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Addressing Barriers to Uptake of Breast Cancer Chemoprevention for Patients and Providers

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OVERVIEW

Breast cancer is the most common malignancy among women in the United States, and the primary prevention of this disease is a major public health issue. Because there are relatively few modifiable breast cancer risk factors, pharmacologic interventions with antiestrogens have the potential to significantly affect the primary prevention setting. Breast cancer chemoprevention with selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene, and with aromatase inhibitors (AIs) exemestane and anastrozole, is underutilized despite several randomized controlled trials demonstrating up to a 50% to 65% relative risk reduction in breast cancer incidence among women at high risk. An estimated 10 million women in the United States meet high-risk criteria for breast cancer and are potentially eligible for chemoprevention, but less than 5% of women at high risk who are offered antiestrogens for primary prevention agree to take it. Reasons for low chemoprevention uptake include lack of routine breast cancer risk assessment in primary care, inadequate time for counseling, insufficient knowledge about antiestrogens among patients and providers, and concerns about side effects. Interventions designed to increase chemoprevention uptake, such as decision aids and incorporating breast cancer risk assessment into clinical practice, have met with limited success. Clinicians can help women make informed decisions about chemoprevention by effectively communicating breast cancer risk and enhancing knowledge about the risks and benefits of antiestrogens. Widespread adoption of chemoprevention will require a major paradigm shift in clinical practice for primary care providers (PCPs). However, enhancing uptake and adherence to breast cancer chemoprevention holds promise for reducing the public health burden of this disease.

Unlike cardiovascular disease, limited pharmacologic options exist for the primary prevention of cancer. Antiestrogens, such as SERMs and AIs, have been shown to reduce breast cancer incidence by up to 50% to 65% among women at high risk.[1–5] Based on this evidence, the U.S. Preventive Services Task Force (USPSTF) and other professional organizations recommend that clinicians discuss chemoprevention with women at high risk.[6–8] An estimated 15% of women age 35 to 79 in the United States may be eligible for

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chemoprevention,[9] but less than 5% of women at high risk who are offered an antiestrogen for primary prevention agree to take it.[10] Compounding this underutilization is the large proportion of women who may be unaware of their high-risk status because of an inability to routinely screen for high risk in the primary care setting. Other reasons for low chemoprevention uptake include insufficient knowledge about antiestrogens on the part of clinicians and patients, multiple competing demands for PCPs, and concerns about side effects.[10,11] Even the term "chemoprevention" has negative connotations, because it sounds like "chemotherapy." The perception among patients and PCPs is that medications used to treat cancer and prescribed by oncologists may have many toxicities. The risks and benefits of chemoprevention need to be placed in the context of pharmacologic interventions used to treat or prevent other chronic conditions (e.g., aspirin or statins for cardiovascular disease, bisphosphonates for osteoporosis). Further research is needed to determine how knowledge about breast cancer risk and chemoprevention options are best communicated to women to promote breast cancer prevention strategies.

BREAST CANCER RISK ASSESSMENT

Based on age and breast cancer risk, an estimated 15% of women in the United States meet high-risk criteria and may be eligible for chemoprevention.[9] Known breast cancer risk factors include family history, reproductive history, and lifestyle factors, such as alcohol intake and obesity.[12] Women with benign breast disease, such as atypical hyperplasia (AH) and lobular carcinoma in situ (LCIS), have up to a 4- to 10-fold increased risk of breast cancer.[13] Genetic determinants, such as germ-line mutations in the *BRCA1* and *BRCA2* genes, confer the greatest effect on breast cancer risk. The Gail model, or Breast Cancer Risk Assessment Tool, which takes into account a woman's age, race, reproductive history, first-degree family history of breast cancer, and benign breast disease including atypia, is the most commonly used model in the United States and has been well validated at the population level.[14] It can be administered to women age 35 or older and provides an individual's absolute 5-year and lifetime risk of invasive breast cancer compared to women of the same age and race in the general population. High-risk criteria used to determine eligibility in chemoprevention trials are at least a 1.67% 5-year risk or 20% or greater lifetime risk of invasive breast cancer. To account for differences in breast cancer risk by race and ethnicity, the Gail model incorporated data from the Women's Contraceptive and Reproductive Experiences[15] and Asian American Breast Cancer Study[16] to provide more sensitive estimates for African American and Asian women, respectively. Few studies have used this model in Hispanic populations.[17,18] Hispanic women have significantly lower breast cancer risk compared to non-Hispanic white women; however, risk differs among Hispanic subgroups in the United States: according to the Gail model, Cubans have a higher 5-year risk ($p < 0.05$) and Dominicans have a higher lifetime risk than Mexicans ($p < 0.001$).[19] Interestingly, eligibility for chemoprevention among U.S. women varies dramatically by race and ethnicity, with 18.7% of whites, 5.7% of blacks, and 2.9% of Hispanics meeting high-risk criteria according to the Gail model.[9]

In women with a strong family history of breast cancer (i.e., two or more affected family members, particularly those with early-age onset), the Tyrer-Cuzick model is useful because it also accounts for second- and third-degree family history of breast and ovarian cancer and

age at diagnosis.[20] This model may be particularly relevant for estimating risk in women with multiple affected family members, as well as LCIS. Women who had a 10-year risk of breast cancer of 5% of more according to the Tyrer-Cuzick model were included in the International Breast Cancer Intervention Study-I (IBIS-I) of tamoxifen and IBIS-II trial of anastrozole compared with placebo.[2,5] A comparison of the breast cancer risk factors included in the Gail and Tyrer-Cuzick models are summarized in Table 1.

High-risk benign breast disease is an important and under-recognized breast cancer risk factor.[21] Over one million benign breast biopsies are performed in the United States each year,[22] with approximately 10% showing AH or LCIS—conferring a relative risk of breast cancer of up to 4 to 10.[23–27] Long-term studies indicate that absolute breast cancer risk in women with AH is approximately 30% at 25 years of follow-up.[25,28] Of note, the Gail model significantly under-predicts breast cancer risk in women with AH ($p < 0.001$),[29] whereas the Tyrer-Cuzick model tends to over-predict risk.[30] Because of the high estrogen receptor (ER) expression in AH and the fact that the majority of breast cancers that develop in women with AH are ER+,[31] these high-risk women derive a greater benefit from chemoprevention than the general high-risk population. In the randomized, placebo-controlled chemoprevention trials, relative risk reduction of breast cancer among the subgroup of 2,009 women with AH ranged from 41% to 79%.[1,2,4,5,21] In a cohort study of women with atypical breast lesions, 10-year breast cancer risk with chemoprevention was 7.5%, compared to 21.3% without chemoprevention.[24] Despite this evidence, chemoprevention uptake remains low among these women at high risk.[32]

BREAST CANCER CHEMOPREVENTIVE AGENTS

Selective Estrogen Receptor Modulators

Table 2 summarizes results of the major randomized controlled trials of SERMs and AIs for the primary prevention of breast cancer. In 1998, the Breast Cancer Prevention Trial (BCPT) demonstrated that the SERM tamoxifen taken for 5 years reduced breast cancer incidence in women at high risk by 49% (number needed to treat [NNT] to prevent one invasive breast cancer was 95 at 5 years and 56 at 10 years).[33,1] The overall results from three additional randomized controlled trials confirmed that tamoxifen decreased breast cancer risk by 30% to 40% compared to placebo.[34–37] In particular, long-term follow-up data (median of 16 years) from the IBIS-I trial demonstrated a persistent protective effect of tamoxifen (NNT was 22 at 20 years).[2] The magnitude of this risk reduction is comparable to what has been observed with preventive agents for cardiovascular disease.[38–40]

Another SERM, raloxifene, has been shown to reduce the incidence of breast cancer in postmenopausal women for the treatment and prevention of osteoporosis.[41,42] Updated analyses from the Study of Tamoxifen and Raloxifene (STAR) trial demonstrated that raloxifene had 76% of the efficacy of tamoxifen for breast cancer prevention among postmenopausal women at high risk with a more favorable side effect profile.[3] Based on the results of these trials, tamoxifen was approved by the U.S. Food and Drug Administration (FDA) for breast cancer risk reduction among women at high risk in 1998 and raloxifene in 2007.

Aromatase Inhibitors

Data from adjuvant trials have proven to be a useful model for assessing the chemopreventive effects of endocrine therapies, since results of antiestrogens in the primary prevention setting closely mirrored those for adjuvant treatment.[37] In 2011, results from the Mammary Prevention Trial-3 (MAP.3) demonstrated that the AI exemestane given to postmenopausal women at high risk reduced invasive breast cancer incidence by 65% compared to placebo (NNT was 26 at 5 years).[4] High-risk criteria included age 60 or older (49%), a 5-year Gail risk score 1.66% or greater (40%), AH or LCIS (8%), and ductal carcinoma in situ treated with mastectomy (3%).[4] After a median follow-up of 35 months, 11 invasive breast cancers occurred in the exemestane arm compared to 32 in the placebo group (annual incidence of 0.19% vs. 0.55%; $p = 0.002$).[4] In the group comparing exemestane compared to placebo, more grade 2 or higher arthritis (6.5% vs. 4.0%) and hot flashes (18.3% vs. 11.9%) were seen. However, overall quality of life did not differ between the two arms, and no significant differences in new-onset osteoporosis, clinical skeletal fractures, cardiovascular events, or other malignancies were seen.

Another third-generation AI was investigated in the IBIS-II trial, which randomly assigned postmenopausal women at high risk, age 40–70, to receive either anastrozole or placebo for 5 years.[5] With a median follow-up of 5 years, 40 breast cancers (invasive and noninvasive) occurred in the anastrozole arm compared to 85 in the placebo group (hazard ratio 0.47; 95% confidence interval 0.32– 0.68; $p < 0.0001$). In the anastrozole group compared to placebo, more arthralgia (51% vs. 46%), vasomotor symptoms (57% vs. 49%), vaginal dryness (19% vs. 16%), and hypertension (5% vs. 3%) occurred. In general, there appear to be fewer serious side effects with AIs compared to tamoxifen.

To date, there are no head-to-head trials comparing SERMs to AIs or evaluating extended hormone therapy for up to 10 years in the primary prevention setting. Also, these antiestrogens have no effect on the incidence of ER– tumors, which are associated with a poorer prognosis compared to ER+ breast cancer and are more common in younger women, black women, and *BRCA1* mutation carriers. In addition, limited data exist on the efficacy of antiestrogens for breast cancer risk reduction in women with hereditary breast cancer syndromes, such as *BRCA1* and *BRCA2* mutation carriers.[43,44] Of note, none of these chemoprevention trials were adequately powered to detect a difference in breast cancer–specific or overall mortality.

Chemoprevention Guidelines

Based on this evidence, the USPSTF, American Society of Clinical Oncology, and the National Comprehensive Cancer Network published consensus guidelines on breast cancer chemoprevention.[6–8] Premenopausal and postmenopausal women at high risk, defined as a 5-year Gail risk 1.67% or greater or LCIS, may take tamoxifen for 5 years for the primary prevention of breast cancer. Younger women (age 35–50), those without a uterus, and those at higher risk for breast cancer derive the greatest clinical benefit from tamoxifen. Postmenopausal women at high risk also have the options of raloxifene, exemestane, and anastrozole for breast cancer risk reduction. Because of the increased risk of uterine cancer, follow-up for women on tamoxifen should include annual gynecologic examinations with a

timely work-up of abnormal vaginal bleeding, but routine endometrial biopsies in the absence of vaginal symptoms is not recommended. SERMs are contraindicated in women with a history of thromboembolism, such as deep vein thrombosis, pulmonary embolus, stoke, or transient ischemic attack. In addition, the STAR trial excluded women with uncontrolled diabetes or hypertension, those with atrial fibrillation, and those on hormone replacement therapy.[45]

Figure 1 depicts a potential algorithm for clinical decision making about antiestrogens for breast cancer chemoprevention based on menopausal status, history of thromboembolism, risk of osteoporosis, and prior hysterectomy. For premenopausal women at high risk, tamoxifen is currently the only FDA-approved drug for the primary prevention of breast cancer. Younger women (age 35–50) at high risk derive the greatest clinical benefit from tamoxifen because the risk of serious side effects, such as thromboembolism and uterine cancer, is negligible compared to placebo. For postmenopausal women at high risk with an intact uterus, raloxifene may be favored over tamoxifen, whereas tamoxifen may be preferable in women with a prior hysterectomy because of its greater efficacy in breast cancer risk reduction.[3] Both SERMs are contraindicated in women with a prior history of thromboembolism, but AIs may be offered to postmenopausal women. SERMs may be favored over AIs among postmenopausal women at high risk with low bone density, although presence of osteoporosis is not an absolute contraindication to taking an AI. Overall, both SERMs and AIs are effective chemopreventive agents; therefore, the choice will depend on personal preferences and acceptable toxicity profiles.

BARRIERS TO UPTAKE OF BREAST CANCER CHEMOPREVENTION

Low Uptake of Breast Cancer Chemoprevention

An estimated 10 million U.S. women age 35 to 79 are eligible for breast cancer chemoprevention.[9] Based on a systematic review and meta-analysis of patient decisions about chemoprevention, less than 5% of women at high risk who are offered an antiestrogen for primary prevention agree to take it.[10] The main reason for this is the perception of patients and physicians that chemoprevention does not offer a favorable risk– benefit profile.[46–49] After the 1999 FDA approval of tamoxifen for primary prevention in women at high risk, data from the National Health Interview Survey indicated that the prevalence of tamoxifen use among women without a personal history of breast cancer was 0.2% in 2000 and decreased to 0.08% in 2005.[32] Similarly, after raloxifene's FDA approval in 2007, its use for breast cancer risk reduction decreased.[45] It remains to be seen whether there will be greater acceptance of AIs for primary prevention.

Lack of Routine Breast Cancer Risk Assessment in Clinical Practice

Despite the online availability of both the Gail and Tyrer-Cuzick models, only 18% of PCPs report use of software to calculate breast cancer risk.[50] In a cross-sectional survey of over 300 PCPs, use of the Gail model for breast cancer risk assessment varied by medical specialty (37% internal medicine, 33% family medicine, 60% gynecology), as well as ever recommending or prescribing breast cancer chemoprevention (9% internal medicine, 8% family medicine, 30% gynecology).[51] Barriers to routine breast cancer risk assessment in the

primary care setting include time constraints during clinic visits and lack of familiarity with risk assessment tools and chemoprevention.[52] There may also be concerns about the accuracy of breast cancer risk prediction models.

Risks and Benefits of Chemoprevention

Concerns about potential side effects, such as uterine cancer, thromboembolic events, and menopausal symptoms, are the main contributors to a woman's unwillingness to initiate chemopreventive agents for breast cancer and a physician's reluctance to prescribe them.[46–48,53–56] In the BCPT, the net benefit achieved with tamoxifen varied by age, race, and level of breast cancer risk, such that an estimated 2.5 million women in the United States could derive a net benefit from the drug.[1] In the STAR trial, raloxifene was associated with a lower risk of thromboembolic events, benign uterine complaints, and cataracts than tamoxifen.[45,57] Although women on tamoxifen reported more gynecologic and vasomotor symptoms,[45] overall quality of life was similar for both SERMs.[57] In the MAP.3 and IBIS-II trials, AIs decreased bone mineral density compared to placebo but did not increase the risk of fractures.[4] In contrast, SERMs have a favorable effect on bone density with about a 32% reduction in fracture incidence.[33,41,42]

The general perception among patients and providers is that use of antiestrogens for primary prevention does not confer a favorable risk– benefit profile. Based on results from the STAR trial, per 1,000 women at high risk, tamoxifen would prevent 40 breast cancers compared with causing 2.25 uterine cancers and 3.3 thromboembolic events, whereas raloxifene would prevent 31 breast cancers compared with causing 2.47 thromboembolic events.[3] Freedman et al developed a model to predict the risks and benefits of SERMs for women older than 50 based on age, race/ethnicity, breast cancer risk, and presence of a uterus, which may provide a more personalized risk– benefit profile.[58] Whereas the side effects diminish after stopping chemoprevention, the protective effect on breast cancer risk persists after discontinuation.[36] Unlike preventive therapies for other chronic diseases, which often require life-long treatment, breast cancer chemoprevention for 5 years can confer long-term benefits with side effects limited to during active treatment.

Low chemoprevention uptake occurs because of the lack of effective strategies to inform both PCPs and women at high risk about the risks and benefits of antiestrogens. Physicians who felt insufficiently informed about risk-reducing options were less than half as likely to prescribe a SERM for breast cancer prevention than physicians who felt sufficiently trained.[59] Physician recommendation and health care provider communication are among the most influential factors to influence chemoprevention uptake.[46,48,60]

Lack of Intermediate Biomarkers to Predict Response to Chemopreventive Agents

The lack of well-validated intermediate biomarkers for short-term breast cancer risk assessment, analogous to low-density lipoprotein cholesterol for cardiovascular disease or T-score on a bone density scan for osteoporosis, is another barrier to uptake of antiestrogens. Even if a woman at high risk agrees to take chemoprevention, there is no way to assess whether she is deriving a benefit from the agent except with long-term follow-up to determine whether she remains free of breast cancer. Mammographic density (MD), a strong

predictor of breast cancer risk,[61,62] may also serve as a predictive biomarker of response to breast cancer chemoprevention. In the IBIS-I trial, tamoxifen given for 18 months caused a significant decrease in MD compared to placebo, particularly among premenopausal women ($p < 0.001$).[63] Cuzick et al demonstrated that at least a 10% reduction in MD with tamoxifen was associated with a 63% reduction in breast cancer risk.[64] Compared to other qualitative methods of measuring MD, the Cumulus technique provides quantitative measurements and has been strongly associated with breast cancer risk in epidemiologic studies.[65,66] However, more automated methods for measuring MD or volumetric density are needed, which would be applicable in the clinical setting.[67,68]

Measurement of endogenous hormone levels, such as plasma estrone sulfate, testosterone, prolactin, and sex hormone-binding globulin, have been shown to improve breast cancer risk prediction in postmenopausal women.[69] Changes in estradiol and testosterone levels may also serve as good breast cancer risk biomarkers for weight loss interventions.[70] However, assay variability with low hormone levels, particularly in postmenopausal women, may hamper their clinical utility.[71]

Predictors of Poor Adherence to Endocrine Therapy

The effectiveness of chemoprevention depends not only on initiation of therapy but also on long-term adherence. In the chemoprevention trials, adherence at 5 years ranged from 64% to 85%[1,4,36,57]; however, clinical trial participants are often more compliant than the general population. Veronesi et al reported that women in a chemoprevention trial were less likely to adhere to tamoxifen than patients with breast cancer treated in the adjuvant setting.[72] In the Sister Study cohort, 46% of women taking tamoxifen for primary prevention discontinued within 4.5 years.[73] In BCPT and MAP.3, ethnic minorities and women with low income had less drug adherence.[74,75] Women from racial/ethnic minorities and those who are uninsured are less likely to seek breast cancer preventive care, perhaps contributing to higher rates of late-stage diagnosis.[76,77] Understanding predictors of poor uptake and adherence to breast cancer chemoprevention will aid in the development of targeted interventions for certain patient subgroups.

INTERVENTIONS TO INCREASE UPTAKE OF BREAST CANCER CHEMOPREVENTION

Results from recent intervention trials to increase chemoprevention uptake targeting both patients and providers are summarized in Table 3. In a recent randomized controlled trial of a web-based decision aid that informed women about the risks and benefits of SERMs,[78] only 0.5% of eligible participants had started raloxifene and none had started tamoxifen. In a study called the “Ready, Set, GO GAIL!” project, PCPs systematically screened more than 5,700 women age 35–70 with the Gail model; 868 (15.2%) met high-risk criteria and were eligible for chemoprevention, only 128 (14.7%) of these women were referred for specialized risk counseling, 60 (6.4%) completed the consultation, and 17 (2%) started a SERM.[79] In the BreastCARE intervention trial, women in the primary care setting were randomly assigned to usual care or a tablet-based patient intake tool that generated individualized breast cancer risk profiles for patients and their physicians.[80] Although more

women at high risk were referred for specialized risk counseling with the intervention compared to the control arm (18.8% vs. 4.1%), discussions about chemoprevention were still limited (1% vs. 0%).

Interventions designed to increase chemoprevention uptake, involving reading materials or decision aids, met with limited success, ranging from 0.5% to 5.6%.[48,49,55,78,81] Few studies have assessed the effect of automated decision support for PCPs.[82,83] Two studies used a computer-based tool to improve referrals for genetic testing, but they were not integrated into clinic workflow.[84] Given that breast cancer chemoprevention is not widely diffused in the primary care setting, more effective tools are needed to accurately identify women at high risk and educate both patients and providers about the risks and benefits of chemoprevention options. Studies that involved consultation at a breast clinic reported chemoprevention uptake ranging from 11% to 58%.[46,53,54,60,85–87] Therefore, higher chemoprevention uptake may be achieved with health professionals who have sufficient knowledge and training about breast cancer risk and risk reduction strategies. Given that many community practices may not have access to high-risk clinics, PCPs need to be at the front line of chronic disease prevention, including breast cancer chemoprevention.

Strategies to minimize toxicities to antiestrogens include administering lower or intermittent dosing, developing alternative drug delivery methods such as topical therapy, and identifying novel chemopreventive agents with fewer side effects. For example, clinical trials of oral low-dose tamoxifen of 1, 5, or 10 mg daily or 10–20 mg weekly have demonstrated similar biologic efficacy to standard-dose tamoxifen (20 mg daily) with fewer side effects.[88–95] Since tamoxifen is a prodrug that requires hepatic activation, Mauvais-Jarvis et al developed a topical form of trans-4-hydroxytamoxifen (4-OHT), the active metabolite of tamoxifen, which would maximize local drug levels with fewer systemic side effects.[96] Thus far, topical tamoxifen has been tested for the treatment of mastalgia[97] and in two presurgical (window of opportunity) trials in women with breast cancer.[98,99] Finally, novel chemopreventive agents—including aspirin, NSAIDs, metformin, vitamin D, and vaccines to tumor-associated antigens—which may have a more favorable side effect profile compared to SERMs and AIs and perhaps activity against ER– breast cancers, are currently under investigation.[100]

CONCLUSION

Breast cancer chemoprevention with antiestrogens has proven efficacy in high-risk populations, but uptake remains low. Preventive therapy for cancer is currently less well established compared to other chronic conditions, such as cardiovascular disease, and could benefit from lessons learned.[101] Health care providers can do more in the area of cancer prevention by identifying high-risk populations in the primary care setting. Chemoprevention needs to be integrated into broader strategies of preventive care, which may include nonpharmacologic interventions such as lifestyle modification. Given the high compliance rates for breast cancer screening, incorporating formal risk assessments at the time of screening mammography may represent a “teachable moment” when women are already engaging in a health behavior related to breast cancer. Novel health information

technologies such as electronic health records and patient health portals may be a method for integrating information about breast cancer risk and chemoprevention into clinic workflow.

Breast cancer incidence continues to increase in most countries,[102] and the economic burden of cancer in the United States is expected to substantially increase[103] because of greater intensity of health care usage[104,105] and increasing costs of cancer care.[106–109] These rising medical costs will disproportionately affect racial/ethnic minorities and low-income and under-insured individuals. U.S. health care providers can do more in the area of cancer prevention by targeting high-risk populations. Promoting chemoprevention uptake among women at high risk will require a major paradigm shift in clinical practice if antiestrogens are to be widely adopted in the primary care setting.

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KEY POINTS

- Breast cancer chemoprevention with antiestrogens is underutilized despite several randomized controlled trials demonstrating up to a 50% to 65% relative risk reduction of breast cancer incidence among women at high risk.
- Approximately 10 million women in the United States may be eligible for breast cancer chemoprevention, but less than 5% of women at high risk who are offered an antiestrogen for primary prevention agree to take it.
- Reasons for low chemoprevention uptake include lack of routine breast cancer risk assessment in the primary care setting, insufficient knowledge about antiestrogens on the part of clinicians and patients, and concerns about side effects.
- Interventions designed to increase identification of women at high risk and chemoprevention uptake, including written materials, decision aids, and incorporating breast cancer risk assessment tools into clinical practice, have met with limited success.
- Because of the proven efficacy of breast cancer chemopreventive agents, widespread use of antiestrogens for primary prevention among women at high risk has the potential to significantly improve the public health burden of this disease.

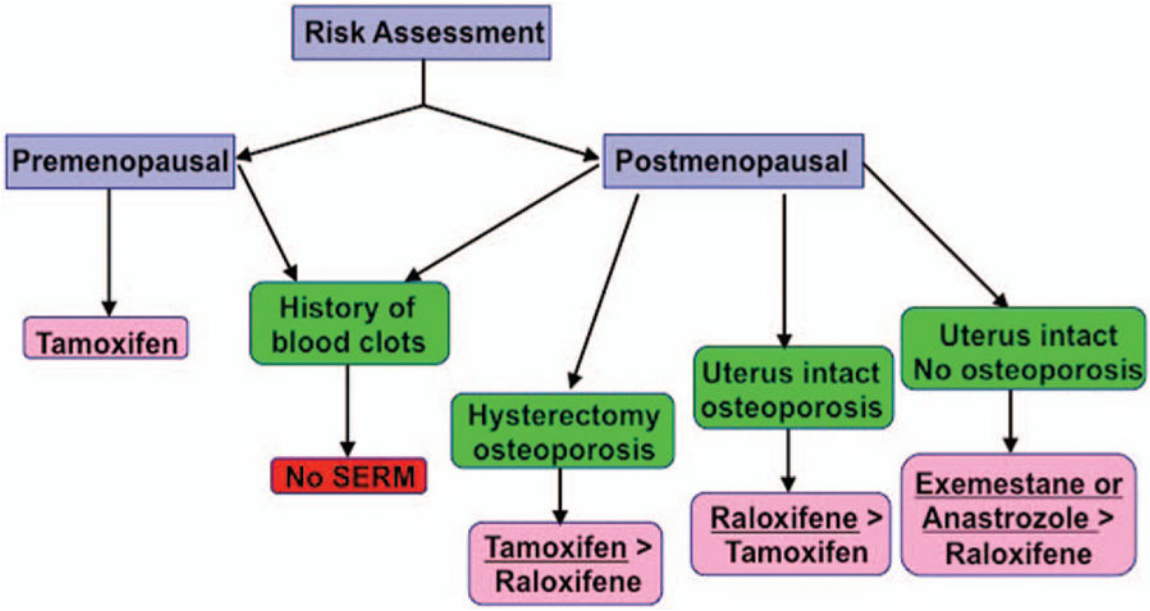

FIGURE 1. Choice of Selective Estrogen Receptor Modulator or Aromatase Inhibitor for Breast Cancer Chemoprevention

Choice is based on menopausal status, history of thromboembolism, prior hysterectomy, and risk of osteoporosis (based upon the author's personal algorithm and not a guideline recommendation).

TABLE 1.

Comparison of Breast Cancer Risk Factors in the Gail and Tyrer-Cuzick Models

Gail Model	Tyrer-Cuzick Model
Age (35 or older)	Age
Race/ethnicity (white, black, Hispanic, Asian American [Chinese, Japanese, Filipino, Hawaiian, other], unknown)	Ashkenazi Jewish descent
Age at menarche	Age at menarche
Age at first live birth	Age at first live birth
	Menopausal status
	Age at menopause
	Use of hormone replacement therapy
	Body mass index
Number of benign breast biopsies	
Benign breast biopsy with atypical hyperplasia (excludes LCIS, DCIS, or invasive breast cancer)	Benign breast biopsy including hyperplasia with or without atypia and LCIS
Number of first-degree relatives with breast cancer	Number of first-, second-, and third-degree relatives with breast or ovarian cancer, bilateral breast cancer, and age at diagnosis
	BRCA mutation status

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

TABLE 2.

Updated Results from Major Randomized Controlled Trials of Selective Estrogen Receptor Modulators and Aromatase Inhibitors for Breast Cancer Chemoprevention

Trial	No. of Participants	Eligibility, High-Risk Criteria for Breast Cancer	Intervention	Median Follow-up (Months)	Breast Cancer Incidence	Breast Cancer Risk Reduction RR or HR (95% CI)
BCPT, 2005[1]	13,388	Age ≥ 35, 5-yr Gail risk score > 1.66% if age 35–59 or ≥ 60 or LCIS	Tamoxifen 20 mg/d × 5 yrs versus placebo	84	3.59 versus 6.29[a]	0.57 (0.46–0.70)
IBIS-I, 2014[2]	7,154	Age 35–70, 10-fold risk if age 35–39, or 4-fold risk if age 40–44, or 2-fold risk if age 45–70	Tamoxifen 20 mg/d × 5 yrs versus placebo	192	7.0versus 9.8%[b]	0.71 (0.60–0.83)
STAR, 2010[3]	19,747	Age ≥ 35, postmenopausal, 5-yr Gail risk score > 1.66%	Raloxifene 60 mg/d versus tamoxifen 20 mg/d × 5 yrs	81	5.02 versus 4.04[a]	1.24 (1.05–1.47)
MAP.3, 2011[4]	4,560	Age ≥ 35, postmenopausal, 5-yr Gail risk score > 1.66% if age 35–59 or age ≥ 60 or AH, LCIS, DCIS with mastectomy	Exemestane 25 mg/d × 5 yrs versus placebo	35	0.19versus 0.55%[c]	0.35 (0.18–0.70)
IBIS-II, 2013[5]	3,864	Age 40–70, postmenopausal, 4-fold risk if age 40–44, or 2-fold risk if age 45–59, or 1.5-fold risk if age 60–70	Anastrozole 1 mg/d × 5 yrs versus placebo	60	2% versus 4%[b]	0.47 (0.32–0.68)

Abbreviations: SERM, selective receptor estrogen modulators; AI, aromatase inhibitor; AH, atypical hyperplasia; BCPT, Breast Cancer Prevention Trial; CI, confidence interval; DCIS, ductal carcinoma-in-situ; HR, hazard ratio; IBIS, International Breast cancer Intervention Study; LCIS, lobular carcinoma in situ; MAP, Mammary Prevention Trial; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.

[a]Invasive breast cancer incidence rate/1,000 women.

[b]All breast cancers, invasive and noninvasive.

[c]Annual incidence of invasive breast cancers.

TABLE 3.

Intervention Trials to Increase Uptake of Breast Cancer Chemoprevention

Authors, Year	No. of Participants	Eligibility	Intervention	Outcomes
Fagerlin et al 2011[79]	1,197	Age 40–74, postmenopausal, 5-yr Gail risk score > 1.66%	Tailored online decision aid “Guide to Decide”	0% tamoxifen and 0.5% (2 patients) raloxifene uptake with intervention
Owens et al 2011[80]	868	Age 35–70, 5-yr Gail risk score ≥ 1.7% or lifetime risk ≥ 20%	“Ready, Set, GO GAIL!” project, clinic-based intervention to implement Gail model in women’s health clinic	Completion of high-risk consultation, 6.4% (60 patients); chemoprevention uptake, 2% (17 patients)
Kaplan et al 2014[81]	1,235	Age 40–74, scheduled for clinic visit at two primary care practices, spoke English, Spanish, or Chinese	BreastCARE, tablet-based breast cancer risk assessment that generated individualized reports for patients and their physicians	Referral to high-risk clinic, 18.8% versus 4.1% among women at high risk (307 patients); discussion of chemoprevention, 1% versus 0%