Barriers to the Use of Breast Cancer Risk Reduction Therapies

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Abstract

Evidence from randomized clinical trials supports the use of tamoxifen, raloxifene, exemestane, and anastrozole for the reduction of risk of invasive breast cancer, predominately estrogen receptor-positive tumors. Revised clinical guidelines now strongly recommend that physicians offer high-risk women medication for breast cancer risk reduction. Although only a small portion of eligible women receive risk reduction medication, evidence suggests higher acceptance among women with atypical hyperplasia or lobular carcinoma in situ. Among physicians, barriers for prescribing risk reduction medications include inadequate training in risk assessment, lack of reimbursement for prevention counseling, and the unavailability of easily accessible and user-friendly prediction tools for estimating risk/benefit profiles. Strategies to improve uptake among women have focused on providing education about breast cancer risk and information that accurately conveys the risks and benefits of risk reduction medications. Priority areas of research that have been identified to improve the use of risk reduction medications are the (1) development of risk assessment tools that more accurately identify women most likely to benefit, (2) identification of circulating or tissue biomarkers that can predict and monitor responsiveness of treatment, and (3) better understanding of patient-related barriers, including patients' subjective beliefs and experiences. (*J Natl Compr Canc Netw* 2015;13:927–935)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Understand the barriers clinicians face for prescribing breast cancer risk reduction medications
- Explain several strategies to educate women on breast cancer risk and risk reduction strategies
- Identify research areas to improve the use of risk reduction medication for women who are at high risk for breast cancer

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Evidence for Risk Reduction Therapies for Invasive Breast Cancer

Several randomized clinical trials have provided evidence for the efficacy of selective estrogen receptor modulators (SERMs) for the primary prevention of invasive breast cancer.¹⁻⁵ The Breast Cancer Prevention Trial (BCPT) enrolled women based on either age of 60 years or older, or age 35 to 59 years with a modified Gail model 5-year predicted risk of breast cancer of 1.66% or greater or a history of lobular carcinoma in situ (LCIS). BCPT randomized women to receive tamoxifen or placebo, and results showed that the tamoxifen arm had a significant reduction in the risk of developing an estrogen receptor (ER)-positive tumor (relative risk [RR], 0.38; 95% CI, 0.28–0.50), and had no risk reduction benefit for ER-negative tumors (RR, 1.31; 95% CI, 0.86–2.01).¹ Tamoxifen was associated with a 2.5-fold increased risk of endometrial carcinoma and an increased risk of thromboembolic events and cataracts.¹ The European randomized trials of tamoxifen compared with placebo demonstrated a more modest benefit of tamoxifen (39%–22%) for reducing the risk of ER-positive tumors.²⁻⁴

The initial results of the Study of Tamoxifen and Raloxifene (STAR) trial after 47 months of follow-up demonstrated that raloxifene was as effective as tamoxifen in reducing the overall risk of breast cancer (RR, 1.02; 95% CI, 0.82–1.28) and ER-positive tumors (RR, 0.93; 95% CI, 0.72–1.24) in high-risk postmenopausal women. The raloxifene arm experienced fewer adverse events, including thromboembolic events, endometrial cancer, and cataracts.⁵ Similar risks between the treatment arms were seen for ischemic heart disease, fractures, and stroke. With a longer median follow-up time of 81 months, raloxifene has proven to be 76% as effective as tamoxifen in reducing the overall risk of invasive breast cancer (RR, 1.24; 95% CI, 1.05–1.47).⁶

Two aromatase inhibitors have been investigated for the primary prevention of breast cancer. MAP.3 was a randomized placebo-controlled trial designed to investigate the use of exemestane for the primary prevention of invasive breast cancer. The study included a postmenopausal population that was similar to the one studied in the BCPT and STAR trials. At a median follow-up of 35 months, exemestane reduced the overall risk of breast cancer (RR, 0.35; 95% CI, 0.18–0.70), ER-positive tumors (RR, 0.27; 95% CI, 0.12–0.60), and ER-negative tumors (RR, 0.80; 95% CI, 0.21–2.98) compared with placebo.⁷ Arthritis and

hot flashes, but not osteoporosis or clinical fractures, were more frequent in the exemestane arm. Another phase III trial, IBIS-II, randomized 3864 high-risk postmenopausal women to receive either placebo or anastrozole.⁸ At a median follow-up of 60 months, a statistically significant reduction of 50% was seen in the overall risk of developing invasive breast cancer, and a 58% reduction in the risk of developing ER-positive tumors among women assigned to the anastrozole arm. Musculoskeletal adverse events, vasomotor symptoms, dry eyes, and hypertension were reported more frequently among women in the anastrozole group than in those in the placebo arm. No significant differences were observed in the frequency of thromboembolic events, cerebrovascular events, or myocardial infarction. Tamoxifen and raloxifene are the only 2 risk reduction medications approved by the FDA for breast cancer prevention.

Guidelines for Breast Cancer Risk Reduction Therapies

In 2013, the US Preventive Services Task Force (USPSTF) reaffirmed its 2002 recommendation for the use of breast cancer risk reduction medications. The recommendation states that clinicians should engage in shared, informed decision-making with women at an increased risk for breast cancer regarding medications to reduce this risk. Furthermore, clinicians should offer to prescribe tamoxifen or raloxifene for those at an increased risk for breast cancer and at low risk for adverse medication effects (B recommendation).⁹ Based on the Freedman et al¹⁰ risk-benefit tables for women aged 50 years and older, the task force concluded that most women with a 5-year risk of breast cancer of 3.0% or greater would be expected to have greater benefit than harm. The B recommendation did not include women with a history of ductal carcinoma in situ or LCIS.⁹

In July 2013, ASCO updated its clinical practice guidelines on the use of tamoxifen, raloxifene, or exemestane for breast cancer risk reduction.¹¹ A stronger recommendation was issued for risk reduction medication and instead of stating “may be offered,” the language was modified to “should be discussed as an option.” The ASCO guidelines define high-risk women as those with a 5-year risk of 1.66% or greater or those with LCIS.

A recommendation for the use of tamoxifen and raloxifene is also supported by NCCN.¹² Based on

the results of the MAP.3 trial and the IBIS-II trial, both exemestane and anastrozole were included as choices for breast cancer prevention. The NCCN recommendation for exemestane and anastrozole was limited to postmenopausal women aged 35 years or older with a modified Gail model 5-year risk of 1.7% or more, or a history of LCIS (Table 1).¹²

Uptake of Breast Cancer Risk Reduction Therapies in the United States

Despite more than a decade of scientific evidence demonstrating the clinical benefit associated with the use of risk reduction medications, population-based estimates in the United States indicate that the uptake of tamoxifen and raloxifene has remained low. Waters et al¹³ used data from the National Health Interview Survey and projected that 0.03% (n=20,598) and 0.2% (n=96,890) of eligible women in the United States used tamoxifen or raloxifene, respectively, in 2010. This contrasts with estimates that there are approximately 2 million women in the United States for whom the benefits would be expected to outweigh the risks.¹⁴ Nicholas et al¹⁵ examined tamoxifen uptake for breast cancer prevention within The Sister Study, a cohort of 50,884 US and Puerto Rican women aged 35 to 74 years enrolled between 2003 and 2009. The study found that 1046 of 50,884 participants (2%) reported ever using tamoxifen.¹⁵

Whether women seen in high-risk clinical settings are more motivated to use risk reduction medications has not been well described; published studies are listed in Table 2. In a comprehensive review of 5 studies that reported on the use tamoxifen or raloxifene for breast cancer prevention among women seen in the high-risk clinical setting, the mean uptake was 14.8% (range, 0.5%–51.0%), and the largest study consisted of 162 women.¹⁶ One of these studies¹⁷ evaluated uptake in high-risk women who initially refused tamoxifen and then were offered it again after the disclosure of their random periareolar fine-needle aspiration results. This study found that the uptake rate was 0% (0 of 51) in women found to have nonproliferative or hyperplastic cytology, 7% (2 of 30) in women with borderline atypia, and 50% (9 of 18) among women with atypia. Other studies^{18–25} not included in the previous review have shown varied uptake rates in the high-risk setting ranging from 2.0% to 54.4%. In the study that re-

ported the lowest uptake rate of 2.0%,²¹ most of the high-risk consultations (85%) were conducted by primary care providers (PCPs). The study that reported the highest uptake rate of 54.4% evaluated acceptance of risk reduction medications at a breast surveillance clinic that provided comprehensive risk assessment and counseling.²⁴ Aktas et al²⁵ found that the use of risk reduction medication among eligible postmenopausal women was 23% (2% for tamoxifen, 14% for raloxifene, and 7% for exemestane). Among 2459 women with a diagnosis of atypia in 1999 or later who received care at 1 of 3 hospitals in Boston, the overall uptake of risk reduction medication was 18.9%, with the highest uptake among women with LCIS (33.4%) or severe atypia (40.8%).²⁶ Because this study was based on a systematic retrieval of pathology reports, the specific clinical settings in which the women were seen are unknown. However, the results are consistent with previous evidence demonstrating that use of risk reduction medication is more acceptable among women with a high-risk benign breast lesion^{15,23,27}; these women are also the ones who have the greatest risk reduction (86%) with the use of tamoxifen.¹

The uptake of risk reduction medications has not been studied extensively in the primary care setting. Armstrong et al²⁸ surveyed 350 PCPs between 2002 and 2004 and found that only 27% had prescribed tamoxifen for breast cancer prevention. Corbelli et al²⁹ assessed the frequency of prescribing risk reduction medications for breast cancer among providers across primary care specialties. They found that only 13% reported having recommended or prescribed preventive medication (9% internal medicine, 8% family medicine, 30% gynecology).

Physician Barriers to Prescribing Breast Cancer Risk Reduction Therapies

Typically, the first interaction high-risk women have with physicians is in the primary care setting; therefore, PCPs play a pivotal role in the implementation of various methods of breast cancer risk reduction. A significant barrier faced by PCPs in prescribing risk reduction medications is the difficulty in identifying women who would be eligible to receive treatment. In a community cohort, Brewster et al³⁰ evaluated the prevalence of women for whom the benefits would outweigh the risks of tamoxifen for risk reduction. They found that a PCP

Table 1 Summary of Recommendations for Use of Chemopreventive Agents for Breast Cancer Risk Reduction by Major Guidelines

	US Preventive Service Task Force Moyer⁹	ASCO Visvanathan et al¹¹	NCCN Bevers et al¹²
Population	Asymptomatic women aged ≥ 35 y; with no prior diagnosis of BC, DCIS, or LCIS; and at increased risk for BC	Women with no personal history of BC and at increased risk of developing BC, defined as those with a 5-y projected absolute risk of $\geq 1.66\%$ (based on the NCI BC Risk Assessment Tool or an equivalent measure) or women diagnosed with LCIS	Healthy premenopausal and postmenopausal women aged ≥ 35 y, whose life expectancy is ≥ 10 y, and have a $\geq 1.7\%$ 5-y risk for BC as determined by the modified Gail model, or who with prior thoracic radiation < 30 y of age or history of LCIS or ADH
Risk assessment	<p>Not any one particular risk prediction model is endorsed</p> <p>Clinicians can use any of following tools:</p> <ul style="list-style-type: none"> • NCI Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool) • Breast Cancer Surveillance Consortium model (https://tools.bscsc-scc.org/BC5yearRisk) • Other risk assessment models developed Rosner and Colditz,⁵⁴ Chlebowski,⁵⁵ Tyrer and Cuzick,⁵⁶ and others <p>There is no single cutoff for defining increased risk</p>	<ul style="list-style-type: none"> • Gail model • NCI Breast Cancer Risk Assessment Tool (http://www.cancer.gov/bcrisktool) • Other validated models (including Tyrer-Cuzick⁵⁶) • Eligibility criteria used in the various BC chemoprevention trials 	<ul style="list-style-type: none"> • Risk models that are NCI Breast Cancer Risk Assessment Tool (http://www.cancer.gov/bcrisktool) • Other risk assessment models for women with strong family history of BC or ovarian cancer (Claus, BRCAPRO, Tyrer-Cuzick, and BOADICEA)
Recommendations	Clinicians should offer to prescribe risk reducing medications, such as tamoxifen or raloxifene, for asymptomatic women; aged ≥ 35 y; with no prior diagnosis of BC, DCIS, or LCIS; and at increased risk for BC and at low risk for adverse medication effects (B recommendation)	<p>Tamoxifen (20 mg/d for 5 y) should be discussed as an option to reduce the risk of ER-positive BC in women at increased risk of BC aged ≥ 35 y</p> <p>Raloxifene (60 mg/d for 5 y) and exemestane (25 mg/d for 5 y) should also be discussed as options for BC risk reduction in postmenopausal women</p>	<p>Category 1 recommendation as an option to reduce BC risk in healthy premenopausal and postmenopausal women aged ≥ 35 y, whose life expectancy is ≥ 10 y, and who have a $\geq 1.7\%$ 5-y risk for BC as determined by the modified Gail model, or who with prior thoracic radiation aged < 30 y or history of LCIS or ADH</p> <p>Category 1 recommendation is for use of raloxifene, AI (exemestane and anastrozole) to reduce BC risk is limited to healthy postmenopausal women aged ≥ 35 y who have a $\geq 1.7\%$ 5-y risk for BC as determined by the modified Gail model, or who have had prior thoracic radiation < 30 y of age or history of LCIS or ADH</p>

Abbreviations: ADH, atypical ductal hyperplasia; AI, aromatase inhibitor; BC, breast cancer; DCIS, ductal carcinoma in situ; ER, estrogen receptor; LCIS, lobular carcinoma in situ.

would need to screen 26 women aged 40 to 49 years and 142 women aged 60 to 70 years with a uterus using the modified Gail model to find 1 woman who would eligible for counseling and have a favorable risk/benefit ratio with tamoxifen.³⁰ Corbelli et al²⁹ assessed the frequency of use of the Gail model among providers across primary care specialties. They found that only 40% of provid-

ers reported having used the Gail model (37% internal medicine, 33% family medicine, 60% gynecology), and the most commonly cited barriers for its use were lack of time and familiarity. Only approximately 15% and 9% of PCPs, reported by Armstrong et al²⁸ and Sabatino et al,³¹ respectively, felt confident about using Gail risk scores to identify high-risk women.

Breast Cancer Risk Reduction Therapies

Table 2 Studies That Evaluated Real Uptake Rates of Breast Cancer Risk Reduction Medications in the High-Risk Clinical Setting

Study	Number of Participants	Clinic Type	High-Risk Setting	Uptake of Risk Reduction Medication
Port et al, ³⁶ 2001	43	Surgical Oncology Department at Memorial Sloan Kettering Special Surveillance Breast Program	Yes	4.7% (2/43) for tamoxifen
Bober et al, ³⁵ 2004	129	Cancer Risk and Prevention program at Beth Israel Deaconess Medical Center, STAR or P-2 Trial, Oncological practice	Yes	2 mo: 28.7% (37/129 opted to take tamoxifen) + 27.1% (35/129 opted to enroll into the STAR trial) 4 mo: 25.6% (33/129 were on tamoxifen) + 25.6% (33/129 were STAR participants)
Tchou et al, ¹⁸ 2004	219	Lynn Sage Breast Center	Yes	42% (57/137) 137/219 were offered tamoxifen
Taylor and Taguchi, ⁵⁷ 2005	89	Oncology Referral Center	Yes	1.1% (1/89) for tamoxifen 6.7% (6/89) for raloxifene
Goldenberg et al, ¹⁷ 2007	99	Duke University Medical Center	Yes	Initially: 0% (0/99) Within 3 mo, post-RPFNA biomarker analysis: 0% (0/51) for nonproliferative or hyperplastic cytology 7% (2/30) for borderline atypia 50% (9/18) for atypia
Fagerlin et al, ⁴⁰ 2010	632	Henry Ford Health System, Michigan Group Health, Washington	Not specified	0.5% (3/632) at 3 mo Participants received an online individually tailored decision aid
Layeequr et al, ¹⁹ 2009	105	University-based high-risk breast clinic	Yes	31.3% (15/48) 48 of 105 were offered tamoxifen based on eligibility and contraindications
Oppong and King, ²⁰ 2011	998	Surgical Oncology Department at Memorial Sloan Kettering Cancer Center	Yes	16.0% (163/998) for LCIS surveillance population 120 (74%) used tamoxifen, 55 (34%) used raloxifene, and 3 used anastrozole (a small number used >1 agent)
Owens et al, ²¹ 2011	868	Aurora Health Care, Wisconsin	Mixed	2.0% (17/868) 85% of high-risk consultations were performed by primary care providers and 15% were referred to the breast center
Coopey et al, ²⁶ 2012	2459 (patients diagnosed with atypia in 1999 and beyond)	Massachusetts General Hospital Brigham and Women's Hospital Newton Wellesley Hospital	Not specified	18.9% (466/2459) for overall uptake 33.4% (125/374) for LCIS 40.8% (97/238) for severe atypia
Razzaboni et al, ²² 2013	471 (women who were eligible and who took part in the informative step)	Modena Familial Breast and Ovarian Cancer Center, Italy	Yes	29% (137/471) Participants agreed to participate in the IBIS II trial
Donnelly et al, ²³ 2014	1279	Genesis Breast Cancer Prevention Centre FHC, United Kingdom	Yes	10.6% (136/1279) 1279 women were eligible for tamoxifen
Roetzheim et al, ²⁴ 2015	219 (women whose 5-y risk of breast cancer was ≥1.7%)	Moffitt Cancer Center	Yes	54.4% (118/219 women who accepted a recommendation and began therapy) 73 (61.9%) took only tamoxifen, 34 (28.8%) took only raloxifene, and 11 (9.3%) took some combination of the 2 drugs
Aktas et al, ²⁵ 2015	90	Yale Breast Cancer Prevention Clinic	Yes	23% (13/56) 56 of 90 postmenopausal women were eligible for chemoprevention 1 (7.7%) took tamoxifen, 8 (61.5%) took raloxifene, and 4 (30.8%) took exemestane

Abbreviations: LCIS, lobular carcinoma in situ; RPFNA, random periareolar fine needle aspiration.

Additional barriers reported by physicians for not prescribing risk reduction medications include lack of time,^{31,32} insufficient information about risk reduction options,^{31,32} insufficient training in counseling,^{31,32} and insufficient reimbursement.³² Armstrong et al²⁸ found that PCP prescription of risk reduction medication was strongly associated with patient demand, ease of determining high-risk eligibility, and the belief that the benefits of tamoxifen outweighed the risks.²⁸ Interestingly, physician concern about the side effects was not found to be associated with the prescription of risk reduction medications.²⁸ These findings suggest that efforts to address logistical factors, such as a quick determination of a woman's eligibility and a tool that can be used to balance the risks and benefits, are needed in the busy primary care setting. To facilitate this process, risk-benefit models for breast cancer risk reduction need to be interactive and available online to both physicians and patients.³³ In addition, risk-benefit models should incorporate, in a patient-friendly format, additional modeled end points, such as lifetime risk with and without the use of risk reduction medication and the competing risks of treatment-related comorbidities.

Several studies have shown that the higher a woman's risk of breast cancer, the more likely she will be prescribed a risk reduction medication.^{15,23,27} In a survey of oncologists, 73% reported discussing risk reduction medications with their patients.³⁴ Therefore, targeting educational interventions to physicians and surgeons who specialize in risk assessment and counseling and who interact with subsets of women referred to high-risk breast clinics may provide the best opportunity to rapidly improve risk reduction medication use, and ultimately decrease the incidence of breast cancer.

Patient Barriers to Accepting Breast Cancer Risk Reduction Therapies

Fear and concerns about side effects of treatment are the most common barriers women cite to accepting breast cancer risk reduction medications,^{35–38} and the most feared side effects reported for the SERMs are endometrial cancer and thromboembolic events.³⁶ Moreover, most women perceive that their risk of developing these side effects would be 40% or greater even after they are presented with the balance of risks and benefits.³⁶ The toxicity profile of the aromatase inhibitors has been thought to be more acceptable to women

than that of the SERMs; however, Aktas et al²⁵ found that the reasons cited by patients for deciding against exemestane were primarily concerns about worsening bone density and vasomotor and arthralgia symptoms.

A higher self-perceived risk of developing breast cancer is positively associated with acceptance of risk reduction medications,^{35,38} and uptake has been shown to be significantly higher among women with a history of atypical hyperplasia or LCIS^{17,20,26} who have a 5-year risk of breast cancer of approximately 6%.¹ However, many women have the perception that risk reduction medication will not substantially lower their risk of developing breast cancer.^{39,40} In addition, the lack of a surrogate tissue biomarker of risk may contribute to the lower uptake of risk reduction medication among women who meet eligibility criteria based on family history and reproductive risk factors versus women who have a tissue diagnosis of a high-risk benign breast lesion (eg, atypical ductal hyperplasia or LCIS).⁴¹

Interestingly, studies assessing the acceptance of risk reduction medications among high-risk women have shown a higher percentage of acceptance among women faced with a hypothetical decision (24.7%) versus those who actually initiate treatment (14.8%),¹⁶ and the reasons for the discrepancy are multifactorial. Recognition of the importance of a woman's individual beliefs and experiences on her acceptance of risk reduction medication is an emerging area of research. Korfage et al⁴² reported that 62% of women enrolled in the control arm of a randomized decision aid intervention study and who did not receive education about risk reduction medication had a negative attitude about treatment. Ralph et al⁴³ examined 107 high-risk women and showed that a significant factor in decisions regarding whether to take SERMs was related to the women's individual beliefs about the benefits and risks of treatment, which may not have been influenced by their physician's recommendation but rather by their experiences, such as knowledge of a relative who may have experienced side effects or developed breast cancer while on treatment. Risk counseling that addresses a woman's subjective feelings of breast cancer risk and beliefs about treatment efficacy is needed.

Cost and health insurance coverage are important factors associated with acceptance of risk reduction medication, particularly among low-income women.^{39,44} The impact of the Accountable Care Act mandate requiring insurance coverage of risk reduc-

tion medications (B recommendation by the USPSTF), with no copayment or deductible on the use of tamoxifen or raloxifene, has not yet been determined.⁵ Other studies have found that education and lower income were inversely associated with the use of risk reduction medications.^{38,45–47} Although women who are provided with an educational decision aid about breast cancer prevention were shown to be more likely to make an informed choice, their willingness to take risk reduction medication after receiving a decision aid has been disappointingly low, ranging from 4% to 6%,^{48,49} and the actual uptake rate of risk reduction medication was less than 1%.⁴⁹ In another randomized trial, Korfage et al⁴² investigated the impact of an online decision aid on informed intentions and decisions of high-risk women. The authors found that the decision aid increased informed decision-making about risk reduction medication, although the impact on knowledge diminished over time (54% at posttest to 18% at 3-month follow-up).

Conclusions

Approximately 232,000 women are diagnosed with invasive breast cancer annually in the United States, and most tumors are ER-positive.^{50,51} Although tamoxifen, raloxifene, exemestane, and anastrozole have not been shown to reduce mortality when given in the prevention setting, the benefit despite their treatment-related side effects in reducing breast cancer incidence is a valuable prevention goal. Significant physician- and patient-related barriers are summarized in this article (Figure 1). Other barriers to the use of breast cancer risk reduction medication that need to be addressed include the low discriminatory accuracy of current risk assessment tools in accurately predicting women who will develop breast cancer,⁵² the inability to prospectively identify women at risk for an ER-positive versus ER-negative tumor, and the lack of reliable validated biomarkers to measure preventive drug effectiveness.⁵²

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Posttest Questions

1. Which of the following barriers are reported by physicians for not prescribing risk reduction medications to women with high risk of developing breast cancer?
 - a. Lack of time
 - b. Difficulty in identifying women who would be eligible to receive medication
 - c. Insufficient reimbursement for prevention counseling
 - d. All of the above
 - e. None of the above
2. Clinicians need to be better educated on patient demand for risk reduction medication, eligibility criteria for women, and beliefs that medications outweigh the risk. Therefore,

which of the following strategies is NOT appropriate for educating patients on risk reduction medications?

- a. Use an interactive risk-benefit model that is accessible to both patients and clinicians
 - b. Refer the patient to a psychologist
 - c. Apply tools that allow clinicians to quickly identify patient eligibility
 - d. Discuss lifetime risk with and without the use of risk reduction medication
3. True or False: Counseling that addresses a woman's feelings of breast cancer risk and beliefs about treatment efficacy is important.