the newest breast cancer chemoprevention agent. It is a SERM approved initially by the US Food and Drug Administration (FDA) for the treatment and prevention of osteoporosis in postmenopausal women. The first

Table 4.
NSABP P-1: BCPT-Tamoxifen as Chemoprevention

Type of Breast Cancer	Reduction
Invasive	49%
Noninvasive	50%
ER+	69%
ER-	No difference

Fisher B et al.²⁰

suggestion that raloxifene might have a beneficial effect on breast cancer risk reduction came from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. This trial, a multinational, double-blind, placebo-controlled trial, enrolled 7705 women aged 31 to 80 years who had been postmenopausal for at least 2 years and had osteoporosis. Participants were randomized to receive raloxifene 60 mg/d or 120 mg/d, or placebo. The study found that raloxifene reduced the risk of vertebral fracture in postmenopausal women with osteoporosis by 30%.²³

Although women with a history of breast cancer or who were taking estrogen were excluded from the study, all participants were monitored for the occurrence of breast cancer. Results showed that 3 years of raloxifene therapy decreased the

overall incidence of invasive breast cancer by 76%.²⁴ Raloxifene reduced the risk of ER+ invasive breast cancer by 90%, but had no effect on the incidence of ER- invasive cancer. Unlike tamoxifen, raloxifene did not appear to increase the incidence of endometrial cancer.²¹ It was associated with a 3 times higher risk of venous thromboembolic events compared with placebo.²⁴

As a 4-year continuation of MORE, the Continuing Outcomes Relevant to Evista (CORE) trial found the relative risk of developing breast cancer was decreased significantly in women treated with raloxifene, compared with placebo.²⁵ During the 8 years of the combined MORE and CORE studies, the incidence of invasive breast cancer was reduced 66% with raloxifene, compared with placebo. The rate of ER+ invasive breast cancer was 76% less in the raloxifene arm than the placebo arm.

The skeletal and cardiovascular effects of raloxifene in the CORE study were similar to those seen in the MORE trial. No increase in the incidence of uterine bleeding, endometrial hyperplasia, and endometrial cancer was seen in the raloxifene and placebo groups after 8 years of treatment.

Commentary

Managing Side Effects of Chemopreventive Agents

Robin L. Coyne, RN, FNP-CS

The side effect profiles for tamoxifen and raloxifene are well established. Millions of women are candidates for these medications, yet few have started breast cancer chemoprevention (see Commentary: Barriers to Chemoprevention, page 5.)

Serious side effects of tamoxifen include a 2.5-fold increased risk for uterine cancer, particularly in women ≥50 years of age. Therefore, both pre- and postmenopausal women for whom chemoprevention with tamoxifen is being considered should

undergo a gynecologic assessment before beginning therapy. In addition, women who have not had a hysterectomy should be counseled about and monitored for the signs or symptoms of endometrial cancer, especially abnormal vaginal bleeding. Unlike tamoxifen, raloxifene did not appear to increase the incidence of endometrial cancer. Therefore, uterine side effects are an important aspect of the discussion of chemoprevention.

Tamoxifen and raloxifene increase the risk for thromboembolic events. The BCPT found that the risk of deep venous thrombosis (DVT), pulmonary emboli (PE), and stroke in women taking tamoxifen was increased by 60%,

301%, and 59%, respectively. These events occurred more frequently in women ≥50 years. Women in the MORE study who were taking raloxifene were at 3 times greater risk of DVT or PE compared to those taking placebo.

Modifiable side effects of tamoxifen and raloxifene include, but are not limited to, vasomotor symptoms, vaginal dryness, leg cramps, and weight gain. Nonhormonal therapies, lifestyle modification, and stress reduction may alleviate hot flashes and night sweats. Over-the-counter lubricants or vaginal estrogen are often effective in treating vaginal dryness. A well-balanced diet and healthy lifestyle that includes regular exercise are encouraged.

Sources:

American Cancer Society. Guidelines for early detection of cancer, 2003. *CA Cancer J Clin.* 2003;53:27-43. Cummings SR, Eckert S, Krueger K, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene

Evaluation [erratum in *JAMA.* 1999;282:2124]. *JAMA.* 1999;281:2189-2197.

Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet.* 2003;361:296-300.

Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer:

current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst.* 2005;97:1652-1662.

Morrow M, Jordan VC. Tamoxifen for the prevention of breast cancer in the high-risk woman. *Ann Surg Oncol.* 2000;7:67-71.

Study of Tamoxifen and Raloxifene (STAR): Tamoxifen Versus Raloxifene as Chemoprevention

Results from these studies led to a head-to-head, multicenter, double-blind, randomized trial of raloxifene versus tamoxifen in 19,747 postmenopausal women at increased risk for breast cancer, which was defined as a personal history of LCIS or a 5-year predicted risk of breast cancer of ≥ 1.66 by the Gail model.²⁶ In this phase 3 NSABP STAR P-2, women were randomized to receive either tamoxifen 20 mg/d for 5 years or raloxifene 60 mg/d for 5 years. Patients with a history of invasive breast cancer or DCIS were excluded from the study.

Raloxifene and tamoxifen were equivalent in preventing invasive breast cancer (Figure 1A).²⁶ Fewer noninvasive breast cancers were found in the tamoxifen group compared with the raloxifene group; however, this difference was not statistically significant (Figure 1B).²⁶

There were 84% fewer cases of endometrial hyperplasia, with or without atypia, and fewer uterine cancer cases in the raloxifene arm compared with the tamoxifen arm. The incidence of stroke was similar in both groups, but DVT, PE, and cataracts were less common in women receiving raloxifene (Table 5).²⁶ No significant differences in patient-reported outcomes, which included physical health, mental health, and depression, were seen between the treatment groups.²⁷ The tamoxifen group, however, reported better sexual function than the women in the raloxifene group. Participant-reported side effects were generally mild-to-moderate in severity. In general, women receiving tamoxifen reported more gynecologic problems, vasomotor symptoms, leg cramps, and bladder control problems; women in the raloxifene group reported more musculoskeletal problems, dyspareunia, and weight gain.

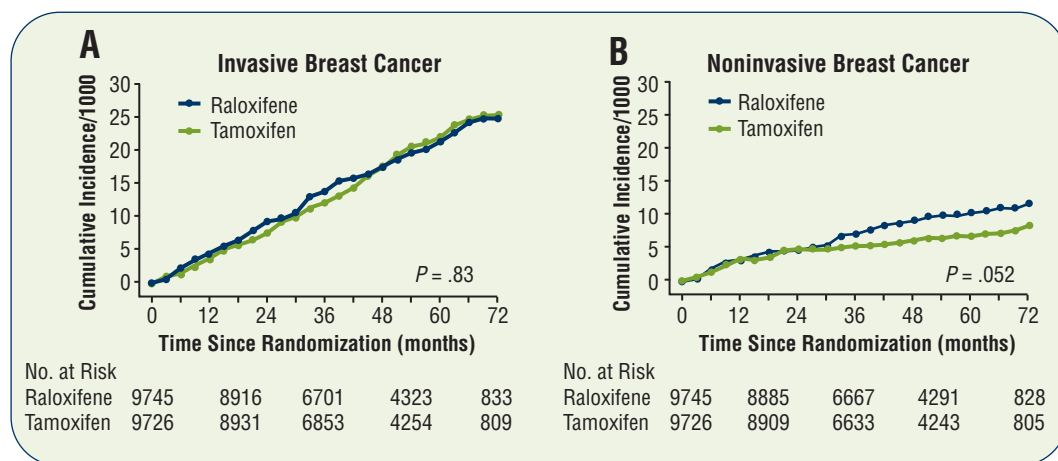


Figure 1. NSABP STAR P-2 results. (A) Raloxifene was as effective as tamoxifen in reducing the risk of invasive breast cancer. (B) The risk of noninvasive breast cancer was lower in the tamoxifen group; but it did not reach statistical significance. Vogel VG et al.²⁶

Table 5.

STAR Trial: Incidence of Breast Cancer and Adverse Events

End Point	Tamoxifen (n = 9872)	Raloxifene (n = 9875)	Risk Ratio (95% CI)
Invasive uterine cancer	36	23	0.62 (0.35-1.08)
Uterine hyperplasia	84	14	0.16 (0.09-0.29)
Hysterectomy	244	111	0.44 (0.35-0.56)
Fractures	104	96	0.92 (0.69-1.22)
Cataracts	394	313	0.79 (0.68-0.92)
Ischemic heart disease	114	126	1.10 (0.85-1.43)
Stroke	53	51	0.96 (0.64-1.43)
PE and DVT	141	100	0.70 (0.54-0.91)

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Agents Under Evaluation for Chemoprevention

Prospective studies are underway to determine the effectiveness of aromatase inhibitors (AIs), which are used to treat breast cancer in postmenopausal women, as chemopreventive agents. The National Cancer Institute of Canada Clinical Trials Group MAP.3 trial (ExCel study) and the International Breast Cancer Intervention Study-2 (IBIS-2) are double-blind, placebo-controlled, multinational trials. ExCel, which will include women in the United States, is evaluating exemestane; IBIS-2 is studying anastrozole outside the United States. Another study, IBIS-2 DCIS is evaluating the use of anastrozole in women who had surgery to remove a hormone receptor-positive DCIS.

PCE Takeaways

- The primary care clinician is on the frontline of breast cancer risk assessment. This assessment should include inherited and population-based risk factors.
- Genetic counseling should be considered in women with a significant family history of breast cancer.
- Although the Gail model does have limitations, it is useful in women ≥ 35 years of age who do not appear to have a gene mutation for breast cancer.
- Risk reduction interventions should be tailored to the patient and include lifestyle changes, chemoprevention, and prophylactic surgery.
- Currently, 2 chemopreventive agents, raloxifene and tamoxifen, have been shown to reduce the risk of breast cancer.

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and Prevention Strategies
Breast Cancer: Risk Assessment**



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