Tamoxifen vs Raloxifene vs Exemestane for Chemoprevention

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Abstract

Clinical trial data on selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) have demonstrated reduced breast cancer incidence in the prevention setting among high-risk women. We conducted an extensive review of clinical trials and recent published reports of barriers to uptake of breast cancer chemoprevention, to provide health care professionals with information to improve decision-making regarding chemoprevention. Despite the positive results of these trials, uptake of chemoprevention has been low due to barriers in identifying high-risk women, lack of understanding of risks and benefits, as well as concerns about side effects. Interventions designed to increase uptake have met with limited success. Clinicians can support women in informed decision-making about SERMs and AIs by effectively communicating breast cancer risk and enhancing knowledge about the risks and benefits of chemoprevention. Promoting uptake and adherence to chemoprevention holds promise for reducing the public health burden of this disease.

Keywords

Breast cancer; Chemoprevention; Selective estrogen receptor modulator; SERM; Aromatase inhibitor; AI; Prevention; Risk

Introduction

Breast cancer confers significant morbidity and mortality on women in the U.S., and the primary prevention of this disease is a major public health issue. Breast cancer risk assessment and available interventions for prevention, such as chemoprevention, are underutilized in the U.S. Selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene, have been shown to reduce breast cancer incidence by up to 50% among high-risk women [1, 2]. Approximately 15% of women age 35–79 years are at increased risk for breast cancer development and are potentially eligible for a SERM [3], but uptake has been poor in the prevention setting [4]. Reasons for lack of SERM uptake for chemoprevention include inadequate time for counseling, an insufficient level of knowledge and information about risk-reduction strategies, and public misconceptions about the risks of SERMs [5]. A recent clinical trial of the aromatase inhibitor (AI), exemestane, among high-risk postmenopausal women reported promising results after short-term follow-up with a

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favorable safety profile [6]. We conducted an extensive review of chemoprevention trials of SERMs and AIs, as well as recent published reports of barriers to uptake of breast cancer chemoprevention, to provide up-to-date information for health care professionals to improve clinical decision-making.

Breast Cancer Chemopreventive Agents

Selective Estrogen Receptor Modulators (SERMs)

Table 1 summarizes the results of randomized controlled trials of SERMs and AIs for the primary prevention of breast cancer. In 1998, the Breast Cancer Prevention Trial or NSABP-P1 trial demonstrated that the SERM, tamoxifen, given for 5 years reduced breast cancer incidence in high-risk women by 49% (absolute risk of 2.48% vs. 4.25% for placebo, p<. 001) [1, 7]. The updated results from 3 additional randomized placebo-controlled trials of tamoxifen (International Breast cancer Intervention Study [IBIS-1], Royal Marsden and Italian trials) demonstrated a 30–40% reduction in estrogen receptor (ER)-positive invasive breast cancer [8–10]. Conversely, tamoxifen had no effect on the incidence of ER-negative tumors. Of note, none of these chemoprevention trials were adequately powered to assess the effects of tamoxifen on breast cancer mortality. Also, limited data exist on the efficacy of tamoxifen for breast cancer risk reduction in *BRCA1* and *BRCA2* mutation carriers.

Another SERM, raloxifene, has been shown to reduce the incidence of breast cancer in clinical trials for the treatment and prevention of osteoporosis [11, 12]. Among postmenopausal women with osteoporosis, raloxifene given for up to 7 years reduced the incidence of invasive breast cancer by 76%, with the majority of the benefit restricted to ER-positive tumors [11]. More recently, the Raloxifene Use for The Heart (RUTH) trial among postmenopausal with coronary heart disease (CHD) risk factors demonstrated that raloxifene reduced the risk of invasive breast cancer and vertebral fracture, but had no affect on the risk of CHD [13]. Two additional SERMs, lasofoxifene and arzoxifene, tested in postmenopausal women with osteoporosis demonstrated similar 70–80% reductions in ER-positive breast cancer incidence compared to placebo [14–16]. However, the results of these trials suggest that these agents do not offer major clinical benefits for breast, bone, or cardiovascular health over currently available SERMs [17].

The Study of Tamoxifen and Raloxifene (STAR) trial is the largest breast cancer chemoprevention trial to date with 19,747 women randomized and a median of 81 months of follow-up [2, 18]. Updated analyses from the STAR trial showed that raloxifene retained 76% of the long-term efficacy of tamoxifen in preventing invasive breast cancer among high-risk postmenopausal women with a more favorable side effect profile [18]. The difference in endometrial cancer risk between the two SERMs while not significant in the initial report was significantly higher for the tamoxifen group with longer follow-up. Based upon the results of these trials, tamoxifen was approved by the U.S. Food and Drug Administration (FDA) for breast cancer risk reduction among high-risk women in 1998 and raloxifene in 2007.

Aromatase Inhibitors (AIs)

The risk of developing contralateral tumors is 50% lower in postmenopausal breast cancer patients receiving an AI compared to tamoxifen in the adjuvant setting [19, 20]. Data from adjuvant trials have proven to be a useful model for testing the chemopreventive effects of hormonal therapies, since the results of the prevention trials closely mirrored those of adjuvant studies [21]. The MAP.3 trial, a randomized double-blind placebo-controlled trial of exemestane 25mg daily for 5 years in 4560 high-risk postmenopausal women, is the first chemoprevention trial of an AI [6]. The primary outcome was incidence of invasive breast cancer, with combined invasive and noninvasive breast cancer as well as ER-positive tumors

as secondary endpoints. Postmenopausal women with at least one of the following risk factors were enrolled: age 60 years or older, a 5-year breast cancer risk greater than 1.66% according to the Gail model, prior atypical hyperplasia (AH) or lobular carcinoma *in situ* (LCIS), or ductal carcinoma *in situ* (DCIS) with mastectomy [6, 22]. The majority of participants were white (93%), and the main high-risk criteria were age 60 years or older (49%), Gail risk >1.66% (40%), AH or LCIS (8%), and DCIS (3%) [6]. After a median follow-up of 35 months, 11 invasive breast cancer events occurred in the exemestane arm compared to 32 in the placebo group. Exemestane reduced invasive breast cancer incidence by 65% (absolute risk of 0.48% vs. 1.41% for placebo, p=0.002) [6]. In the exemestane group, more grade 2 or higher arthritis (6.5% vs. 4.0% for placebo) and hot flashes (18.3% vs. 11.9% for placebo) were seen. Approximately 85% of women were compliant with study treatments and early discontinuation for toxic effects was 15.4% in the exemestane group vs. 10.8% for placebo. No significant differences in new-onset osteoporosis, clinical skeletal fractures, cardiovascular events, or other malignancies were detected, and overall health-related quality of life did not differ between the two groups. The main limitations of the trial were the relatively short-term follow-up of 3 years, the small number of breast cancer events, and the lack of a direct comparison to SERMs.

Another third-generation AI, anastrozole, is being actively investigated in the prevention setting in the IBIS-II trial, which randomizes high-risk postmenopausal women ages 40 to 70 years to either anastrozole (1mg/d) or placebo for 5 years [23]. The primary endpoint is invasive breast cancer incidence. To date, there are no head-to-head trials comparing SERMs to AIs in the primary prevention setting. The Study to Evaluate Letrozole and Raloxifene (STELLAR) or NSABP-P4 was designed to address this question [24]. However, a National Cancer Institute review panel halted initiation of the STELLAR trial due to financial constraints and concerns about low uptake of chemoprevention.

Barriers to Uptake of Breast Cancer Chemoprevention

Based on age and breast cancer risk, an estimated 10 million women in the U.S. may be eligible for chemoprevention [3], but less than 5% of high-risk women agree to take a SERM [4]. Data from the National Health Interview Survey (NHIS) indicated that the prevalence of tamoxifen use among women without a personal history of breast cancer was merely 0.2% in 2000 and decreased to 0.08% by 2005 [25]. Similarly, raloxifene use decreased after FDA approval of this drug for breast cancer risk reduction [5]. It remains to be seen whether there will be greater acceptance of AIs in the prevention setting.

Identification of high-risk women

Low SERM uptake is partly due to the lack of effective strategies to identify high-risk women. The Gail model (www.cancer.gov/bcrisktool) or Breast Cancer Risk Assessment Tool (BCRAT), which takes into account a woman's age, race, reproductive history, family history, and benign breast disease, is the most commonly used model in the U.S. and has been well-validated at the population level [26]. It can be used in women age 35 years or older and provides an individual's absolute 5-year and lifetime risk of invasive breast cancer compared to 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 breast cancer. The Gail model recently incorporated the Women's Contraceptive and Reproductive Experiences (CARE) [27] model and Asian American Breast Cancer Study (AABCS) [28] model to provide more sensitive estimates for black and Asian American women, respectively. Few studies have used this model in Hispanic populations [29, 30]. Eligibility for chemoprevention among U.S. women varies dramatically by race/ethnicity: 18.7% of whites, 5.7% of blacks, 2.9% of Hispanics [3]. Not meeting high-risk criteria may be an initial barrier to chemoprevention uptake among minority groups.

In women with a strong family history of breast cancer (*i.e.,* two or more affected family members, particularly those with an early age of onset), the IBIS or Tyrer-Cuzick model (www.ems-trials.org/riskevaluator), is useful, because it incorporates a detailed family history including second- and third-degree family history of breast and ovarian cancer and their age at diagnosis [31]. The IBIS model estimates the risk of developing invasive breast cancer and DCIS and the probability of carrying a mutation in the *BRCA1* and *BRCA2* genes [31]. This model may be particularly relevant for calculating risk in women with affected family members. Despite the availability of both the Gail and IBIS breast cancer risk assessment tools on-line, only 18% of primary care physicians report use of software to calculate breast cancer risk [32]. Barriers to assessment of risk in the primary care setting include time constraints during clinic visits and lack of confidence in knowledge about risk assessment [33].

To address this barrier of poor identification of high-risk women, the "Ready, Set, GO GAIL!" project screened for high-risk women with routine use of the Gail model in women age 35 to 70 years who presented for a comprehensive physical examination at the Aurora Health Care women's center in Wisconsin [34]. During the first year, 5,718 Gail model scores were calculated and 15.2% of women were deemed high risk. At our institution, we are embarking on a project entitled the Breast cancer Family-based Intervention Trial (BFIT) which will target women with a first-degree family history of breast cancer in the clinic and community-based settings [35]. These women may be at high risk for breast cancer owing to shared hereditary and lifestyle factors and may be unaware of their elevated risk. Providing information and education about personal risk at a time when a close relative is diagnosed with breast cancer represents a "teachable moment" when women may want to take personal action for disease prevention.

Risks and Benefits of Chemoprevention

Another reason for low SERM uptake is the perception of patients and physicians that chemoprevention does not offer a favorable risk-benefit ratio [36–39]. Whereas the side effects diminish after stopping 5 years of tamoxifen, the protective effect on breast cancer risk persists for up to 10 years. In the IBIS-1 trial in which participants remained blinded after the primary results were published, no diminution of benefit was observed for up to 10 years after randomization [10]. Although the short-term absolute benefits of tamoxifen may seem small, if the risk-reducing effects of chemoprevention persist for a woman's lifetime, then the absolute benefit in terms of breast cancer risk reduction would exceed 10% (among women with a lifetime risk >20%). 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 the period of active treatment.

Concern about potential toxicities, such as endometrial cancer, thromboembolic events and menopausal symptoms, is the main contributor to a woman's unwillingness to try a SERM and a physician's reluctance to prescribe it [36–38, 40–43]. In a meta-analysis of chemoprevention trials, Cuzick *et al.* [21] reported a 2.4-fold increase in endometrial cancer (absolute risk of 0.37% vs. 0.15% for placebo) and a 1.9-fold increase in thromboembolic events (absolute risk of 0.83% vs. 0.44% for placebo) with tamoxifen use. In the NSABP-P1 trial, the elevated risk of endometrial cancer was only observed in women over age 50 [1]. In other trials, the risk of endometrial cancer and thromboembolic events was not observed after stopping tamoxifen [8, 10]. Increased vaginal discharge (55% vs. 34% in controls) and hot flashes (78% vs. 65% in controls) and a 14% increase in the incidence of cataracts were reported with tamoxifen during treatment [44]. In the STAR trial, raloxifene was associated with a lower risk of thromboembolic disease, benign uterine complaints, and cataracts compared to tamoxifen [2, 45]. Women on tamoxifen reported more gynecologic and vasomotor symptoms [2], however, overall quality of life was similar in both arms of the

STAR trial [45]. AIs do not have the serious side effects of tamoxifen, but are associated with an increased risk of fracture, musculoskeletal side effects, and elevated cholesterol [46–48]. Tamoxifen and raloxifene have a similar favorable effect on bone density with about a 32% reduction in fracture incidence [1, 11, 12].

Low SERM uptake is partly due to fear of side effects, but also due to the lack of effective strategies to inform high-risk women and their health care providers about the risks and benefits of chemoprevention. Physicians who felt insufficiently informed about risk reduction options were less than half as likely to prescribe a SERM than physicians who felt sufficiently trained [49]. Physician recommendation and health care provider communication are among the most influential factors to impact SERM use [36, 38, 50]. Freedman *et al.* recently published models to predict the risks and benefits of SERMs for women over age 50, based upon age, race/ethnicity, 5-year Gail risk score, and presence of a uterus [51]. Tools such as this can be incorporated into the clinical setting as an aid for health care providers and high-risk women in chemoprevention decision-making.

Adherence to Endocrine Therapy

The efficacy of chemoprevention depends not only on initiation of therapy, but also long-term adherence and persistence of therapy for the planned duration. Poor adherence to tamoxifen tends to attenuate the drug's therapeutic effects [52]. In a study with 12 years of follow-up, breast cancer patients with 80% or higher adherence had a 26% lower risk for recurrence compared with patients with <80% adherence [53]. In the adjuvant setting by year 4 to 5 of treatment, the full adherence rate drops to 50% [54, 55]. In the SERM chemoprevention trials, adherence at 5 years ranged from 64% to 76.3% [1, 10, 45], with the caveat that 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 breast cancer patients treated in the adjuvant setting, because higher perceived health risk increases adherence [56]. In the NSABP-P1 trial, low income and Hispanic ethnicity were associated with low adherence [57]. A substudy of the MAP.3 trial also found worse adherence for ethnic minorities vs. whites [58]. Recognizing predictors of adherence to endocrine therapies will assist in the development of targeted interventions that promote adherence to chemoprevention.

Interventions to Increase Uptake of Breast Cancer Chemoprevention

A systematic review published in 2010 addressed patient decisions about breast cancer chemoprevention and found that perceived vulnerability to breast cancer correlated with increased uptake, whereas concern for adverse effects was associated with reduced uptake [4]. This meta-analysis included 13 studies, which were limited by the use of descriptive study designs and the lack of validated survey instruments or reproducible sampling strategies that would enhance generalizability of the results. Table 2 summarizes more recent intervention studies designed to increase SERM uptake for chemoprevention. Interventions involving reading materials or decision aids met with limited success, ranging from 0.5% to 5.6% [38, 39, 42, 59, 60]. In a recent randomized controlled trial of a web-based decision aid which informed women about the risks and benefits of SERMs [59], only 0.5% of 712 eligible participants started raloxifene and none started tamoxifen.

Since discussions about chemopreventive agents, which are prescription medications, are traditionally initiated by physicians, clinic-based interventions may be more effective. In the "Ready, Set, GO GAIL!" project [34], women deemed high risk according to the Gail model (5-year risk 1.7% or lifetime risk 20%) either had a high-risk consultation with their primary care provider or were referred to a comprehensive breast cancer center. However, only 14.7% of high-risk women were referred to the breast center, and only 6.4% completed

the consultation. Overall SERM uptake for eligible women was 2% with this clinic-based intervention. Therefore, most intervention studies designed to increase uptake of breast cancer chemoprevention have yielded disappointing results.

However, studies that involved consultation at a specialized breast center reported SERM use ranging from 11% to 58% [36, 40, 41, 50, 61, 62]. Variation in SERM uptake may have been due to the strength of the physician's recommendation [63]. In our experience at an urban academic breast center, we have a high-risk population comprised of women from diverse racial and ethnic backgrounds (55% white, 32% Hispanic, 7% black, and 6% Asian) who mainly have benign breast disease (AH and LCIS). Our SERM uptake rate among eligible women was 30% in the primary prevention setting [64]. Therefore, higher chemoprevention uptake may be achieved with health professionals that have sufficient knowledge and training about breast cancer risk and risk reduction strategies.

Chemoprevention Guidelines

In 2009, the American Society of Clinical Oncology (ASCO) published consensus guidelines on breast cancer chemoprevention [65]. High-risk premenopausal and postmenopausal women, defined as a 5-year Gail risk 1.67% or LCIS, may take tamoxifen for 5 years to reduce the risk of ER-positive breast cancer for up to 10 years. Tamoxifen is favored in high-risk premenopausal women and postmenopausal women with a hysterectomy, whereas raloxifene is preferred for use among high-risk postmenopausal women with an intact uterus and those at risk for osteoporosis. Due to the increased risk of uterine cancer, follow-up for women on tamoxifen should include a baseline gynecologic examination before the initiation of treatment and annually thereafter, with a timely work-up for abnormal vaginal bleeding. Routine endometrial biopsies are not recommended in the absence of abnormal vaginal bleeding. SERMs are contraindicated in women with a history of deep vein thrombosis, pulmonary embolus, stoke, or transient ischemic attack. In addition, the STAR trial excluded women on hormone replacement therapy, those with uncontrolled diabetes mellitus or hypertension, and atrial fibrillation [2]. In 2010, the National Comprehensive Cancer Network (NCCN) published similar clinical practice guidelines for breast cancer risk reduction [66]. However, these guidelines do not incorporate AIs for breast cancer chemoprevention among high-risk postmenopausal women.

Figure 1 represents a potential algorithm for decision-making about SERMs and AIs for breast cancer chemoprevention based upon menopausal status, history of blood clots, risk of osteoporosis, and prior hysterectomy. For high-risk premenopausal women without a personal history of thromboembolic events, the only proven chemopreventive agent is tamoxifen. In the chemoprevention trials, the greatest clinical benefit and fewest side effects were derived from tamoxifen use in young high-risk women, age 35–50 years. If tamoxifen is contraindicated due to a history of blood clots, then participation in a clinical trial or consideration of an AI after menopause is a potential option. Similarly, among high-risk postmenopausal women with a history of thromboembolism all SERMs are contraindicated, therefore, exemestane is currently the only proven agent for breast cancer prevention. If the woman is at highrisk for osteoporosis, then SERMs may be preferred over AIs do to the beneficial effects on reducing fracture risk, although presence of osteoporosis is not an absolute contraindication to taking an AI. For postmenopausal women with a prior hysterectomy, tamoxifen may be favored over raloxifene due to its greater efficacy in lowering invasive breast cancer risk [18]. Overall, all three drugs are effective chemopreventive agents for high-risk postmenopausal women, therefore, the choice will depend upon personal preferences and acceptable toxicities.

Conclusions

Breast cancer chemoprevention has proven efficacy in high-risk populations [1, 2, 18], but these benefits will only be translated to the general population if women adopt and adhere to these chemopreventive agents. Preventive therapy for cancer is currently less well established than in other chronic conditions, such as CHD, and could benefit from lessons learned [67]. Health care providers can do more in the area of cancer prevention by targeting high-risk populations. Chemoprevention needs to be integrated into wider strategies of preventive care that also include non-pharmacologic approaches such as lifestyle modification. Breast cancer screening represents an opportunity to provide advice about breast cancer risk and options for prevention. Therefore, individual risk assessment and risk modification should become an integral part of breast cancer screening programs.

Further research is needed to determine how knowledge about breast cancer, actual and perceived risk, and strategies for prevention are best communicated to high-risk women. Another important research area is the development of novel chemopreventive agents targeting ER-negative breast cancer. Promising agents that are actively being investigated include pharmacologic drugs, such as bisphosphonates, metformin, statins, aspirin, and other non-steroidal anti-inflammatory drugs, as well as dietary supplements, such as omega-3 fish oils, vitamin D, and green tea extract [68]. The high costs of large-scale chemoprevention studies have prompted the search for intermediate markers of breast cancer development. Validation of intermediate biomarkers which correlate with breast cancer risk, such as mammographic density [69], will reduce the time and expense associated with new prevention drug development and will allow breast cancer prevention research to accelerate and expand. Improving short-term breast cancer risk assessment will also allow us to identify high-risk women who are likely to derive benefits from chemoprevention.

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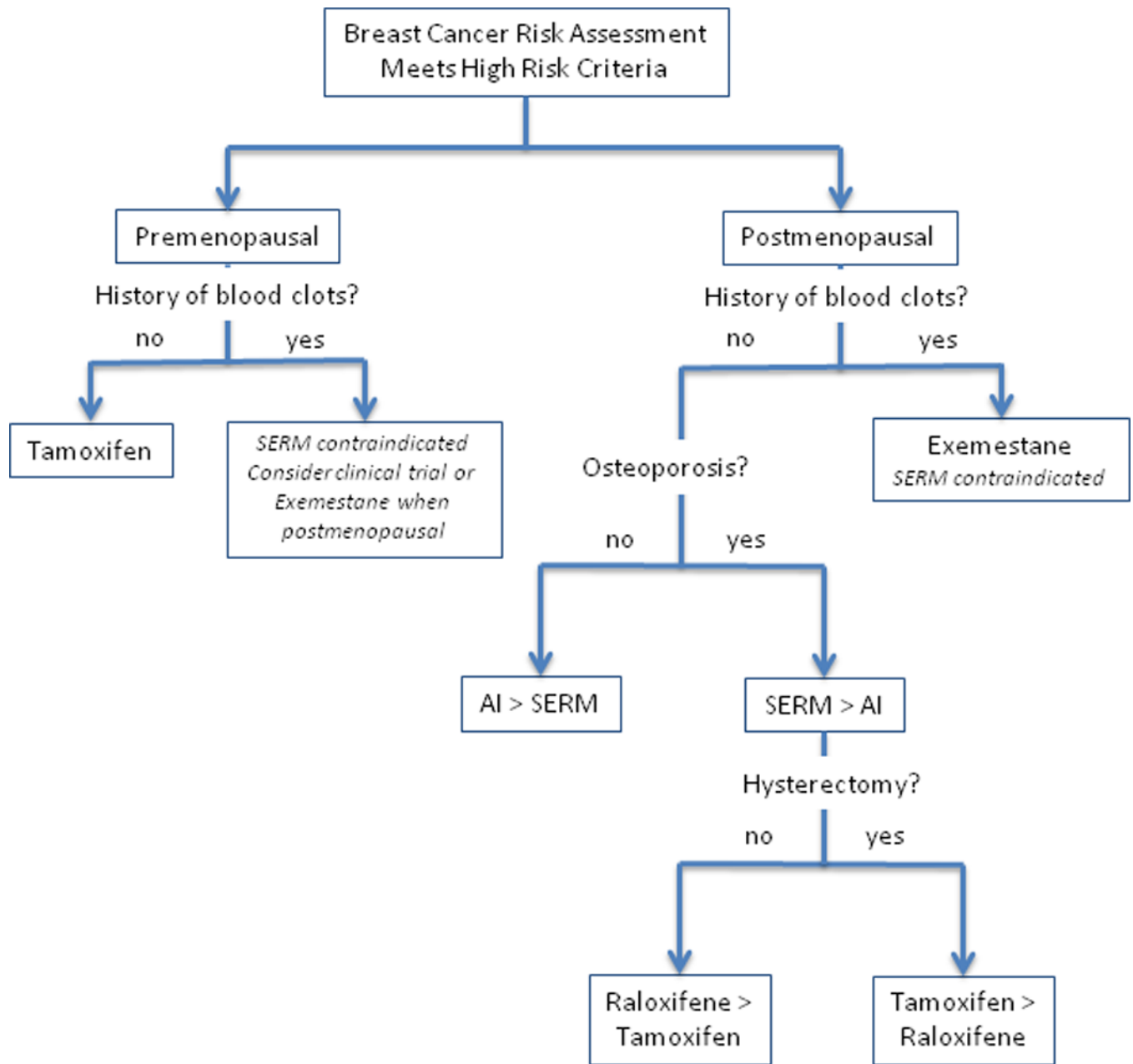
Fig. 1.
Algorithm to determine appropriate chemopreventive agent in high risk women based upon menopausal status, history of blood clots, risk of osteoporosis, and prior hysterectomy. AI, aromatase inhibitor; SERM, selective estrogen receptor modulator.

Table 1

Breast cancer chemoprevention trials of selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs)

	No. of Participants	Eligibility	Duration of Intervention (years)	Median Follow-up (months)	Invasive BC rate/1000 person-years	Invasive BC RR (95% CI)	ER-positive BC RR (95% CI)	ER-negative BC RR (95% CI)
Tamoxifen (20mg/d) vs. Placebo								
NSABP P-1 (2005) [7]	13,388	Age ≥60 yrs or 35–59 yrs and 5-yr Gail risk >1.66% or LCIS	5	84	3.59 vs. 6.29	0.57 (0.46–0.70)	0.38 (0.28–0.50)	1.31 (0.86–2.01)
IBIS-1 (2007) [10]	7145	Age 45–70 yrs with 2-fold risk or 40–44 yrs with 4-fold risk or 35–39 yrs with 10-fold risk	5	96	4.34 vs. 5.88	0.74 (0.58–0.94)	0.66 (0.50–0.87)	1.00 (0.61–1.65)
Royal Marsden Trial (2007) [8]	2494	Age 30–70 yrs, 1° relative with BC at age<50 or 1° bilateral BC or 1° BC plus another 1° or 2° or BBD with 1° relative	8	158	4.8 vs. 6.1	0.78 (0.58–1.04)	0.61 (0.43–0.86)	1.4 (0.7–2.6)
Italian Study (2007) [9]	5408	Age 35–70 yrs, avg BC risk, hysterectomy	5	132	1.77 vs. 2.21	0.80 (0.56–1.15)	0.77 (0.51–1.16)	1.10 (0.59–2.05)
Raloxifene (60mg or 120mg/d) vs. Placebo								
MORE (1999) [11]	7705	Age <80 yrs, at least 2 yrs postmenopausal, osteoporosis	3	40	0.87 vs. 3.61	0.24 (0.13–0.44)	0.10 (0.04–0.24)	0.88 (0.26–3.00)
CORE (2004) [12]	5213	Subset of MORE cohort	4	95	2.1 vs. 5.2	0.41 (0.24–0.71)	0.34 (0.18–0.66)	1.13 (0.29–4.35)
RUTH (2006) [13]	10,101	Age ≥55 yrs, at least 1 yr postmenopausal, CHD or at increased risk for CHD	5	67	0.15 vs. 0.27[*]	0.56 (0.38–0.83)	0.45 (0.28–0.72)	1.44 (0.61–3.36)
Lasofoxifene (0.25mg or 0.5mg/d) vs. Placebo								
PEARL (2010) [15]	8556	Age 59–80 yrs, postmenopausal, osteoporosis	5	60	0.41 vs. 1.97	0.21 (0.08–0.55)	0.17 (0.05–0.57)	0.35 (0.04–3.34)
Arzoxifene (20mg/d) vs. Placebo								
GENERATIONS (2011) [16]	9354	Age 60–85 yrs, postmenopausal, osteoporosis	4	48	0.25 vs. 0.58[*]	0.44 (0.26–0.76)	NS	NS
Raloxifene (60mg/d) vs. Tamoxifen (20mg/d)								
STAR (2010) [18]	19,747	Age ≥35 yrs, postmenopausal, 5-yr Gail risk ≥1.66%	5	81	5.02 vs. 4.04	1.24 (1.05–1.47)	0.93 (0.72–1.24)	1.15 (0.75–1.77)
Exemestane (25mg/d) vs. Placebo								
ExCel/MAP3 (2011) [6]	4560	Age ≥35 yrs, postmenopausal, Age >60 yrs or 5-yr Gail risk ≥1.66% or prior	5	35	0.19 vs. 0.55[*]	0.35 (0.18–0.70)	0.27 (0.12–0.60)	0.80 (0.21–2.98)

No. of Participants	Eligibility	Duration of Intervention (years)	Median Follow-up (months)	Invasive BC rate/1000 person-years	Invasive BC RR (95% CI)	ER-positive BC RR (95% CI)	ER-negative BC RR (95% CI)
	AH, LCIS, DCIS with mastectomy						

Abbreviations: AH, atypical hyperplasia; BC, breast cancer; BBD, benign breast disease; CI, confidence interval; CHD, coronary heart disease; CORE, Continuing Outcomes Relevant to Evista; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; GENERATIONS, Global Investigation to Determine Efficacy of Arzoxifene on At-risk Postmenopausal Patients; IBIS, International Breast cancer Intervention Study; LCIS, lobular carcinoma *in situ*; MORE, Multiple Outcomes of Raloxifene; NS, not stated; NSABP, National Surgical Adjuvant Breast and Bowel Project; PEARL, Postmenopausal Evaluation And Risk-reduction with Lasofoxifene; RR, relative risk; RUTH, Raloxifene Use for The Heart; STAR, Study of Tamoxifen and Raloxifene.

*
Annual Incidence (%)

Table 2

Summary of intervention studies of uptake of breast cancer chemoprevention

Author (Year)	Intervention	N	Population	Age Range, years (Mean)	Chemoprevention Uptake
Fagerlin *et al.* (2010) [39]	Tailored on-line decision aid "Guide to Decide"	632	5-yr Gail risk 1.66% Healthcare Organizations (Henry Ford Health System in Michigan; Group Health in Washington State)	40–74 (59)	0.9% TAM
Loehberg *et al.* (2010) [60]	None; screened for participation in IBIS-II	2524	Age 50–69 yrs Mammography screening programs in Germany	50–69 (59.5)	0.7% participation rate in AI trial
Fagerlin *et al.* (2011) [59]	Tailored on-line decision aid "Guide to Decide"	1197	Age 40–74 yrs, postmenopausal, 5-yr Gail risk 1.66% Healthcare Organizations (Henry Ford Health System in Michigan; Group Health in Washington State)	46–74 (62)	0% TAM 0.5% RAL
Owens *et al.* (2011) [34]	"Ready, Set, GO GAIL!" project High-risk consultation by primary care provider or referral to breast center	868	Age 35–70 yrs, 5-yr BC risk 1.7% or lifetime risk 20% Aurora Health Care in Wisconsin	35–70	2%

Abbreviations: AI, aromatase inhibitor; BC, breast cancer; IBIS, International Breast cancer Intervention Study; RAL, raloxifene; TAM, tamoxifen.