

Fighting Breast Cancer: A Call for a New Paradigm

By Mark Binstock, MD, MPH

Breast cancer is more common than all types of cancer except skin cancer.¹ Breast cancer is also the second leading cause of cancer death in women¹ and is the leading cause of all death among women aged 40-59 years.² The lifetime risk of a woman being diagnosed with breast cancer is 14.2%.³ The mortality rate for breast cancer—26 per 100,000 women—has remained essentially unchanged over the past 60 years.³

At present, efforts to control breast cancer are focused on mammography—a procedure that has proved effective at reducing mortality from breast cancer among women aged 50 to 75 years^{4,5} but does not reduce the incidence of breast cancer. Mammography also does little, if anything, to reduce the risk of mortality from breast cancer in women aged under 50 years or over 75 years.^{4,5} To control breast cancer more effectively, we must move beyond mammography and focus on strategies that will reduce the incidence of breast cancer as well as the mortality rate from the disease. We need to add breast cancer risk assessment to our conventional triad of mammography, Clinical Breast Exam (CBE) and Breast Self Exam (SBE). Fortunately, such breast cancer risk tools are available and validated although not widely used in clinical practice.

Tools for Assessing Risk for Breast Cancer

The Gail Model⁶ is a risk assessment tool that combines seven risk factors (age, number of first degree female relatives with a history of breast cancer, age at first live birth, number of prior breast biopsies, history of biopsy-proven atypical hyperplasia, age at menarche and race) to calculate five-year and lifetime risk for breast cancer. A simple way to calculate a Gail score for a given patient is via the Web site: www.breastcancerprevention.com.⁷

A handheld calculator also is available for this purpose and is distributed free of charge by Astra Zeneca (1-800-236-9933-1-3).

Chemoprevention

Calculating a Gail score for an individual woman helps the clinician to determine whether chemoprevention of breast cancer is an appropriate approach. The landmark PCBT trial of the National Surgical Adjunctive Breast Prevention Consortium (P1) showed that chemoprevention of breast cancer can be effective.⁸ This randomized, double-blind study examined tamoxifen vs placebo among 13,388 participants who were at increased risk for breast cancer as defined by a Gail score >1.66. Study participants who received tamoxifen had 49% fewer cases of invasive breast cancer (89 cases) than did women who received placebo (175 cases) ($p = 0.00001$).⁸

Another important finding was that chemopreventive use of tamoxifen was associated with certain risks.⁸ In particular, more cases of endometrial cancer were seen in tamoxifen users (36 cases) than in placebo users (15 cases), and this pattern was observed for stroke (38 cases vs 24 cases), pulmonary embolism (18 cases vs 6 cases), and deep vein thrombosis (35 cases vs 22 cases).⁸ The risk of complications from tamoxifen use is a function of age, hysterectomy status, and race.⁸ So, although tamoxifen will reduce the risk of breast cancer in all women at higher risk for breast cancer (Gail score >1.66), tamoxifen is not an appropriate choice for all such women: Some will have an unfavorable benefit-to-risk ratio. Unfortunately, deciding which women will benefit from primary prevention with tamoxifen is not intuitive and depends not

only on the Gail score value but on a woman's race, age, and hysterectomy status.

Fortunately, existing mathematical models can be used to ascertain which women and at what Gail score net benefit over harm will be obtained after race, age, and hysterectomy status are known.⁹ For example, a white woman aged 45 years with an intact uterus and whose Gail score is ≥ 1.5 would receive a net benefit from tamoxifen; but if her Gail score was <1.5, her risk of harm would be greater than her benefit. On the other hand, an African-American woman aged 45 years with an intact uterus would need a Gail score of 2.5 or more to receive a net benefit from tamoxifen. In general, compared with non-Hispanic white women, African-American women need a higher Gail score at the same age and hysterectomy status to receive a net benefit from tamoxifen (Table 1).⁹

The risk of complications from tamoxifen use is a function of age, hysterectomy status, and race.⁸

Special High-Risk Groups

Women with a history of lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS) who have not had bilateral mastectomy are at especially high risk for breast cancer (five-year risk between 6.5% and 14.7%) and therefore present a special situation. Women with this diagnosis who are between 35 and 59 years of age who have not had a hysterectomy can receive a net benefit from chemoprophylaxis with tamoxifen. Non-Hispanic white women between 35 and 79 years of age (and African-American women between 35 and 59 years of age) who have had a hysterectomy also receive a net benefit from this chemoprophylaxis.

In a similar manner, women with a remote history of breast cancer who have not yet

Mark Binstock, MD, MPH, is Director of Women's services for the Ohio Permanente Medical Group. E-mail: mark.binstock@kp.org.



Table 1. Net benefit^a of Tamoxifen chemoprevention in non-Hispanic white and African-American women at high risk for breast cancer

	Age	Hysterectomy	Gail score
Non-Hispanic white women	35-49	No	≥1.5
	50-59	No	≥4.0
	35-59	Yes	≥1.5
	60-69	Yes	≥3.5
African-American women	35-39	No	≥1.5
	40-49	No	≥2.5
	50-59	No	≥6.5
	35-39	Yes	≥1.5
	40-49	Yes	≥2.0
	50-59	Yes	≥5.5

^a Defined by Gail score.

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undergone a five-year course of tamoxifen chemotherapy also are at high risk for breast cancer (five-year risk 3.4%) and may be appropriate candidates for chemoprophylaxis with tamoxifen. In particular, non-Hispanic white women aged between 35 and 69 years (and African-American women aged between 35 and 49 years) who have had a hysterectomy receive a net benefit from this chemoprophylaxis as do women aged between 35 and 49 years who have not had a hysterectomy.⁹

Evidence-Based Chemoprevention Strategies

Evidence-based guidelines exist supporting the role of chemoprevention of breast cancer. For example, the United States Prevention Services Task Force developed a guideline¹⁰ in response to the P1 trial listed above calling for consideration of chemoprevention in high-risk women. Tamoxifen chemoprevention consists of tamoxifen 20 mg orally once daily for five years. In a similar manner, the American College of Obstetricians and Gynecologists and the American Society of Clinical Oncology have embraced breast cancer chemoprevention.¹¹ The US Food and Drug Administration (FDA) has approved tamoxifen for this indication.¹²

Because the side effects of tamoxifen are most serious in women older than 50 years, it is best used in women younger than 50 years who are at high risk for breast cancer.

Given the serious side effects of tamoxifen, research is being focused on other chemoprophylactic agents (eg, raloxifene) that may have a better risk-benefit ratio. One finding from the MORE Trial¹³ (an osteoporosis treatment clinical trial) was a 76% reduction in the incidence of newly diagnosed invasive breast cancer with no increased risk for endometrial cancer. For raloxifene, risks of deep vein thrombosis and pulmonary embolus are similar to the risk observed for either tamoxifen or estrogen replacement therapy.

New and Future Chemoprevention

On the basis of results of the MORE Trial, the NSABP initiated the STAR Trial (Study of Tamoxifen and Raloxifene)¹⁴ for primary prevention of breast cancer. The purpose of the study was to determine whether raloxifene is at least as effective as tamoxifen for preventing breast cancer and with fewer side effects and less toxicity. Recruitment for the STAR Trial has now been completed, and KP nationally has been a large contributor to enrollment. Answers will be forthcoming in the near future as to whether raloxifene or tamoxifen is a better chemoprophylactic agent.

Early studies^{15,16} have shown that another class of drugs—the aromatase inhibitors—affords secondary chemoprevention. For example, letrozole reduced by 50% the recurrence of new cancer among 5000 women with

early-stage breast cancer who had already received tamoxifen for five years.¹⁵ In addition, anastrozole reduced recurrences by 64% and death by 82% among estrogen receptor-positive women who had received tamoxifen for two or more years.¹⁶ Because of such findings, NSABP is contemplating initiation of chemoprophylactic trials of aromatase inhibitors compared with selective estrogen receptor modulators (SERMs), a class of drugs that includes tamoxifen and raloxifene. The COX-2 inhibitors represent another class of drugs that hold promise for breast cancer chemoprevention.^{17,18}

Risk Assessment—Missed Opportunities

Despite the availability of the Gail risk assessment tool, it has not yet found widespread use in clinical practice. Use of the tool has largely been limited to identifying patients eligible for chemoprophylactic research trials, such as the STAR Study. However, a tremendous opportunity exists for the tool to be used more directly in patient care and case management. An estimated ten million high-risk women eligible for tamoxifen have a Gail score above 1.67% and are aged 35 years or older.¹⁹ Further, for an estimated 2.5 million women, tamoxifen chemoprophylaxis would present a net benefit over risk.¹⁹ This net benefit would vary by age, race, and hysterectomy status of the drug recipient. A possibility is that, with widespread use of the Gail score and intervention for appropriate women, 29,000 cases of breast cancer could be prevented.¹⁹ This opportunity will be missed unless we alter our approach to risk assessment. *An ideal scenario would be for a Gail score to be calculated each time a woman undergoes screening mammography and for this value to be included in the radiology report.* Both the ordering clinician and the patient would be informed of the risk value and—on the basis of the result and the woman's race, age, and hysterectomy status—would be informed of the opportunity for chemoprophylaxis if appropriate. The woman and her health care practitioner would then be responsible for pursuing this option further.

Genetic (BRCA) Testing

For most women, the Gail score is adequate for breast cancer risk assessment. However, use of this tool is not a valid option for families who have a BRCA 1 or 2 autosomal dominant mutation. About 5% of women with breast cancer have the BRCA mutation.²⁰ Having a mutation of the BRCA 1 or 2 gene increases the risk of breast cancer far more than does any other known risk factor for this disease. Among women with mutation of the BRCA 1 or 2 gene, the risk of breast cancer by age 40 years is between 10% and 20%; by age 50 years, the risk is between 33% and 50%; and by age 70 years, the risk is between 56% and 87%.^{21,22}

Testing should be offered to women who have a high likelihood (ie, >10%) of having a mutation of the BRCA 1 or 2 gene. This strategy is recommended by the American Society of Clinical Oncology.²³ In particular, genetic testing should be considered under the following circumstances: 1) Two or more family members with breast cancer of early onset (ie, before age 50 years); 2) a family history of ovarian cancer and early-onset breast cancer; 3) a personal history of breast cancer at any age and a family history of breast cancer occurring before age 50 years; 4) a personal history of breast cancer occurring before age 50 years; 5) a personal history of ovarian cancer occurring at any age and a family history of either ovarian cancer or early-onset breast cancer; 6) a personal history of ovarian cancer and breast cancer occurring at any age. For women of Ashkenazi Jewish ancestry, in addition to the above criteria, several categories are associated with a high (>10%) risk of mutation: 1) a personal history of ovarian cancer occurring at any age; and 2) a family history of either ovarian cancer or early-onset breast cancer.

For women who test positive for mutation of the BRCA 1 gene, mutation of the BRCA 2 gene, or mutation of both genes, chemoprevention and prophylactic surgery can diminish the hereditary risk for breast

cancer. These interventions are associated with life expectancy gains comparable to the gains achieved by using chemotherapy for malignancy.²⁴ Prophylactic bilateral mastectomy represents an effective (though extreme) strategy for reducing breast cancer among women with BRCA mutations.²⁵ Prophylactic oophorectomy not only reduces the risk for ovarian cancer but also reduces the risk for breast cancer in women with BRCA mutations. For example, prophylactic oophorectomy reduced the risk of breast cancer in women with BRCA mutations by nearly 50%.²⁶ In addition, a recent study²⁷ showed magnetic resonance imaging (MRI) to be superior to mammography among women who had a familial or genetic predisposition to breast cancer.

Conclusion

Breast cancer risk assessment should be promoted, because it is a prerequisite for selecting appropriate candidates for risk reduction interventions. Currently, chemoprevention in selected women at high risk for breast cancer is the only proven method of lowering the incidence of breast cancer.

As a first step, each region and/or the Care Management Institute should review the United States Prevention Services Task Force evidence-based guidelines on breast cancer chemoprevention.¹⁰ Strong consideration should be given to endorsing or modifying such a guideline for KP use and to encourage or at the minimum be permissive as to best practice. A sample guideline is available from the author upon request.

For regions who mail patients notification letters of their mammogram results, consideration should be given to adding the following text to all of the letters:

"If you are age 35-69, you are encouraged to determine your five-year breast cancer risk through the Web site www.breastcancerprevention.org/raf_source.asp. If your five-year breast cancer risk is 1.5% or above you may be a candidate for risk reduction by taking a

drug called Tamoxifen for five years. Determination of who are good candidates for Tamoxifen is dependent not only on your five-year breast cancer risk but also your age, race and whether or not your uterus has been removed. If you are interested in learning more, call {region or subregion contact number} or your primary care provider. Finally, if your five-year breast cancer risk is 1.5% or above, you should get mammograms every year."

Hopefully in the future, individualized risk assessment and automated triage for chemoprevention can be incorporated into mammogram reports and/or KP HealthConnect. For example, Best Practice Alerts (BPA) promoting tamoxifen chemoprophylaxis could be programmed targeting women with pathology reports showing LCIS, DCIS, or remote invasive breast cancer. A Gail score questionnaire could appear periodically (eg, every five years) for women aged 35-59 years. A KIOSK approach with a self-administered risk assessment questionnaire could be adopted in conjunction with mammography. This approach has already been implemented as part of osteoporosis (DXA) screening in the KP Ohio Region and has been a tremendous aid to recruiting for the STAR study and appropriately offering other women chemoprevention.

Breast cancer risk assessment is not a panacea. Most women who have breast cancer as well as those who will develop it in the future are low risk. However, implementing breast cancer risk assessment and selected chemoprevention will reduce breast cancer incidence and mortality for those at high risk. KP is ideally situated to incorporate these strategies in a population-based approach. Too many lives have been lost; we should seize the opportunity. ❖

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Too Busy

Success usually comes to those who are too busy to be looking for it.

— Henry David Thoreau, 1817-62, naturalist and poet