Breast Cancer: Targets and Therapy

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REVIEW

Current strategies for the prevention of breast cancer

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Abstract: Due to the high incidence of breast cancer in the United States, optimal strategies for its prevention are imperative. This entails identification of women who are at an increased risk for breast cancer and an integrative approach that includes effective screening methods as well as nutritional, pharmacologic, and surgical management. Several breast cancer risk-assessment tools, such as the Gail and Claus models, can help clinicians determine the quantitative risk of breast cancer. The role of selective estrogen receptor modulators, such as tamoxifen and raloxifene, for the prevention of breast cancer has been well established. Several other agents, such as aromatase inhibitors, are currently being investigated. The potential adverse effects of these chemopreventive agents, which include an impact on the quality of life, must be discussed with the patient before deciding on this approach. Additionally, breast cancer risk factors have been identified over the years; some of them are modifiable, but others are not. Although there is no conclusive evidence to suggest the protective role of specific dietary components, alcohol consumption and obesity are associated with an increased breast cancer risk; thus lifestyle changes can lead to a lower risk of developing breast cancer. Surgical approaches, including bilateral risk-reduction mastectomy and salpingo-oophorectomy, are usually limited to women with a hereditary predisposition to development of breast cancer. The objective of this review is to summarize the various approaches directed at reducing the incidence of breast cancer.

Keywords: chemoprevention, tamoxifen, raloxifene, prophylactic surgery

Introduction

Breast cancer continues to be the most common cancer diagnosed in women in the United States, with a median age at diagnosis of 61 years.[1,2] It was estimated that approximately 232,340 new cases of invasive breast cancer (IBC) and 64,640 new cases of ductal carcinoma in situ (DCIS) were estimated to be diagnosed in 2013.[3] The current lifetime risk of a woman developing breast cancer in the US is estimated to be one in eight (12.3%), which is an increase compared to the one in eleven (9.09%) lifetime risk in the 1970s. This apparent increase is believed to result from longer life expectancy, increased detection through sensitive screening methods, changes in reproductive patterns, and an increasing prevalence of obesity. Breast cancer is the second leading cause of cancer death after lung cancer.[2] The American Cancer Society projected approximately 39,620 breast cancer related-deaths in 2013.[3] The incidence and death rates of breast cancer increase with age; 79% of new cases and 88% of breast cancer deaths were reported in women who were 50 years of age or older in the year 2013.[3] Breast cancer incidence is higher in non-Hispanic white women compared to African-American women (except prior to the age of 40 years), while the mortality rate is higher among African-American women overall.[1,3,4]

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Several breast cancer risk factors have been identified. These are broadly classified as modifiable and non-modifiable risks. The latter includes age, race/ethnicity, genetics/family history, and age at menarche. Modifiable risk factors include diet, alcohol consumption, body mass index (BMI), exogenous estrogen use, smoking, and physical inactivity.[5] The woman's age at the birth of her first child, her age at menopause, and her breast-feeding status are considered potentially modifiable.[6] Additionally, mammographic breast density (MBD), alone or in combination with other risk factors, has been demonstrated to be associated with an increased risk of breast cancer.[7–12] Percentage dense area (PDA) is the most common measurement of mammographic density. A four- to six-fold greater risk of breast cancer has been reported in women having more than 75% of the total area on mammogram occupied by dense area.[13] In addition to PDA, absolute dense area of the breast obtained on assessment of PDA has been reported to be an independent risk factor for breast cancer, and its inclusion in risk-assessment tools has been proposed.[14] Female survivors of Hodgkin's disease that were treated with chest irradiation are known to be at an increased risk of breast cancer, with the cumulative absolute risks of breast cancer varying with type of therapy, age at end of follow-up, time since diagnosis, and radiation dose.[15] Hence, due to the rising incidence of breast cancer and several of the risk factors being non-modifiable, strategies for the primary prevention of breast cancer represent an important area of interest. The objective of this review is to synopsize the different approaches directed at reducing the incidence of breast cancer.

Assessment of breast cancer risk

Several breast cancer risk-assessment tools are currently available. The earliest and most widely used risk-assessment tools include the Gail and Claus models.[16,17] The Gail model, which is based on the Breast Cancer Detection Demonstration Project, provides an estimate of a woman's risk of developing breast cancer during the ensuing 5-year period and her overall lifetime risk.[17] The components of this model include age at menarche, age at first live birth, patient's current age, number of first-degree relatives with IBC, race/ethnicity, number of prior breast biopsies, and the results of these biopsies. The original model was based on data from white non-Hispanic women; however, the subsequent model for African-American women as well as Asian and Pacific Island women was developed based on additional studies and the National Cancer Institute's Surveillance, Epidemiology, and End Results program.[18,19] This model is not applicable to women with a prior history of IBC, DCIS, or lobular carcinoma in situ (LCIS). The Claus model includes information on the patient's age, first- and/or second-degree relatives with IBC, and age of relatives at the time of their diagnosis;[16] however, this model does not include any of the nonhereditary risk factors. The updated Claus model includes the risk of IBC in women with a family history of ovarian cancer.[20] Breast cancer risk-assessment models, such as the BRCAPRO[21] and Tyrer-Cuzick models,[22] also take into account *BRCA-1/2* mutation carrier status.

Breast cancer risk-reduction strategies

Pharmacotherapy (chemoprevention)

The effects of various pharmacologic agents on the incidence of IBC and noninvasive breast cancer have been investigated in several prospective randomized clinical trials.[23]

Chemoprevention is defined as:

> the use of pharmacologic or natural agents that inhibit the development of invasive breast cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells in which such damage has already occurred.[24]

In this review, we will discuss the role of selective estrogen receptor modulators (SERMs), such as tamoxifen, raloxifene, arzoxifene, and lasofoxifene, as well as aromatase inhibitors (AIs) such as exemestane.

Tamoxifen chemoprevention studies

National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P1)

The NSABP-P1 trial, which was initiated in 1992, randomized 13,388 women to receive either 20 mg of tamoxifen or a placebo daily for 5 years.[25] Inclusion criteria for the study were women older than 60 years of age or those between the ages of 35 and 59 years with a 5-year predicted IBC risk of at least 1.66% as determined by the modified Gail model[17] or having a history of LCIS. Women were excluded from the study if they had a history of deep venous thrombosis, pulmonary embolism, or breast cancer, or if they had taken oral contraceptives, androgens, and estrogen or progesterone replacement therapy for at least 3 months prior to randomization. The primary end point of the trial was to determine the incidence of IBC. Secondary end points included the incidence of noninvasive breast cancers, invasive cancers other than that of the breast and

uterus, osteoporotic fractures, vascular events, ischemic heart disease, quality of life measurements, and death from any cause.

After a median follow-up of 54.6 months, a 49% reduction in the risk of IBC was observed in the patients treated with tamoxifen (relative risk [RR] =0.51; 95% confidence interval [CI]: 0.39 to 0.66). The cumulative incidence of IBC through 69 months was 43.4 versus 22.2 per 1,000 women in the placebo and tamoxifen groups, respectively. Tamoxifen was found to be effective across all age groups, in patients with a history of LCIS or atypical ductal hyperplasia, and in those with any category of predicted 5-year risk. Tamoxifen reduced the occurrence of IBC in the estrogen receptor (ER)-positive tumors by 69% (RR =0.31; 95% CI: 0.22 to 0.45), but no significant difference in the occurrence of ER-negative tumors was observed.

The incidence of endometrial cancer was elevated in the patients treated with tamoxifen (RR =2.53; 95% CI: 1.35 to 4.97), with most cases occurring in women who were ≥50 years of age. All endometrial cancers in the tamoxifen group were International Federation of Gynecology and Obstetrics stage I. Similarly, vascular events, such as pulmonary embolism (RR =3.10; 95% CI: 1.15 to 19.27) and deep venous thrombosis (RR =1.60; 95% CI: 0.91 to 92.86), were observed with an increased frequency in women who received tamoxifen. An increase in the incidence of stroke was notable in the tamoxifen group (RR =1.59; 95% CI: 0.93 to 2.77); however, this was not statistically significant. The vascular events occurred more frequently in women ≥50 years of age. No difference in the incidence of myocardial infarction, severe angina, and acute ischemic syndrome was evident between the two groups, with the average annual rate of ischemic heart disease being 2.37 versus 2.73 per 1,000 women in the placebo and tamoxifen groups, respectively; however, a reduction in hip, spine, and radius (Colles') fracture was reported in the tamoxifen group. Due to prespecified rules prior to the start of the study, the NSABP-P1 was stopped when a statistically significant reduction in breast cancer incidence with tamoxifen was observed. Women in the placebo arm were then offered tamoxifen, making it difficult to accurately assess the effect of tamoxifen on breast cancer mortality.

In 2005, the NSABP provided the 7-year follow-up results of the above study, which continued to show a reduced incidence of both IBC (RR =0.57; 95% CI: 0.46 to 0.70) and noninvasive breast cancer (RR =0.63; 95% CI: 0.45 to 0.89).[26] A similar increase in the incidence of stroke, deep venous thrombosis, and cataracts were noted with increased follow-up. A 32% reduction in osteoporotic fractures were noted with tamoxifen.

Italian Tamoxifen Prevention Study

The Italian Tamoxifen Prevention Study randomized 5,408 women who had previously undergone a hysterectomy to receive tamoxifen or placebo.[27] The initial results of the trial failed to demonstrate an overall benefit of tamoxifen after a median follow-up of 46 months; however, a statistically significant reduction in IBC was observed among women who received tamoxifen and were also on hormone replacement therapy. The possible lack of benefit from tamoxifen in this study could possibly be due to inclusion of women with low-to-normal risk of breast cancer and of patients receiving concurrent hormone replacement therapy (approximately 14% of all participants). After 11 years of follow-up, the investigators found a statistically significant reduction in the incidence of ER-positive breast cancer among women at high risk (defined as women taller than 160 cm, with at least one intact ovary, with no full-term pregnancy before the age of 24 years, and younger than age 14 years at menarche) treated with tamoxifen (6.26 versus 1.50 per 1,000 woman-years; RR =0.24; 95% CI: 0.10 to 0.59).[28]

The Royal Marsden Hospital Tamoxifen Chemoprevention Trial

The Royal Marsden Hospital Tamoxifen Chemoprevention Trial, which randomized 2,494 women aged 30 to 70 years who also had a family history of breast cancer to tamoxifen or placebo, failed to demonstrate a decreased incidence of ER-positive breast cancer (30 cases in the tamoxifen arm versus 39 in the placebo arm; hazard ratio [HR] =0.77; 95% CI: 0.48 to 1.23).[29] In 2007, the investigators provided an update to this trial with an extended follow-up of 20 years and this showed a statistically significant decrease in the risk of ER-positive breast cancer in the tamoxifen arm (23 cases in the tamoxifen arm and 47 in the placebo arm; HR =0.48; 95% CI: 0.29 to 0.79).[30] The adverse events seen with tamoxifen in the European trials were similar to the NSABP-P1 trial.

International Breast Cancer Intervention Study (IBIS-I)

Another trial testing the efficacy of tamoxifen among women at increased risk of breast cancer in the UK, Australia, and New Zealand was initiated in 1992.[31] With a median follow-up of 49.6 months, the investigators showed that tamoxifen decreased the incidence of breast cancer by 32% (RR =0.68; 95% CI: 0.50 to 50.92). With further follow-up (up to 96 months), the incidence continued to be lower in

the tamoxifen group (27% reduction in IBC; RR =0.73; 95% CI: 0.58 to 50.91).[32] Similar to the NSABP-P1 experience, the benefit of tamoxifen was only seen in ER-positive tumors and an increased risk of thromboembolic events with tamoxifen was reported; however, in contrast to the NSABP-P1 results, the use of hormone replacement therapy for postmenopausal symptoms (at the lowest possible dose) was permitted in the trial and the increased risk of endometrial cancer with tamoxifen was not statistically significant.

In 2003, an overview of the abovementioned tamoxifen prevention trials was published, and there was no reduction in ER-negative IBC; however, there was a statistically significant decrease in the incidence of ER-positive IBC, by 48%.[33] The consensus of endometrial cancer and venous thromboembolic events had a RR of 2.4 and 1.9, respectively; women aged 50 years or older had an increased risk. Overall, there was no effect on the all-cause mortality, but there was a high degree of heterogeneity across various trials.

Several studies have demonstrated that tamoxifen decreases MBD.[34–36] A case-control study nested within the IBIS-I showed a 10% or greater reduction in breast density at the 12- to 18-month mammogram in 46% of women in the tamoxifen group.[37] These women were noted to have a 63% reduction in breast cancer risk (odds ratio [OR] =0.37; 95% CI: 0.20 to 0.69; *P*=0.002). The women who experienced less than a 10% reduction in breast density with tamoxifen had no risk reduction (OR =1.13; 95% CI: 0.72 to 1.77; *P*=0.60). Similar reductions in MBD in the placebo group were not associated with decreased risk of breast cancer; hence, the authors concluded that a 12- to 18-month change in MBD was a good predictor of response to tamoxifen for the prevention of breast cancer.

Raloxifene chemoprevention studies

Raloxifene is an oral, second-generation SERM, which has estrogenic effects on the bone, lipid metabolism, blood clotting, and antiestrogenic effects on the breast and uterus. The US Food and Drug Administration (FDA) initially approved raloxifene for the prevention and treatment of osteoporosis in postmenopausal women.[38]

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial

In this trial, 7,705 postmenopausal women with osteoporosis were randomly assigned to receive raloxifene (60 mg or 120 mg per day) or placebo.[39] The initial results of this trial reported a 30% reduction in the risk of vertebral fractures associated with an increase in bone mineral density in the spine and femoral neck, but the incidence of non-vertebral fractures was not significantly different. The incidence of IBC, which was a secondary end point of the study, was decreased by 76% during the 3 years of treatment and by 72% at 4 years of treatment with raloxifene. The number needed to treat (NNT) to prevent one case of breast cancer was 126.[40,41] Similar to the tamoxifen trials, the benefit of raloxifene was limited to ER-positive breast cancer and an increased risk of venous thromboembolism was observed (RR =3.1; 95% CI: 1.5 to 6.2). Unlike tamoxifen, raloxifene did not increase the risk of endometrial cancer (RR =0.8; 95% CI: 0.2 to 2.7).

The Continuing Outcomes Relevant to Evista (CORE) trial

This was a double-blind, placebo-controlled study that investigated the efficacy of an additional 4 years of raloxifene compared with placebo in decreasing the incidence of IBC in women who had participated in the MORE trial.[42] The primary breast cancer analysis included a total of 5,213 patients (3,996 who had completed MORE when CORE began and 1,217 who were still participating in MORE when CORE began). The 4-year incidences in the raloxifene group of IBC and ER-positive IBC were reduced by 59% and 66%, respectively. Over the 8 years of both trials, the incidences of IBC and ER-positive IBC were reduced by 66% (HR =0.34; 95% CI: 0.22 to 0.50) and 76% (HR =0.24; 95% CI: 0.15 to 0.40), respectively, in patients who received raloxifene.

The Study of Tamoxifen and Raloxifene (STAR) trial (NSABP-P2)

This study was a double-blind, randomized controlled trial that included 19,747 postmenopausal women aged 35 years and older with increased risk of breast cancer,[43] defined as a personal history of LCIS or a 5-year predicted risk for IBC of at least 1.66% as determined by the Gail model.[17] Women with a history of cerebral vascular accidents, transient ischemic attack, pulmonary embolism, deep venous thrombosis, uncontrolled diabetes, uncontrolled hypertension, or atrial fibrillation were excluded from the study. Women were randomly assigned to receive 20 mg of tamoxifen per day plus a placebo or 60 mg of raloxifene per day plus a placebo for a 5-year period. The primary end point was the development of biopsy-proven IBC. The secondary end points of the trial included the incidence of noninvasive breast cancer, uterine cancer, cardiovascular events, stroke, transient ischemic attack, pulmonary embolism, deep venous thrombosis,

osteoporotic fractures, cataracts, life, and death from any cause. Quality of life events were also evaluated. Based on the modified Gail score, the median 5-year risk of developing IBC was 4.03%. The mean age of participants at the time of randomization was 58.5 years and the mean time of follow-up was 3.9 years. Over 70% of women had a history of IBC in a first-degree maternal relative, and more than 20% reported a history of atypical lobular or ductal hyperplasia on breast biopsy prior to enrollment. Approximately 9% of women had a history of LCIS.

There was no difference between the effects of tamoxifen and raloxifene on the incidence of breast cancer. There were 163 cases of IBC in the women assigned to the tamoxifen group, compared to 168 cases in the raloxifene group. The rate per 1,000 woman-years was 4.3 in the tamoxifen group and 4.4 in the raloxifene group (RR =1.02; 95% CI: 0.82 to 1.28). The pathological characteristics of the tumors showed no difference between the treatment groups regarding the distribution by tumor size, nodal status, or ER level. The incidence of noninvasive breast cancer was lower in the tamoxifen group (1.51 per 1,000 women) compared to the raloxifene group (2.11 per 1000 women); however, this difference did not reach statistical significance. There were 57 cases of noninvasive breast cancer among women assigned to the tamoxifen arm and 80 cases among those assigned to raloxifene (RR =1.40; 95% CI: 0.98 to 2.00). There were fewer cases of uterine malignancies in the raloxifene group (23 cases) compared to the tamoxifen group (36 cases), although this difference was also not statistically significant. Annual incidence rates were 1.99 per 1,000 women and 1.25 per 1,000 women in the tamoxifen and raloxifene groups, respectively (RR =0.62; 95% CI: 0.35 to 1.08). It is important to note that approximately 50% of patients in either group had had a hysterectomy prior to enrollment in the trial. The incidence of uterine hyperplasia with or without atypia was significantly less in the raloxifene group. The number of hysterectomies performed for nonmalignant indications was statistically fewer in the raloxifene group (244 tamoxifen versus 111 raloxifene; RR =0.29; 95% CI: 0.30 to 0.50). In addition, no statistically significant difference in the incidence of other malignancies, such as colorectal, lung, leukemia/hematopoietic, or other cancers, were observed between the two treatment groups.

Similarly, no statistically significant differences between the two groups were observed regarding the incidence of stroke, transient ischemic attack, and osteoporotic fractures at the hip, spine, and radius; however, a 30% decrease in the incidence of pulmonary embolism and deep venous thrombosis was noted in the raloxifene arm (100 versus 141 events in the raloxifene versus tamoxifen groups, respectively; RR =0.70; 95% CI: 0.54 to 0.91). Fewer women who received raloxifene developed cataracts (RR =0.79; 95% CI: 0.68 to 0.92). Similar mortality was reported in the two groups (101 deaths in tamoxifen group versus 96 in the raloxifene group; RR =0.94; 95% CI: 0.71 to 1.26).

With respect to patient-reported outcomes for physical health, mental health, and depression, no significant differences were noted between the two SERMs, although relatively better sexual function was reported in the tamoxifen group.[44] Women in the raloxifene cohort reported more musculoskeletal symptoms, such as joint pain, muscle stiffness, and generalized aches and pains. They also more frequently reported vaginal dryness, dyspareunia, and weight gain. In contrast, women in the tamoxifen cohort reported more vasomotor symptoms, including leg cramps and difficulty with bladder control. They also reported genital irritation, vaginal discharge, and bleeding.

Based on the data from STAR and other raloxifene trials, the FDA approved raloxifene for the prevention of IBC in postmenopausal women at increased risk of breast cancer or in postmenopausal women with osteoporosis.[38]

An updated analysis of the STAR trial was performed in 2010 with a median follow-up time of 81 months.[45] There continued to be no statistically significant difference in the incidence of IBC between tamoxifen and raloxifene (RR =1.24; 95% CI: 1.05 to 1.47). There were 137 cases of noninvasive breast cancer in the raloxifene group, and 111 cases in the tamoxifen group (RR =1.22; 95% CI: 0.95 to 91.59); as such, the difference between the two groups was smaller when compared to the original report. Unlike in the initial study, there was a statistically significant decrease in the risk of endometrial cancer with raloxifene (RR =0.55; 95% CI: 0.36 to 30.83). In addition, statistically significant reductions in the incidence of thromboembolic events (RR =0.75; 95% CI: 0.60 to 60.93) and uterine hyperplasia (RR =0.19; 95% CI: 0.12 to 10.29) were reported. No significant mortality differences between raloxifene and tamoxifen were noted.

The Raloxifene Use for the Heart (RUTH) study

The RUTH study also affirmed the benefits of raloxifene in breast cancer.[46] This trial randomized 10,101 postmenopausal women (mean age =67.5 years) with coronary heart disease or risk factors for the same to 60 mg of raloxifene or placebo daily. After a median follow-up of 5.6 years, no difference between the two groups was noted regarding the

cardiovascular end points; however, the incidence of IBC, particularly the ER-positive type, was significantly reduced in the raloxifene group (40 versus 70 events; HR =0.56; 95% CI: 0.38 to 0.83; absolute risk reduction, 1.2 IBCs per 1,000 women treated for 1 year). Similar to other studies, raloxifene was associated with an increased risk of fatal stroke (59 versus 39 events; HR =1.49; 95% CI: 1.00 to 2.24; absolute risk increase, 0.7 per 1,000 woman-years) and venous thromboembolism (103 versus 71 events; HR =1.44; 95% CI: 1.06 to 1.95; absolute risk increase, 1.2 per 1,000 woman-years).

Additional SERMS

The Postmenopausal Evaluation and Risk Reduction with Lasofoxifene (PEARL) study randomly assigned 8,556 postmenopausal women with osteoporosis to receive a placebo or either 0.25 mg or 0.5 mg of lasofoxifene per day.[47,48] A significant reduction in the incidence of ER-positive breast cancer (HR =0.19; 95% CI: 0.07 to 0.56) was reported in women assigned to 0.5 mg of lasofoxifene per day. In addition, the incidence of vertebral and non-vertebral fractures, coronary heart disease events, and stroke were also reduced in this group. A smaller effect on the incidence of ER-positive IBC was noted with 0.25 mg of lasofoxifene per day.

The investigational SERM, arzoxifene, has also been evaluated in postmenopausal women with breast cancer. The GENERATIONS trial was a large, multicenter, double-blind, placebo-controlled study that compared daily dosing of 20 mg of arzoxifene to placebo in 9,354 postmenopausal women with osteoporosis or low bone mass.[49,50] The median follow-up was 48 months. The incidence of IBC was decreased in women assigned to the arzoxifene group (22 cases versus 53 in the placebo group; HR =0.41; 95% CI: 0.25 to 0.68). This reduction was primarily seen in ER-positive breast cancer, which was similar to results with other SERMs.

Role of AIs

High aromatase levels in breast tissues and high circulatory estrogen levels are known risk factors for IBC.[51] Anastrozole, letrozole, and exemestane are known to decrease circulating estrogen levels in postmenopausal women by inhibiting the enzyme aromatase, which catalyzes the conversion of androgens to estrogens. The role of AIs in the adjuvant treatment of postmenopausal women with receptor-positive IBC is well established. A 37% to 55% reduction in the incidence of contralateral breast cancer has been reported with the use of AIs in clinical trials.[52–54] The main side effects of AIs include arthralgia and accelerated bone resorption, and, overall, its safety profile is relatively more favorable when compared to tamoxifen.

AI chemoprevention studies

The NCIC CTG MAP.3 trial

The NCIC CTG MAP.3 trial was a prospective trial that investigated the role of exemestane in reducing the incidence of IBC in postmenopausal women who were determined to be at increased risk.[55] This double-blind trial randomized 4,560 postmenopausal women, who had at least one of the following: age ≥60 years, Gail 5-year risk score greater than 1.66%;[17] prior atypical ductal or lobular hyperplasia or LCIS; or DCIS with mastectomy, to either 25 mg of exemestane per day or placebo. The median age of women who participated in the trial was 62.5 years and the median Gail risk score was 2.3%. The investigators reported a reduction in the incidence of IBC in women assigned to exemestane group (eleven cases) compared with those in the placebo group (32 cases) at a median follow-up of 35 months. A 65% relative reduction in the annual incidence of IBC (0.19% versus 0.55%; HR =0.35; 95% CI: 0.18 to 0.70; P=0.002) with exemestane was reported. The NNT to prevent one case of IBC with exemestane therapy was 94 in 3 years. The annual incidence of IBC plus DCIS (20 in the exemestane group and 44 in the placebo group) was 0.35% and 0.77% in the exemestane and placebo groups, respectively (HR =0.47; 95% CI: 0.27 to 0.79). Eighty-eight percent of women in the exemestane group and 85% in the placebo group experienced adverse events that included hot flashes and arthritis as the most common adverse events in both groups. There were no significant differences between the two groups regarding secondary end points, such as new osteoporosis, skeletal fractures, cardiovascular events, and cancers other than IBC. No treatment-related deaths were reported. Women taking exemestane reported slightly worse menopause-related quality-of-life events when compared with placebo (7% more overall).

IBIS-II

IBIS-II is a multicenter, randomized, double-blind, placebo-controlled Phase III trial that evaluated the AI anastrozole in postmenopausal women at high risk for breast cancer (family history, atypical hyperplasia or LCIS, nulliparity or age 30 or above at first birth, mammographic opacity covering at least 50% of the breast).[56] Anastrozole (1 mg/day) was associated with a 53% reduction in the incidence of IBC and DCIS (primary end point) when compared with placebo after a median follow-up of 5 years (HR =0.47; 95% CI: 0.32 to

68.0; $P<0.0001$). Similar to most chemoprevention trials, the protective effect of anastrozole was seen in ER-positive IBC with no significant effect in the ER-negative subgroup. The total mortality was 0.9% for both arms. Interestingly, a reduction in the incidence of skin, gastrointestinal, and gynecologic cancers, as well as other cancers, was noted in the anastrozole group (2% versus 4%; RR =0.58; 95% CI: 0.39 to 0.85). A significant increase in the incidence of musculoskeletal events such as aches and pain, vasomotor symptoms, dryness of the eyes, and hypertension were observed in the anastrozole arm. Bone fractures occurred in 7.7% of those on placebo compared to 8.5% of women receiving anastrozole. Based on the results of this trial, anastrozole may be an effective chemopreventive option for postmenopausal women.

Recently, a meta-analysis based on individual participant data from nine randomized prevention trials using tamoxifen, raloxifene, arzoxifene, and lasofoxifene was reported.[57] These included The Royal Marsden Hospital Tamoxifen Trial, IBIS-I, NSABP-P1, Italian Tamoxifen Prevention Study, MORE/CORE, RUTH, STAR, PEARL, and GENERATIONS. Median follow-up time was 65 months. Overall, a 38% reduction in the incidence of breast cancer (including DCIS) was noted (HR =0.62; 95% CI: 0.56 to 0.69), with the largest reduction in the first 5 years of follow-up compared to years 5 to 10. The estimated 10-year cumulative incidence was 6.3% in the control group and 4.2% in the SERM group. It was determined that 42 women would need to be treated to prevent one breast cancer event in the first 10 years of follow-up. A statistically significant overall reduction by 31% in the incidence of DCIS was reported, with 38% reduction in the tamoxifen trials but no effect for raloxifene.

The investigators noted a significant reduction in all breast cancers and ER-positive breast cancers with 0.5 mg of lasofoxifene per day compared with placebo; however, there was a nonsignificant increase in the incidence of ER-negative IBC (HR =1.43; 95% CI: 0.43 to 1.66) and a nonsignificant decrease for DCIS (HR =0.76; 95% CI: 0.26 to 2.21) with lasofoxifene (both 0.5 mg and 0.25 mg per day). Similarly, arzoxifene decreased overall IBC and ER-positive breast cancer incidence by 58% and 70%, respectively. No effect was noted on ER-negative breast cancers, while there was a small reduction in DCIS (HR =0.30; 95% CI: 0.08 to 1.09). Overall, a higher rate of endometrial cancer was noted in women receiving a SERM as compared with placebo (HR =1.56; 95% CI: 1.13 to 2.14; $P=0.007$). This increase was limited to the first 5 years of follow-up and primarily to the tamoxifen trials. No increase in the incidence of endometrial cancer was seen in the raloxifene trials. An increased risk was also seen with arzoxifene (HR =2.26; 95% CI: 0.70 to 7.32; $P=0.2$).

An overall increase in the incidence of venous thromboembolic events was noted, with both tamoxifen and raloxifene demonstrating a similar risk (OR =1.60; 1.21 to 2.12; $P=0.001$ versus OR =1.45; 1.18 to 1.76; $P<0.0001$). The rate was higher for arzoxifene and lasofoxifene. Overall, no effect of SERMs was noted for myocardial infarction, stroke, or transient ischemic attack. The authors reported a 34% reduction in vertebral fractures and smaller reduction for non-vertebral fractures.

Other chemopreventive agents under investigation

The protective role of aspirin on the risk of breast cancer has been investigated in several studies, with mixed conclusions. Moderate reduction in breast cancer risk was reported in few studies;[58,59] however, no difference in the incidence of breast cancer was observed with alternate-day dosing of low-dose aspirin after 10 years of follow-up in a randomized trial.[60] Similarly, in a report by the Nurses' Health Study, no association was found between the use of aspirin, nonsteroidal anti-inflammatory drugs, or acetaminophen and the incidence of breast cancer;[61] however, in this study, there was a suggestion of the possible role of aspirin use as a secondary chemopreventive agent on those women who had a prior diagnosis of IBC. Aspirin use has been associated with a decreased risk of breast cancer death.[62]

Hyperinsulinemia has been reported to be an independent risk factor for breast cancer.[63] A recent meta-analysis of seven observational studies demonstrated a protective effect of metformin on breast cancer risk in postmenopausal women with diabetes (combined OR =0.83; 95% CI: 0.71 to 0.97).[64] A lower incidence of breast cancer was also seen in the diabetic postmenopausal women participating in the Women's Health Initiative clinical trials who received metformin (HR =0.75; 95% CI: 0.57 to 0.99);[65] however, dedicated randomized clinical trials will be needed to assess the efficacy of metformin for primary prevention of breast cancer. Evidence from preclinical studies demonstrates that 27-hydroxycholesterol, a primary metabolite of cholesterol, mimics estrogen and can drive the growth of breast cancer cells.[66] Data from observational studies are conflicting, however, and randomized trials to investigate the role of statins in breast cancer are ongoing.

American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines

In July 2013, ASCO updated its clinical practice guidelines for the use of pharmacologic agents to reduce the incidence

of breast cancer.[67] The recommendations included a discussion of the use of tamoxifen (20 mg per day) in women (35 years or older), who are at increased risk of breast cancer. In postmenopausal women, raloxifene (60 mg per day for 5 years) and exemestane (25 mg per day for 5 years) may be an alternative to tamoxifen (we presume anastrozole will also be included in future guidelines after the recent presentation of the results of the IBIS-II trial). Increased risk of breast cancer was defined as a 5-year projected absolute risk of breast cancer ≥1.66% (using the National Institute of Cancer Breast Cancer Risk Assessment Tool[17] or an equivalent measure) or women with LCIS. The use of tamoxifen or raloxifene was not recommended for women with a history of deep venous thrombosis, pulmonary embolism, stroke or transient ischemic attack; during prolonged immobilizations; in women who are pregnant or may become pregnant; or nursing mothers. Discussions with patients and health care providers should include the risks and benefits of the agents under consideration.

Currently, there are no data from Phase III randomized trials on the protective effect of raloxifene and AIs in *BRCA-1/2* mutation carrier, however there are limited data on the effectiveness of tamoxifen for the reduction of breast cancer risk in *BRCA-1/2* mutation carriers. In the NSABP-P1, 19 of the 288 women who developed breast cancer had *BRCA-1/2* mutations. A statistically significant effect on breast cancer risk was not observed with tamoxifen in women with *BRCA-1* (RR =1.67; 95% CI: 0.32 to 10.70) or *BRCA-2* (RR =0.38; 95% CI: 0.06 to 1.56) mutations.[68]

The role of diet and nutrition

The association between various dietary factors and the risk of breast cancer has been controversial due to the lack of randomized prospective studies. An international panel of the World Cancer Research Fund and American Institute for Cancer Research concluded that alcohol intake increased the risk of breast cancer for all age groups.[69] Some of the mechanisms postulated include carcinogenic metabolites of alcohol, such as acetaldehyde or oxygen radicals, interference with folate or estrogen metabolism, and several nutrient deficiencies associated with alcohol intake.[6] A 10% increase in the risk of breast cancer for every 10 grams of alcohol consumed each day was demonstrated in some studies.[70,71] Interestingly, the excess risk due to alcohol consumption may be reduced or mitigated by adequate folate consumption.[72–74] Additionally, the role of dietary fat as a possible risk factor for IBC has been considerably investigated, and a nonsignificant increase in the rate of breast cancer (6% to 11%) was reported.[69,75] In the Women's Health Initiative Randomized Controlled Dietary Modification trial, a nonsignificant decrease in breast cancer risk was noted (RR =0.91; 95% CI: 0.83 to 1.02) in women with a reduced intake of animal fat.[76] Similarly, a large prospective study demonstrated a small increase in the risk of IBC with increased intake of dietary fat.[69] Red meat intake has also been linked to breast cancer risk. A modest association between the two was reported in a meta-analysis of case-control and cohort studies; however, this was not observed in a pooled analysis of prospective studies.[75–77] An increased breast cancer risk was seen among women with high red meat intake in the UK Women's Cohort Study (12% increase risk per 50 g increment of meat each day).[78] The influence of BMI on the risk of breast cancer has also been well characterized. It has also been reported that women with a higher BMI are at a lower risk of breast cancer before menopause, but have an increased risk in the postmenopausal stage.[69] The prospective Nurses' Health Study II, with 116,000 women being followed since 1989, has prespecified objectives to assess the role of risk factors such as dietary fiber, saturated and unsaturated fat, plasma levels of insulin-like growth factor, low-dose oral contraceptive pills, breast-feeding, and physical activity among younger nurses.[79] In summary, there is currently no conclusive evidence based on randomized controlled trials that a specific dietary intervention or weight loss will decrease the risk of developing IBC.

The role of surgery

Up to 10% of breast cancers result from specific genetic mutations in the *BRCA-1*, *BRCA-2* (hereditary breast/ovarian cancer syndrome), *CHEK2* and *p53* (Li–Fraumeni syndrome), and *PTEN* (Cowden syndrome) genes.[80–82] Women who meet one or more of the following familial/hereditary breast cancer risk criteria should be referred to a cancer genetic counselor for further evaluation: individuals from a family with known mutations that increase their risk of breast cancer (*BRCA-1*, *BRCA-2*, CDH1, STK11, and TP53) or genes associated with breast cancer; a family history of two or more breast primaries in a single individual; two or more members with breast primaries on the same side of the family; first- or second-degree relative ≤45 years of age with breast cancer; one or more primary ovarian cancers on the same side of the family; family history of male breast cancer; or one or more family members on the same side of the family with an aggressive early-onset cancer in addition to breast cancer.[83] Risk-reduction surgery may be considered in women who have a strong family history of breast and/or ovarian cancer and in

women with known *BRCA-1/BRCA-2* mutation.[83] For those patients who are carriers of such high-risk mutations but desire to delay or omit risk-reduction surgery, specific guidelines for follow-up have been developed, such as annual mammography and breast magnetic resonance imaging screening, beginning at age 25 years or 10 to 15 years earlier than the younger family member with a diagnosis of breast cancer, and twice-yearly ovarian cancer screening with transvaginal ultrasound and serum CA-125 levels, beginning at age 30 years or 5 to 10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family.[83,84] The US Preventive Services Task Force, ASCO, and the National Comprehensive Cancer Network have outlined indications and guidelines for testing hereditary breast cancer syndromes in select patient populations that have been determined to have an increased probability of being mutation carriers. Several studies have demonstrated that bilateral risk-reduction mastectomy can decrease the risk of developing breast cancer by at least 90% in moderate-to-high-risk women and in known *BRCA-1/2* mutation carriers.[85–88] Additionally, bilateral risk-reduction salpingo-oophorectomy (RRSO) may also decrease the risk of breast cancer in *BRCA-1/2* mutation carriers.[83,89–92] This is likely due to a reduction in estrogen exposure.[83] Rebbeck et al demonstrated a statistically significant reduction in breast cancer risk with RRSO in *BRCA* mutation carriers with an adjusted HR of 0.53 (95% CI: 0.33 to 0.84).[91] In a case-control study by Eisen et al, a breast cancer risk reduction of 56% for *BRCA-1* carriers (OR =0.44; 95% CI: 0.29 to 0.66) and 46% for *BRCA-2* carriers (OR =0.57; 95% CI: 0.28 to 1.15) was reported.[89] RRSO performed before age 40 years (OR =0.36; 95% CI: 0.20 to 0.64 for *BRCA-1* carriers) was associated with a greater risk reduction than after age 40 years (OR =0.53; 95% CI: 0.30 to 0.91). A recent meta-analysis supported the protective role of RRSO in *BRCA-1/2* mutation carriers by demonstrating a statistically significant reduction in risk of breast cancer (HR =0.49; 95% CI: 0.37 to 0.65).[90] Similar risk reductions were observed in *BRCA-1* mutation carriers (HR =0.47; 95% CI: 0.35 to 0.64) and in *BRCA-2* mutation carriers (HR =0.47; 95% CI: 0.26 to 0.84). In contrast, a prospective study by Kauff et al showed a greater reduction in breast cancer risk for *BRCA-2* mutation carriers (HR =0.28; 95% CI: 0.08 to 0.92) compared with *BRCA-1* mutation carriers (HR =0.61; 95% CI: 0.30 to 1.22).[93]

Some of the adverse effects of risk-reduction surgery include the increased probability of osteoporosis, cardiovascular disease associated with premature menopause, vasomotor symptoms that negatively affect quality of life, and psychosocial effects of prophylactic mastectomy. Hence, women who are considering this approach should undergo a multidisciplinary evaluation to discuss the risks and benefits of the surgery as well as options for breast reconstruction.

Discussion

Several large, randomized clinical trials have established the role of SERMs in breast cancer prevention. Currently, in the US, tamoxifen and raloxifene are FDA-approved for this indication. Additionally, the MAP.3 and IBIS-II studies demonstrated that the incidence of ER-positive IBC was decreased by the AIs exemestane and anastrozole, respectively.[55,56] These agents may have a relatively favorable adverse event profile compared to tamoxifen or raloxifene in postmenopausal women; however, head-to-head comparison of the these drugs is needed to ascertain this.

Most chemoprevention trials were similar in purpose and overall design. A majority of the women included in these trials were white (for example, 96.5% in NSABP-P1 and 95.7% in MORE);[25,39] thus, it is difficult to establish if their results can be extrapolated to nonwhite women. As all patients participating in this trial were subjected to scheduled follow-ups with breast exams and regular annual mammography, and considering that these chemopreventive interventions did not show a statistically significant decrease in ER-negative breast cancer and no change in breast cancer-specific or all-cause mortality, it has been proposed that these drugs may be treating only small, occult ER-positive breast cancers, or may be delaying its diagnosis by at least a decade; however, this effect is rather difficult to establish. The role of these agents in women with risk factors such as *BRCA-1/BRCA-2* mutation carrier status, previous chest radiation, and increased MBD has not been well studied in the existing trials. The trials differed in the overall number and median age of women, definition of increased breast cancer risk in the study participants, end points of the study, and compliance and continuation rates of participants.[94] The European studies allowed the use of hormone replacement therapy, while the NSABP-P1 and -P2 studies did not allow this. It is difficult to determine if this influenced the incongruity in the results between these trials. The women included in the Italian trial had a lower risk of breast cancer than the general population, as approximately half of the women (48.3%) had an oophorectomy at the time of study entry.[27]

Freedman et al estimated that over 2 million women in the US could benefit from chemoprevention to reduce the risk of breast cancer.[95] Based on the NSABP-P1, the NNT with daily tamoxifen for more than 5 years to prevent one case of breast cancer is 48 women; the NNT for raloxifene over

4 years is 112 to 125 women, based on the RUTH, MORE, and STAR trials; the NNT for exemestane is 94 in 3 years and 26 in 5 years, based on the MAP.3 trial; and the NNT for anastrozole in the IBIS-II trial to prevent one case of IBC in 7 years was 36 women. These numbers are comparable to the NNT for interventions commonly recommended by primary care physicians, for example, statins for the primary prevention of myocardial infarction, for which the NNT is 60.[96] An analysis of data from the National Health Interview Survey in 2010, however, suggested that there was no overall increase in the use of chemopreventive agents from the year 2000 to 2010, with a slight increase in the use of raloxifene as compared with tamoxifen in postmenopausal women.[97] Possible explanations for the limited use of chemopreventive agents include: difficulty in identifying the ideal candidates for chemoprevention strategies; decreased awareness among high-risk women and health care providers; concerns about adverse effects of the agents; and their impact on quality of life in the absence of a diagnosed cancer. Identifying the optimal candidates for chemoprevention strategies continues to be challenging, as the existing breast cancer risk-assessment models do not incorporate all known risk factors, such as alcohol intake, use of oral contraceptive pills, density of breast tissue, and history of radiation exposure. Additionally, there is significant variability in the risk factors included in different models, and, overall, the threshold for inclusion into these trials had low discriminatory accuracy to predict an individual's real probability of developing breast cancer, as most women aged 60 years and older without other significant risk factors would meet inclusion criteria by age alone.

The decision to use pharmacotherapy and the choice of the agent should be tailored to each woman by considering her age; menopausal status; gynecologic history (early age at menarche, older age at first live birth); medical history (previous thromboembolic events, history of endometriosis or endometrial hyperplasia, history of LCIS or atypical hyperplasia, history of thoracic radiation between the ages of 10 and 30 years);[98] family history of breast cancer; quantified estimate of developing breast cancer using various risk-assessment models, as outlined earlier; and the impact of therapy on the patient's quality of life. This would entail a detailed discussion with the patient about the risks and benefits of each treatment option. Freedman et al developed a benefit/risk index to quantify benefits from utilizing tamoxifen or raloxifene for women older than 50 years based on their 5-year projected risk for IBC, as determined by the Gail model, race, and history of hysterectomy.[99] Based on this decision model, the authors concluded that, over a 5-year period, raloxifene had a better benefit/risk index than tamoxifen in postmenopausal women with an intact uterus, whereas, for postmenopausal women without a uterus, the index was similar for raloxifene and tamoxifen.

An important point that is often overlooked is that active surveillance in most of the discussed trials ended with the completion of therapy, and, thus, important long-term outcomes of safety and efficacy may have been underreported. It may be also be interesting to determine if a longer duration of treatment with these agents is associated with a more favorable benefit/risk index.

It is important to note that the role of chemopreventive agents in patients with hereditary predisposition to breast cancer is not well established. More modern clinical trials are investigating the chemopreventive role of agents such as lovastatin (ClinicalTrials.gov identifier: NCT00285857), atorvastatin (NCT00637481), letrozole (NCT00673335), vitamin D (NCT00976339), and insulin-like growth factor inhibitors (NCT01372644), to name a few.[100–104] Regardless of the choice of the agent, women who receive pharmacotherapy for breast cancer prevention should adhere to recommended surveillance guidelines and be monitored for potential treatment-related adverse events.

Future research needs to include the development of: 1) tools that enable providers to accurately identify women at high risk for breast cancer, particularly hormone-positive breast cancer; 2) agents that may prevent hormone receptor-negative breast cancer; 3) agents with fewer side effects; 4) interventions for effective education and communication of benefits and risks of chemoprevention; 5) clinical trials to discern the effect of chemoprevention in patients with known/suspected hereditary breast cancer; and 6) means to integrate various risk-reduction approaches.

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