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Review Article

Breast cancer chemoprevention: An update on current practice and opportunities for primary care physicians☆

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ABSTRACT

Several risk assessment models have been validated for the estimation of risk of breast cancer in women. Chemoprevention through hormonal therapy is an effective way to reduce the incidence of breast cancer in women with high risk. Selective estrogen receptor modulators, tamoxifen and raloxifene, are approved for this indication by the United States Food and Drug Administration, and aromatase inhibitors have also shown promise in recent studies. These medications are generally well tolerated, except for reported increased rates of fractures and venous thromboembolic events. Despite strong recommendations from several regulatory bodies, advocacy for chemoprevention has been inadequate in practice, more so among the primary care physicians. Studies have identified several barriers in physicians, patients, and the system, contributing to this problem. Lack of knowledge about risk assessment models and chemoprevention options preclude physicians from prescribing these medications with confidence. Fear of potential adverse events, confusion regarding the purpose of the therapy, and need for continued adherence for five years are among the principal reasons for reduced chemoprevention uptake and early discontinuation among patients. Multifaceted interventions directed at education and training of health care professionals, proper counseling of women at high risk, and promotion of the development of improved medications might help ensure better chemoprevention uptake in the target population.

1. Introduction

Breast cancer (BC) continues to be a major public health problem and is the leading cause of death among all cancers in women. The current annual incidence of BC in the United States (US) is 127.5 per 100,000 women. It is estimated that 268,600 new cases will be diagnosed in 2019, with 41,760 estimated deaths. Breast cancer is most frequently diagnosed in women aged 55–64 years (median age at diagnosis-62 years), with incidence and mortality rates increasing with age. However, due to rising level of awareness and successful interventions, the five-year survival rate has improved to 89.9%, and 98.8% for patients with localized BC (without nodal involvement) suggesting the importance of effective screening leading to early detection. High prevalence of various physical and emotional morbidities in patients with BC further increases the importance of administration of screening and prevention interventions (National Institutes of Health, National Cancer Institute, n.d.).

Over the years, various prediction models have been used to identify women at increased risk of developing BC (Corbelli et al., 2014; Tyrer et al., 2004; MacInnis et al., 2013). Based on the ever-expanding body of evidence, guidelines from several authorities have extended strong support to the use of chemoprevention medications in individuals with high risk of BC (Visvanathan et al., 2013; Nelson et al., 2013). Despite these recommendations, a lack of advocacy for chemoprevention persists among physicians (Layeequr Rahman and Pruthi, 2012). Without the routine clinical practice of risk assessment, patients may not be offered appropriate risk-based cancer screening.

This review aims to summarize the commonly used risk assessment models and updated evidence on the various options for chemoprevention and the possible factors for their underutilization. We also discussed the potential role of primary care physicians in overcoming the obstacles in the implementation of chemoprevention guidelines.

2. Methods of risk assessment

Several models have been developed to predict an increased risk of

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BC in women. The Gail model is one of the most familiar risk assessment tools. It has been well validated in the general population and updated for use across races. It is used in women ≥35 years of age to predict their five-year and lifetime risk of developing BC. The score utilizes several risk factors including age at menarche and first live childbirth, number of first-degree relatives with a BC diagnosis, and number of prior breast biopsies in calculation. Individuals with a five-year risk of ≥1.66% are considered to have an elevated risk, and therefore candidates for chemoprevention. The limitations of this model are that it does not apply to women with a prior diagnosis of BC, or patients with a diagnosis of lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS) (Gail et al., 1989; Costantino et al., 1999; Gail et al., 2007; Matsuno et al., 2011). Also, as the score does not account for extended family history beyond first degree relatives, the Gail model tends to underestimate BC risk, especially in women with a strong family history (Quante et al., 2012; Powell et al., 2014).

The Tyrer-Cuzick model, otherwise known as International Breast Intervention Study (IBIS) model, considers a more extensive family history, including a history of BC in higher than first degree relatives, as well as paternal relatives. Ages of family members at the diagnosis of cancer, menstrual history and use of hormone replacement therapy are also included in this model (Tyrer et al., 2004). Women with a lifetime risk of BC ≥20% are considered high risk. In certain population groups (especially in individuals with delayed childbirth), this model performs better compared to the Gail model in risk estimation (Powell et al., 2014). Several other models like the Claus model and the Rosner-Colditz model have also been validated in studies, while modifications continue to make these models more generalizable across different population groups (MacInnis et al., 2013; Claus et al., 1994; Evans et al., 2014; Rice et al., 2017; Rosner et al., 2013). Recent attempts to include other factors such as single nucleotide polymorphisms (SNP), mammographic density, and estradiol levels in risk assessment are promising (Shieh et al., 2017). Studies evaluating the Breast Cancer Surveillance Consortium Breast Density Model, formed by addition of Breast Imaging Reporting and Data System (BI-RADS) density score to the Gail model, showed variable results in terms of improvement in discriminative accuracy of the latter (Tice et al., 2008; Cecchini et al., 2012). A study for the assessment of discriminative accuracy of various models noted Tyrer-Cuzick model (area under curve [AUC]- 0.762) to be most consistently accurate, in comparison with the Gail (AUC – 0.735) and the Claus (AUC – 0.716) models (Amir et al., 2003). Several investigators have succeeded in increasing the C-statistic of the risk prediction model by adding a number of SNPs (commonly associated with BC) with the traditional Gail model (Dite et al., 2013; Gail, 2009). The burden of BC and salient features of commonly used risk assessment models are summarized in Tables 1 and 2.

3. Options for breast cancer risk reduction

3.1. Lifestyle interventions

Excess adipose tissue, specifically white adipose tissue, has been associated with an increase in levels of estrogen, insulin, insulin like growth factor-1 (IGF-1) and proinflammatory cytokines that can have a carcinogenic effect on rapidly developing breast tissue (Bastard et al., 2006; Laudisio et al., 2018; Argolo et al., 2018). Severely obese (body mass index [BMI] ≥ 40 kg/m^2) patients with BC tend to have worse disease-free and overall survival when compared with obese, overweight and normal weight individuals (Widschwendter et al., 2015). A dose-response meta-analysis suggested that the risk of BC in women increases by 2% with every 5 kg/m^2 increase in BMI (Liu et al., 2018). Weight loss (≥10 kg since menopause) has been shown to decrease the risk of BC in postmenopausal women (Eliassen et al., 2006). Bariatric surgeries have led to a significant reduction in absolute dense breast area on mammogram, and, hence, in the risk of BC in postmenopausal women (Alvarez et al., 2018; Winder et al., 2017). Vigorous physical activity has significantly reduced the risk of BC in high risk women, thus suggesting a role of exercise in primary prevention (Tehard et al., 2006). Exercising for at least 4 h per week significantly decreased the risk of breast cancer in women (Thune et al., 1997). A meta-analysis of prospective studies revealed 3% reduction in BC risk with every 10 metabolic equivalent (MET) increment in recreational activity (Wu et al., 2013). Incorporation of smartphone and web-based applications seem to be useful in the enhancement of the degree of weight loss in women at increased risk of BC (Cadmus-Bertram et al., 2016; Hartman et al., 2016). Studies have linked alcohol consumption to a modest increase in BC risk. An analysis of multiple epidemiological studies revealed 32% increase in relative risk of breast cancer with consumption of 35–44 g of alcohol per day (McDonald et al., 2013; Hamajima et al., 2002).

Table 1
Breast cancer-a continuing public health problem.

Current annual incidence	127.5 per 100,000 women.
Estimated new cases in 2019	268,600
Percentage of all new cancer cases	15.2%
Estimated deaths in 2019	41,760
Percentage of women likely to get a breast cancer diagnosis	12.8%

3.2. Role of surgery

Despite the lack of specific guidelines in most countries, there has been an uptrend in contralateral prophylactic mastectomy among patients with sporadic BC in the US. In both affected and unaffected patients, the presence of a significant family history warrants further evaluation and genetic counseling. Bilateral risk-reducing mastectomy (BRRM) is both efficacious and cost-effective in the reduction of risk of BC, although an increased rate of postoperative complications and the perception of negative body image in women remain concerning (Meijers-Heijboer et al., 2001; Rebbeck et al., 2004; Schrauder et al., 2017). National Comprehensive Cancer Network (NCCN) guidelines recommend that RRM should be considered only in women with a known genetic mutation which confers a high risk of BC. Evidence is stronger for BRCA 1/2 carriers, although individuals with mutations like TP53, PTEN, CDH1, or STK11 should also be given the choice of RRM (National Comprehensive Cancer Network, 2018).

3.3. Chemoprevention medication options

3.3.1. Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERM) are well studied for chemoprevention among high risk women. These medications act by modulation of transcription of certain estrogen response elements. Despite reported de novo mutations leading to the development of resistance, this class of medications continues to be effective in the reduction of BC risk (Fan and Craig Jordan, 2014). Table 3 provides a summary of characteristics of trials on SERMs for chemoprevention.

3.3.1.1. Tamoxifen. Several studies have proven the benefit of tamoxifen in the prevention of BC among high-risk women (Fisher et al., 1998; Veronesi et al., 2007; Cuzick et al., 2015). Food and Drug Administration (FDA) approval of tamoxifen for chemoprevention was accelerated based on the promising findings in the National Surgical Adjuvant Breast and Bowel Project P-1 (NSABP-P1) study. In this trial, a total of 13,388 women including healthy individuals aged > 60 years, women 35 to 59 years of age with a predicted risk for BC of at least 1.66% (Gail model), and those with a history of LCIS were randomly allocated to tamoxifen (20 mg/day) or placebo for 5 years. Tamoxifen use led to a 49% (risk ratio [RR] 0.51; 95% CI: 0.39–0.66) reduction in the risk of invasive BC (IBC) compared with placebo, with higher risk

Table 2
Summary of common risk assessment models for breast cancer.

Risk model	Risk factors considered	Score cut-off for high risk	Discriminative accuracy (AUC/C-statistic)	Comments
Gail model	Current age Age at menarche Age at first live birth Previous breast biopsies Race First-degree relatives with breast cancer	5-year risk of 1.66%	AUC – 0.735 [95% CI: 0.666–0.803]	Indicated in women aged > 35 years. Not applicable for women with prior breast cancer/LCIS/DCIS
Tyrer-Cuzick model Or, IBIS model	Current age BMI Age at menarche Age at first live birth Age at menopause Use of HRT Previous breast biopsies (including AH and LCIS) Family history (1st and 2nd degree relatives, onset of BC, bilateral BC, and ovarian cancer)	Lifetime risk of 20%	AUC- 0.762, [95% CI: 0.700–0.824]	Especially useful in individuals with delayed childbirth
Claus model	Current age Number of affected first-degree relatives Number of affected second-degree relatives Age of onset of breast cancer in first- and second-degree relatives	Lifetime risk of 20%	AUC – 0.716 [95% CI: 0.648–0.784]	Particularly useful for estimation of risk for familial breast cancer
BCSC breast density model	Age Race/ethnicity Family history of breast cancer in a first-degree relative History of a breast biopsy with benign breast disease diagnoses if known BI-RADS® breast density on mammogram	NA	C-statistic – 0.660 [95% CI: 0.651–0.669]	Not applicable in women aged > 35 years Not applicable for women with prior breast cancer/LCIS/DCIS

[IBIS-international breast intervention study, LCIS-lobular carcinoma-in-situ, DCIS-ductal carcinoma-in-situ, AH-atypical hyperplasia, HRT-hormone replacement therapy, BMI-body mass index, BCSC-breast cancer surveillance consortium, BI-RADS-breast imaging reporting and data system, NA-not applicable, AUC-area under curve, CI-confidence interval].

reduction observed in elderly individuals. The rate of endometrial cancer was significantly higher (RR 2.53; 95% CI: 1.35–4.97) in the tamoxifen group, although most of these were localized disease (stage I) curable with surgery alone (Fisher et al., 1998). In an extended follow up (11 years) of the Italian randomized tamoxifen prevention trial involving 5408 healthy women with prior hysterectomy, investigators studied the effect of chemoprevention on the incidence of BC, based on the presence of various other predictive factors (e.g., age at entry into study, age at menarche, number of intact ovaries, number of 1st degree relatives with BC, etc.) present in participants. The rate of BC was significantly lower (RR 0.24; 95% CI: 0.10–0.59) among high-risk patients in the tamoxifen group, although no difference was noted in low-risk women. An increase in venous thromboembolic (VTE) events, hot flashes, and hypertriglyceridemia were noted in the tamoxifen group (Veronesi et al., 2007). Recently published IBIS-I trial also showed a statistically significant reduction in BC risk (hazard ratio [HR] 0·71; 95% CI: 0·60–0·83) in high risk women on tamoxifen, with the greatest risk reduction for estrogen receptor (ER)-positive IBC and DCIS. The chemopreventive effect sustained beyond ten years of follow up in this study. There was a significant increase in the incidence of non-melanoma skin cancers in the tamoxifen group (Cuzick et al., 2015). The recently published report of a significant reduction in recurrence of breast intraepithelial neoplasia with tamoxifen administered at a lower dose (5 mg/day) for three years, could influence future research looking into lowering the dose or shortening the duration of chemoprevention to avoid unwanted toxicities (DeCensi et al., 2019). Current research in animal models is focusing on tamoxifen metabolites which have a higher affinity for estrogen receptor. High concentration of these molecules in mammary tissue following transdermal absorption makes a case for the development of innovative approaches for drug delivery (Lee and Khan, 2016).

3.3.1.2. Raloxifene. Raloxifene, initially approved by the FDA for the treatment of postmenopausal osteoporosis in 1997, was later found to decrease the risk for BC. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was performed in 7705 postmenopausal women with osteoporosis with the primary objective to determine the effect of raloxifene on the rate of new vertebral fractures and change in bone mineral density. Predefined secondary endpoints included the risk of cardiovascular disease, BC, and endometrial cancer. Participants were randomly assigned to get raloxifene (60 mg/day or 120 mg/day) or placebo. After four years of follow up, raloxifene group was found to have a statistically significant 76% reduction (HR 0.24; 95% CI: 0.13–0.43) in the incidence of IBC. Notably, there was an increased incidence of VTE in the raloxifene group (Barrett-Connor et al., 2004). This was followed by the Continuing Outcomes Relevant to Evista (CORE) trial, where 4011 participants from MORE study were continued on raloxifene for an additional four years. Women who were assigned to the placebo group continued in the same, whereas those in the raloxifene group continued to receive the medication at the dose of 60 mg/day. At the end of eight years follow up, there was a 66% reduction (HR 0.34; 95% CI: 0.22–0.50) in the incidence of IBC, and the incidence of ER-positive BC was 76% less (HR 0.24; 95% CI: 0.15–0.40) in the raloxifene group compared to placebo. The significant increase in the risk of VTE noted in the MORE trial persisted in this study as well (Martino et al., 2004). In the randomized placebo-controlled Raloxifene Use for The Heart (RUTH) trial, evaluating the effect of raloxifene on the cardiovascular events and BC in postmenopausal women with coronary heart disease (CHD) or multiple risk factors for CHD, a 44% decrease (HR 0.56; 95% CI: 0.38–0.83) in the rate of IBC with a 55% lower incidence of ER-positive cancers were noted in the raloxifene arm. Approximately 40% of the 10,101 participants in the study had an elevated risk of BC as per the Gail model. A significantly increased risk of fatal stroke and VTE was found to be associated with raloxifene in this study (Barrett-Connor et al., 2006).

3.3.1.3. Tamoxifen vs. Raloxifene. In the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2, investigators compared the

Table 3
Characteristics of trials on selective estrogen receptor modulators for chemoprevention in breast cancer.

Study name	Author year	Study design	Number of participants	Intervention arm	Control arm	Duration of treatment (years)	Primary endpoint	Median follow up duration (years)	Results	Adverse events
Tamoxifen										
National surgical adjuvant breast and bowel project P-1 (NSABP-P1)	Fisher et al., 1998	RCT	13,388	Tamoxifen 20 mg/d	Placebo	5	Risk of occurrence of BC	5	1. 49% reduction in the odds of IBC in tamoxifen group [RR = 0.51, 95% CI: 0.39–0.66] 2. Greater risk reduction in elderly individuals	Endometrial cancer and VTE in tamoxifen group
Italian tamoxifen study	Veronesi et al., 2007	RCT	5408	Tamoxifen 20 mg/d	Placebo	5	Rate of BC	11	1. Significant risk reduction in women in high-risk group. [RR = 0.24, 95% CI: 0.10–0.59] 2. No difference in low risk individuals	Hot flashes, vaginal discharge, urinary disturbances, and hypertriglyceridemia in tamoxifen group
International breast cancer intervention study (IBIS)-I	Cuzick et al., 2015	RCT	7154	Tamoxifen 20 mg/d	Placebo	5	Occurrence of BC (invasive and DCIS)	16	1. Significant risk reduction in tamoxifen group [HR 0·71, 95% CI: 0·60–0·83] 2. Greatest risk reduction in invasive ER + BC and DCIS.	Endometrial cancer (nonsignificant)
Raloxifene										
Multiple outcomes of raloxifene evaluation (MORE) trial	Barrett-Connor et al., 2004	RCT	7705	Raloxifene (60 mg/d or 120 mg/d)	Placebo	4	Risk-benefit safety profile of raloxifen	4	Statistically significant 76% reduction in the incidence of IBC in raloxifene group [HR 0.24; 95% CI: 0.13–0.43]	VTE in raloxifene group.
Continuing outcomes relevant to Evista (CORE) trial	Martino et al., 2004	RCT	4011	Raloxifene 60 mg/d	Placebo	8	Incidence of invasive BC	8	1. 66% reduction in risk of IBC in raloxifene group [HR = 0.34; 95% CI: 0.22 to 0.50] 2. 76% reduction in the incidence of ER+ BC.	VTE in raloxifene group.
Raloxifene use for the heart (RUTH) trial	Barrett-Connor et al., 2006	RCT	10,101	Raloxifene 60 mg/d	Placebo	5.6	Incidence of CV events and BC	5.6	1. 44% reduction in incidence of IBC [HR 0.56; 95% CI: 0.38–0.83] 2. 55% reduction in ER+ BC.	VTE and fatal stroke in raloxifene arm
Tamoxifen vs. raloxifene										
NSABP study of tamoxifen and raloxifene (STAR) P-2 trial	Vogel et al., 2006, 2010	RCT	19,747	Tamoxifen 20 mg/d	Raloxifene 60 mg/d	5	Incidence of IBC, uterine cancer, NIBC, bone fractures, and VTE	5	1. Similar incidence of IBC in both groups [RR, 1.02; 95% CI: 0.82–1.28] 2. Fewer NIBC in tamoxifen group (not statistically significant)	1. No difference in incidence of CV events. 2. Less VTE and endometrial cancer in raloxifene group.

[RCT-randomized controlled trial, BC-breast cancer, IBC-invasive breast cancer, NIBC-noninvasive breast cancer, ER-estrogen receptor, DCIS-ductal carcinoma in situ, RR-relative risk, HR-hazard ratio, VTE-venous thromboembolism, CV-cardiovascular].

chemopreventive property of tamoxifen to that of raloxifene in postmenopausal women with increased BC risk (predicted risk score ≥1.66%) as per Gail model. Raloxifene was equally effective as tamoxifen in decreasing the risk for IBC. There was slightly less risk for VTE with raloxifene, whereas the incidences of ischemic heart disease, stroke, and osteoporotic fractures were similar in two SERM arms. Updated analysis of this study revealed significantly less incidence of endometrial cancer with raloxifene in comparison with tamoxifen (Vogel et al., 2006; Vogel et al., 2010).

3.3.1.4. Lasofoxifene. The quest to develop a novel drug for chemoprevention with a more favorable benefit-risk profile led to the discovery of lasofoxifene, a third generation SERM with greater potency (Maeda et al., 2004). The Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) trial evaluated the effect of low doses of lasofoxifene on the incidence of non-vertebral fractures and ER + BC over a five year follow up. In this study with 8556 participants, the risk of total BC and ER+ IBC was reduced by 79% (HR 0.21; 95%: 0.08–0.55) and 83% (HR 0.17; 95% CI:0.05–0.57) respectively, in the lasofoxifene group compared to placebo group. However, lasofoxifene is not yet approved by FDA (LaCroix et al., 2010).

3.3.2. Aromatase inhibitors

SERMs, in general, have not been well accepted as an option for the prevention of BC in women, partly because of the serious adverse events (AE). Hence, investigators began looking at the aromatase inhibitors (AI) as potential options for chemoprevention. Aromatization is the process by which androgens are converted to estrogen. The key enzyme that regulates this process is aromatase (Barros-Oliveira et al., 2017). AIs have been found to be useful for chemoprevention in post-menopausal women only, although these are not currently FDA approved for this indication. Characteristics of important studies on AIs for chemoprevention in BC are summarized in Table 4.

3.3.2.1. Exemestane. Exemestane, a third-generation steroidal AI, irreversibly prevents androgens from binding to the catalytic site of aromatase, thereby reducing the production of estrogen (Van Asten et al., 2014). Its ability to prevent BC in postmenopausal women was studied in the National Cancer Institute of Canada Clinical Trials Group Mammary Prevention.3 trial (NCIC CTG MAP.3). Compared to placebo, exemestane had a 65% relative reduction (HR 0.35; 95% CI: 0.18–0.70) in the annual risk of IBC, with a significantly reduced incidence of total BC in the exemestane group (Goss et al., 2011). The AE profile was similar in both groups. There was no significant difference in the rate of other cancers. This finding is reassuring, especially when compared to tamoxifen, which is known for the increased risk of endometrial and non-melanoma skin cancers (Cuzick et al., 2015). The short follow up duration (median-35 months) limits our understanding of the long-term durability of these promising results.

3.3.2.2. Anastrozole. Anastrozole, a third generation nonsteroidal AI, has a high affinity for aromatase and was the first AI with a proven role in BC risk reduction. The International Breast Cancer Intervention Study II (IBIS-II) trial compared anastrozole with placebo in high-risk postmenopausal women. Researchers found that the predictive cumulative incidence of all BC at seven years in the placebo group was double that in the anastrozole group (HR 0.47; 95% CI: 0.32–0.68). However, there was no apparent benefit for risk reduction of IBC. Results also showed that anastrozole was more likely to reduce the rate of high-grade tumors. Among reported AEs, the number of both total fractures and site-specific fractures did not differ significantly between the anastrozole and placebo groups, although minor musculoskeletal symptoms (e.g., arthralgia, joint stiffness, etc.) were significantly more common in women on anastrozole (Cuzick et al., 2014).

Table 4
Characteristics of trials on aromatase inhibitors for chemoprevention in breast cancer.

Study name	Author year	Study design	No. of participants	Intervention arm	Control arm	Duration of Treatment (years)	Primary endpoint	Median follow up duration (years)	Results	Adverse events
National Cancer Institute of Canada Clinical Trials Group Mammary Prevention.3 trial (NCIC CTG MAP.3)	Goss et al., 2011	Double blind RCT	4560	Exemestane 25 mg/d	Placebo	3	Incidence of IBC	3	1. 65% relative reduction in the annual risk of IBC in exemestane group. [HR 0.35, 95% CI: 0.18–0.70] 2. Significant less incidence of total BC.	No difference in incidence of other cancers between groups.
International Breast cancer Intervention Study (IBIS)-II trial	Cuzick et al., 2014	Double blind RCT	3864	Anastrozole 1 mg/d	Placebo	5	Incidence of BC (IBC or, noninvasive DCIS)	5	Reduction in risk of BC in anastrozole group. [HR 0.47, 95% CI: 0·32–68]	Musculoskeletal symptoms in anastrozole group

[No.-number, RCT-randomized controlled trial, mg/d-milligram per day, BC-breast cancer, IBC-invasive breast cancer, DCIS-ductal carcinoma in situ, HR-hazard ratio].

3.4. Non-endocrine agents

Studies have shown that several natural phenolic compounds (e.g., flavonoids) have a potential role in chemoprevention of BC, mainly via the modification of several epigenetic alterations implicated in carcinogenesis (Pan et al., 2015). The antiproliferative and anti-inflammatory properties of curcumin and its analogs make these compounds a possible chemoprevention agent (Mock et al., 2015). A recent study has shown that Diindolylmethane, a bioactive compound found in cruciferous vegetables promotes favorable changes in estrogen metabolism, thus supporting its possible use in the chemoprevention (Thomson et al., 2016; Thomson et al., 2017). A recently published meta-analysis of 13 prospective cohort studies showed that long-term aspirin use (2–7 times/week for > 5 years) was associated with a reduced risk of BC (Lu et al., 2017).

4. Review of current practice guidelines on chemoprevention

4.1. American Society of Clinical Oncology (ASCO) guidelines

ASCO released its first guideline on interventions to reduce BC incidence in high risk women in 1999. The most recent update to these guidelines was published in 2013. Both SERMs and AIs are included as chemopreventive options (Visvanathan et al., 2013). Consideration of tamoxifen use (20 mg daily for five years) is recommended to reduce the risk of ER-positive BC in premenopausal or postmenopausal women ≥35 years of age with an elevated risk (5-year risk ≥1.66%). It is not recommended to use tamoxifen in individuals with a history of VTE, stroke or transient ischemic attack, and in pregnant or nursing mothers. Raloxifene (60 mg daily for five years) is also recommended for use in only postmenopausal women at increased risk for ER-positive IBC. Among the AIs, exemestane (25 mg daily for five years) is recommended as an alternative to SERMs to reduce the risk of ER-positive IBC. Similar to raloxifene, its use is limited to postmenopausal women. At this time, it lacks FDA approval for the indication of chemoprevention. Its inclusion in ASCO guidelines is based on the promising results from the MAP.3 trial.

4.2. National Comprehensive Cancer Network (NCCN) guidelines

For women at an elevated risk (5-year risk ≥1.66%) who desire risk-reduction therapy and have a life expectancy greater than ten years, the NCCN recommends three strategies of interventions which include lifestyle modification, risk reduction agent, and risk reduction surgery (in individuals with specific genetic mutations). As a chemoprevention agent among premenopausal women, only tamoxifen is recommended. For postmenopausal women, options as per NCCN guidelines include tamoxifen, raloxifene or an AI (in women with contraindications to SERMs) (National Comprehensive Cancer Network, 2018).

4.3. United States Preventive Services Task Force (USPSTF) guidelines

The USPSTF recommends that physicians offer risk reduction interventions for women at increased risk based on BC risk assessment tools. Tamoxifen at 20 mg daily for 5-years is recommended for pre- and postmenopausal women of 35 years of age or older. Raloxifene 60 mg daily for five years is recommended for postmenopausal women. Use of AIs is not endorsed by the USPSTF, due to the lack of FDA approval (U.S. Preventive Services Task Force, 2016). Highlights of guidelines on BC chemoprevention are listed in Table 5.

5. Lack of practice of chemoprevention

Despite the substantial evidence and the advocacy in guidelines from several organizations, there remains a significant lack of implementation of chemoprevention. A recent cross-sectional survey in 250 hospitalized women (50–75 years of age) found that one-third of the population had an elevated risk (as per Gail score) for BC, and yet none of them were on chemopreventive medication, nor were they referred to specialist clinic to discuss the risk reduction options (Khaliq et al., 2016). In another study on the Medicare-eligible cohort of 22,235 women, analysis of responses to a medication use questionnaire found that raloxifene was used in only 2.5% and 4% of women with elevated BC risk score (1.66–3% and ≥3% respectively). Data from review of Part D claims revealed that rate of use of raloxifene was 6.6% in women in the highest risk category (risk score ≥3%). Tamoxifen use was also very low, both in data from the questionnaire (0.24% overall and 0.39% in women with highest risk core) and Part-D claims (0.49% overall). The slightly higher rate of raloxifene use in this study may be due to somewhat more favorable side effect profile of the drug. However, it was noted that the use of raloxifene significantly decreased from 2010 to 2014 (Pinsky et al., 2018).

An online survey was conducted among general practitioners (GP) in the United Kingdom to assess the willingness and comfort level in recommending and managing chemoprevention options. The study aimed to identify the factors affecting the prescription decision and the level of awareness about the National Institute for Health and Care Excellence (NICE) guidelines among GPs providing care for the individuals with family history of BC. Almost half of the providers knew that tamoxifen would reduce the risk for BC yet they were less comfortable discussing the risks and benefits of the chemoprevention agents and were more likely to only continue a prescription initiated by some secondary care provider than to prescribe the drug themselves (Smith et al., 2017). In our institution, we conducted a retrospective review of electronic medical records (EMR) of 1220 women (35 to 78 years of age) attending the clinics of Internal Medicine (IM), Family Medicine (FM), and Obstetrics and Gynecology (OBGYN). We noted that 56.9% of OBGYN, 9.4% of FM, and only 1.66% of IM charts had sufficient histories documented to calculate a Gail score. Even though IM providers showed significantly better adherence to BC screening recommendations compared to OBGYN and FM, none of the charts had documented BC risk score. When we calculated the Gail score on those women based on the available information, 12.2% of our study population was found to have an elevated risk for BC. Unfortunately, none of them was offered chemoprevention (Igid et al., 2018).

6. Barriers to implementation of guidelines

6.1. Physician's barriers

The target population for BC chemoprevention is mostly seen by primary care physicians (PCP), rather than oncologists who routinely prescribe these interventions. PCPs may not be familiar with the various tools used to identify the women at risk of developing BC and may lack the confidence to use those models effectively in their patient population. In a survey on the attitudes and practice of PCPs, it was noted that providers rarely take history related to parity, age at menarche, or prior breast biopsies, and almost never calculate Gail score. The need to address more immediate health issues and lack of confidence in their knowledge on the subject were cited as the most common barriers to assessing risk (Sabatino et al., 2007). In another survey involving physicians, lack of time and information were noted as barriers to counseling patients on chemoprevention (Kaplan et al., 2005). Similarly, GP and physicians working in the family history or clinical genetics settings in the UK again cited unfamiliarity with the concept of chemoprevention and inadequate information on options as the main reasons for lack of practice of chemoprevention. The physicians did not feel comfortable to start chemoprevention on their own, although they were more likely to continue the therapy if someone else has already prescribed it to eligible patients (Smith et al., 2016a). Lack of a validated biomarker to assess the efficacy of preventive therapy often

Table 5
Summary of guidelines for chemoprevention in breast cancer.

Issuing authority	Recommended drug	Indications	Contraindications
American Society of Clinical Oncology (ASCO)	1. Tamoxifen 20 mg/d (premenopausal) 2. Raloxifene 60 mg/d Or, Examestane 25 mg/d (postmenopausal)	Premenopausal or postmenopausal women of ≥35 years of age at an increased risk of breast cancer.	History of VTE, stroke or TIA, and pregnant or nursing mothers.
National Comprehensive Cancer Network (NCCN)	1. Tamoxifen 20 mg/d (premenopausal) 2. Raloxifene 60 mg/d Or, aromatase inhibitor (postmenopausal)	Women at an elevated risk (5-year risk ≥1.7%) who desire risk-reduction therapy and in whom life expectancy is > 10 years.	NA
United States Preventive Services Task Force (USPSTF)	Tamoxifen 20 mg/d or, raloxifene 60 mg/d	Women with increased risk of breast cancer (grade B recommendation)	NA

[ER-estrogen receptor, mg/d-milligrams per day, VTE-venous thromboembolism, TIA-transient ischemic attack, NA-not available].

complicates the scenario further.

6.2. Barriers in patients

A study conducted on women at increased risk of BC showed that their need for a safe chemoprevention option could not be met by currently available drugs (Liede et al., 2017). A substantial proportion of women at risk are likely to decline chemoprevention, and among those who accept, about 40% women can't continue it for the whole period of five years because of various AEs (Roetzheim et al., 2015). In the MAP.3 trial, 19% of women in the exemestane group discontinued treatment within the first year of assignment. Experiencing a decline in various domains on the Menopause-Specific Quality of Life questionnaire within the first six months was significantly associated with early treatment discontinuation, whereas smoking history and employment status of patients were other vital determinants (Meggetto et al., 2017). Fear of these AEs is often prompted by friends and family members, who experienced the same. Also, lack of proper counseling might lead to a confusion with the term 'chemoprevention' being misunderstood as something similar to the dreaded 'chemotherapy.' The need for continued adherence for five years is another recognized barrier. A higher perceived risk of getting BC, a recommendation from a physician, and a referral to the medical oncologist were among the most important factors associated with increased rates of chemoprevention uptake among women (Trivedi et al., 2017; Smith et al., 2016b).

6.3. System barriers

The current regulatory model for drug approval does not encourage the development of chemoprevention agents. Trials for preventive drugs can take many years for completion, and patent laws and intellectual property significantly limit pharmaceutical companies. By the time a trial is finished the new drug may not have patent protection and exclusivity, which poses a significant financial burden for drug companies. Additionally, broad use of chemopreventive medications would most likely occur after they become generic which makes preventive research financing unattractive for investors (Meyskens Jr. et al., 2011). Designing and testing a preventive agent involves healthy subjects, which can be harder to recruit for clinical trials. In addition to that, the acceptable safety profile for preventive drugs differs from conventional treatment drugs, which can further limit recruitment and increase withdrawal from studies. Barriers in administration of chemoprevention are depicted in Fig. 1.

7. Strategies for improvement in chemoprevention uptake

A crucial step in promoting chemoprevention is increasing the awareness among physicians and educating them on risk assessment. Tools like Gail model could be incorporated into the EMR to better facilitate routine use by the providers. The most consistent variable correlating with interest in chemoprevention seems to be perceived vulnerability to BC (Ropka et al., 2010). This finding highlights the importance of training physicians on how to communicate on the risk-benefit aspects to assist women with informed decision-making. One of the most significant limitations in the drive to increase the BC chemoprevention uptake is the lack of evidence of decreased overall mortality with its use. We need further research that includes mortality as an endpoint, as a reduction in mortality would make health care providers more willing to promote and prescribe these medications.

A critical distinction in the acceptable toxicity of a treatment drug versus a prevention drug is the fact that prevention involves disease-free subjects. Studies evaluating lower doses, increased dosing intervals or drug delivery via non-conventional routes might help overcome the fear of associated side effects (Crew et al., 2017). A possible revised nomenclature, like 'primary prevention' to replace the term 'chemoprevention,' might simplify the purpose of this therapy and also alleviate unnecessary fear and confusion in people's minds. Further research is needed to develop reliable and feasible biomarkers to assess the response to chemoprevention (Fabian and Kimler, 2016). National policy changes may be helpful to provide an incentive to the pharmaceutical companies to invest in chemoprevention research (Meyskens Jr. et al., 2011).

8. Conclusion and future directions

Chemoprevention is an important consideration for women at elevated risk of BC with the potential for a significant reduction in risk. While SERMs remain the cornerstone of therapy for chemoprevention, efforts are underway for new drug development and also for exploration of various non-conventional drug delivery routes, to make the risk-benefit profile more favorable for the chemopreventive medications. Despite widely available user-friendly version of guidelines from several societies, different barriers to implementation continue to exist both in patients and physicians. Primary care physicians are pivotal in the initial risk assessment, counseling regarding interventions for risk reduction and in implementing appropriate risk-based screening. Medical schools, residency training programs, and health care policymakers should invest more in the education of providers to ensure adequate implementation of chemoprevention in women at risk of BC.

Authorship contributions

All authors have equally contributed to the manuscript.

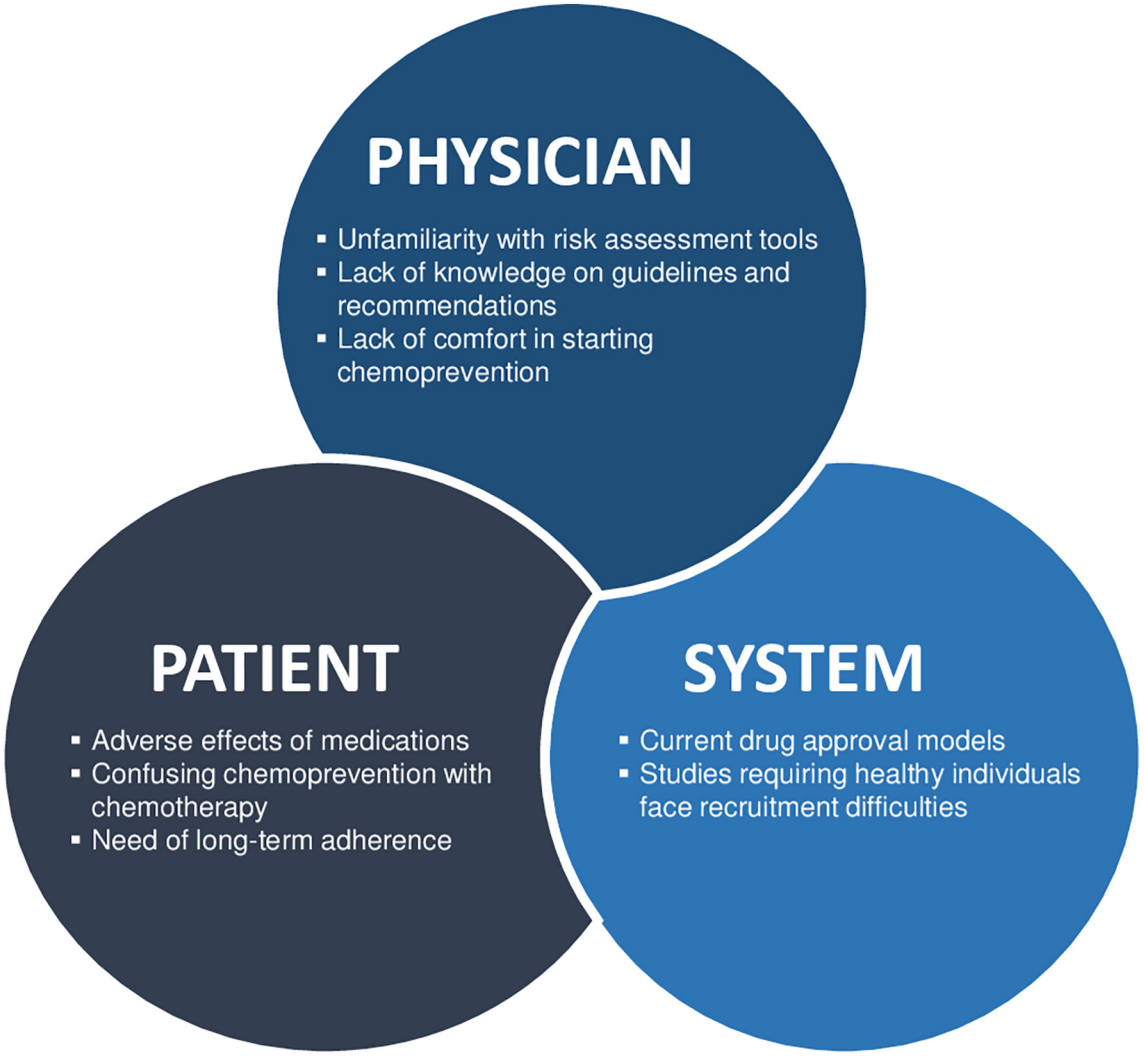

Fig. 1. Barriers in breast cancer chemoprevention.

Declaration of competing interest

None to declare.

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None.

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