Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention

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INTRODUCTION

For women at high risk for breast cancer, endocrine therapy can reduce the risk of invasive and/or in situ breast cancers. This topic will discuss the use of endocrine therapy in women at increased risk for breast cancer. Screening for breast cancer, surgical approaches to prevent breast cancer among high-risk women with a hereditary cancer syndrome, and the risk factors for the development of breast cancer are discussed separately.

- (See "Screening for breast cancer: Strategies and recommendations".)
- (See "Overview of hereditary breast and ovarian cancer syndromes".)
- (See "Factors that modify breast cancer risk in women".)
- (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Risk-reducing surgery'.)

INDICATIONS

For women who are at an increased risk for breast cancer, we agree with guidelines from the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the United States Preventive Services Task Force (USPSTF) and suggest endocrine therapy (tamoxifen, raloxifene, anastrozole, or exemestane) for breast cancer prevention [1-7]. Although any of these are reasonable options, only tamoxifen and raloxifene are approved by

the US Food and Drug Administration (FDA) for primary prevention against breast cancer. Selection criteria used in the breast cancer prevention trials varied somewhat [8-11]. Our criteria are the same as those adopted by ASCO and include [5]:

- Age of 35 years or older with a life expectancy of at least 10 years and one of the following:
  - A history of thoracic radiation administered prior to 30 years of age.
  - A history of lobular carcinoma in situ. (See "Atypia and lobular carcinoma in situ: High-risk lesions of the breast".)
  - A ≥1.7 percent five-year risk for breast cancer. (See "Screening for breast cancer: Strategies and recommendations", section on 'Clinical use of risk prediction models'.)
  - Atypical hyperplasia. (See "Atypia and lobular carcinoma in situ: High-risk lesions of the breast".)

In general, the risk-benefit ratio for primary prevention will be more favorable for younger women, those without a uterus, and those at highest risk of developing breast cancer. Our general approach to choice of agent is based upon whether or not a woman is menopausal, as discussed in the sections below. (See 'Postmenopausal women' below and 'Premenopausal women' below.)

Although mastectomy is an option to prevent breast cancer, it is only recommended in women with a pathogenic/likely pathogenic genetic mutation conferring a high risk for breast cancer, compelling family history, or possibly with prior thoracic radiation at <30 years of age [5]. For those with breast cancer susceptibility gene 1 (*BRCA1*) and breast cancer susceptibility gene 2 (*BRCA2*) mutations who do not undergo mastectomy, limited retrospective data suggest a benefit with tamoxifen [12]. (See 'BRCA carriers' below.)

There are no data on the use of either the selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) for breast cancer prevention in men. Given the low overall incidence of breast cancer in men and the lack of data to inform the benefits versus risks of chemoprevention, we do not use these agents in men as primary prevention against breast cancer.

POSTMENOPAUSAL WOMEN

We agree with guidelines from the United States Preventive Services Task Force (USPSTF) [4,6] and the American Society of Clinical Oncology (ASCO) [5], both of which support the

administration of endocrine therapy for women at high risk for breast cancer. However, it should be noted that none of the primary prevention trials have shown a difference in breast cancer-specific or overall survival.

For postmenopausal women at increased risk for breast cancer, we suggest endocrine therapy for prevention with treatment administered for a total of five years. Both SERMs and AIs appear to be reasonable options, although there are no AIs approved by the US Food and Drug Administration (FDA) for this indication.

Choice of agent — A choice among agents in **postmenopausal** women should be individualized based on their comparative risk profiles and patient preferences.

- For women **with normal bone mineral density**, either a SERM or an AI are appropriate, with a choice between them driven by patient preferences regarding toxicity profiles. SERMs and AIs have not been directly compared in this setting, but indirect comparisons suggest modestly improved outcomes with AIs, and potentially better risk-benefit ratio in older patients. Baseline risk of thromboembolism, cataracts, and uterine cancer increases with advancing age. Thus, for older women (>60 years), especially those with intact uterus, an AI may be more appealing compared with a SERM. However, a SERM is an acceptable alternative for those who wish to avoid the risks of an AI (eg, arthralgias, osteoporosis). We monitor bone mineral density in patients on treatment with AI. (See 'Aromatase inhibitors' below.)

- For postmenopausal women with **baseline osteopenia/osteoporosis**, we suggest a SERM rather than an AI. However, some women who would prefer to avoid the risks of a SERM (eg, thromboembolic disease and endometrial cancer) may reasonably opt for an AI instead, with appropriate treatment for their loss of bone density. (See 'SERMs' below.)

- For postmenopausal women who are not candidates for a SERM (eg, personal history of thromboembolic event), an AI is appropriate.

- When using an AI, both anastrozole and exemestane appear to be comparably effective. (See 'Aromatase inhibitors' below.)

- When using a SERM, we offer raloxifene if patients are more concerned about uterine cancer and thromboembolic risks than their risk of breast cancer. By contrast, for women who are more concerned about breast cancer prevention or have had a hysterectomy, we offer tamoxifen. (See 'Tamoxifen versus raloxifene' below.)

SERMs — Both tamoxifen and raloxifene are reasonable options for women at an increased risk of breast cancer. When administered for prevention in the trials below, treatment was generally administered for five years. Treatment length varies for women with history of invasive breast cancer. SERMs have both estrogen agonist and antagonist activity depending upon the target tissue, as described below. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Duration of endocrine treatment'.)

Raloxifene appears to be a less potent SERM than tamoxifen, with a smaller reduction in new cancers, but the risk of endometrial cancer and thrombosis are also less with raloxifene, as discussed below. (See 'Tamoxifen versus raloxifene' below.)

Tamoxifen

Benefits relative to placebo — In the normal breast and in breast cancer cells, tamoxifen blocks the effects of endogenous estrogen. By contrast, it produces estrogen-like effects in the uterus, bone, liver, and coagulation system. In addition to being a treatment option for hormone receptor-positive breast cancer, it is approved in the United States for use as prevention in women considered at high risk for breast cancer.

The benefits of tamoxifen were summarized using data from four trials in the 2013 USPSTF meta-analysis, updated in 2019 [6,13]. In trials enrolling both pre-and postmenopausal women, compared with placebo, a three- to five-year course of tamoxifen resulted in:

- A reduction in the risk of invasive breast cancer (7 cases in 1000 women over five years; risk ratio [RR] 0.69, 95% CI 0.59-0.84). This was seen as a reduction in the risk of estrogen receptor-positive, but not estrogen receptor-negative, breast cancer.
- A significant reduction in the incidence of nonvertebral fractures (3 cases in 1000 women; RR 0.66, 95% CI 0.45-0.98).
- No difference in breast cancer-specific or all-cause mortality.
- Subset analyses of individual trials showed benefit in both pre- and postmenopausal women. Data specifically in premenopausal women are discussed below. (See 'Tamoxifen' below.)

Longer-term data, available from some of these trials, showed that the benefit of therapy extended beyond the course of treatment. For example, in IBIS-I, the benefit of tamoxifen was fairly constant over time and extended for at least 10 years (ie, five years beyond completion of treatment) [14]. A modeling study, incorporating the data on risk of late recurrence in estrogen

receptor-positive breast cancer, suggested that the lifetime absolute risk reduction associated with a five-year course of tamoxifen and radiographic screening was 95 invasive breast cancers and 42 breast cancer deaths per 1000 high-risk women (defined as having a ≥3 percent five-year risk of developing breast cancer) compared with similar patients who did not undergo chemoprevention or screening [15].

While the benefits of tamoxifen are now well established, treatment is also associated with several risks, as discussed elsewhere. (See "Managing the side effects of tamoxifen and aromatase inhibitors".)

These include the following [4]:

- An increased incidence of thromboembolic events (5 cases in 1000 women with a five-year course of tamoxifen [6]). Of note, the risk of tamoxifen-related thromboembolic events does not appear to be related to the presence of mutations that promote blood coagulation, including factor V Leiden or prothrombin G20210A [16]. (See "Factor V Leiden and activated protein C resistance".)

- An increased incidence of endometrial cancer (4 cases in 1000 women [6]). In one of the trials evaluating tamoxifen versus placebo, IBIS-I, the risk of endometrial cancer was elevated with tamoxifen in the first five years of treatment (odds ratio [OR] 3.76, 95% CI 1.20-15.56), but not after five years (OR 0.64 with 5- to 10-year follow-up, 95% CI 0.21-1.80) [17]. The modeling study discussed above found an absolute increase of 11 cases of endometrial cancer per 1000 women, with a five-year course of tamoxifen [15].

Risks of thromboembolic events and endometrial cancer with tamoxifen are age-related, increasing with advancing age [18].

While the risks of tamoxifen are increased compared with placebo, it is important to note that the overall incidence of adverse events appears to be small. In addition, two studies have addressed quality of life (QOL) issues in women enrolled in placebo-controlled trials of tamoxifen for the prevention of breast cancer [19,20]. Compared with women receiving placebo, tamoxifen use was not associated with any significant differences in depression, anxiety, major psychosocial outcomes, or overall QOL. However, anecdotal evidence suggests that tamoxifen may induce worsening of these events in occasional patients with pre-existing conditions.

Dose and duration — The standard dose of tamoxifen is 20 mg orally daily administered for five years, although lower-dose strategies and a duration of three years have been explored in patients with intraepithelial neoplasia (defined as atypical ductal hyperplasia [ADH], lobular carcinoma in situ [LCIS], and ductal carcinoma in situ [DCIS]). Although we continue to suggest

the 20 mg daily dose for five years given more data and longer follow-up, 5 mg daily is a reasonable alternative for those who are not tolerating the higher dose despite measures to manage side effects, and would otherwise discontinue treatment. Given that 5 mg pills are not commercially available, using 10 mg on alternate days is reasonable due to tamoxifen's long half-life. We encourage patients to complete a five year course, if tolerated, although some patients choose to discontinue earlier, due to toxicities. (See "Managing the side effects of tamoxifen and aromatase inhibitors".)

In a trial enrolling 500 women with intraepithelial neoplasia, patients who were randomly assigned to three years of tamoxifen at 5 mg daily had one-half the neoplastic events (DCIS or invasive cancer) as those assigned to placebo, at a median follow-up of five years (hazard ratio [HR] 0.48, 95% CI 0.26-0.92) [21]. At longer follow up of a median of 9.7 years, there were 25 neoplastic events with tamoxifen and 41 with placebo (HR 0.58, 95% CI 0.35-0.95). The subgroup with DCIS also experienced benefits with low dose tamoxifen (HR 0.50, 95% CI 0.28-0.91) [22]. There was a trend towards greater improvement in post- versus premenopausal patients, although this did not achieve statistical significance [23,24]. Patient-reported outcomes were not different between arms except for a slight increase in frequency of daily hot flashes with tamoxifen [21].

Although the 5 and 20 mg doses have never been directly compared, the relative reduction in invasive cancer for full-dose tamoxifen compared with placebo in NSABP-1 was comparable (risk ratio 0.57) [8].

The majority (70 percent) of patients in this trial had DCIS [21]. These data are discussed in more detail elsewhere. (See "Ductal carcinoma in situ: Treatment and prognosis", section on 'Tamoxifen'.)

Raloxifene — Raloxifene is another option for postmenopausal women who may be at an increased risk for tamoxifen-related complications. Raloxifene has estrogenic effects on bone and lipids, but estrogen antagonist effects on the breast and uterus [25]. In addition to its approval by the FDA as an agent for breast cancer prevention, it is approved for the treatment of postmenopausal osteoporosis.

The benefits and risks of raloxifene were also summarized using data from two trials in postmenopausal women in the 2013 USPSTF meta-analysis, updated in 2019 [6,13]. Compared with placebo, raloxifene resulted in:

- A reduction in the risk of invasive breast cancer (9 cases in 1000 women; RR 0.44, 95% CI 0.24-0.80). As with tamoxifen, the risk was reduced primarily for the development of estrogen receptor-positive breast cancers.

- A reduction in the incidence of vertebral fractures (7 cases in 1000 women; RR 0.61, 95% CI 0.53-0.73).
- No increased incidence of endometrial cancer.
- No difference in breast cancer-specific or all-cause mortality.

Tamoxifen versus raloxifene — The STAR trial directly compared tamoxifen with raloxifene. Tamoxifen was slightly more effective at preventing invasive breast cancer (RR 1.24, 95% CI 1.05-1.47) [26,27]. Although both tamoxifen and raloxifene increased the risk of thromboembolic events compared with placebo (by approximately 7 to 9 events per 1000 women over five years), the risk was greater with tamoxifen (by approximately 5 cases per 1000 women). In addition, tamoxifen resulted in greater risks of cataracts and endometrial cancer (particularly in women 50 years or older).

These data show that both SERMs are effective agents as chemoprevention among women at higher risk of breast cancer. Decisions about whether to start a SERM and which agent are discussed below. (See 'Indications' above and 'Choice of agent' above.)

Aromatase inhibitors — The AIs suppress plasma estrogen levels by inhibition of the enzyme aromatase, which is responsible for the peripheral conversion of androgens to estrogens. Of the AIs, only anastrozole [28,29] and exemestane [30] have been evaluated for primary prevention, and both showed reductions in new breast cancers relative to placebo (HR 0.47 and 0.51 for anastrozole versus placebo in two randomized trials; HR 0.35 for exemestane relative to placebo).

Although AIs have not been directly compared with SERMs for breast cancer chemoprevention, in the adjuvant setting, where AIs are a standard option for postmenopausal women with breast cancer, AIs are slightly superior to tamoxifen. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Versus tamoxifen'.)

Furthermore, a Cochrane network meta-analysis of trials enrolling over 30,000 women at above-average risk for breast cancer suggests that AIs reduce breast cancer incidence by approximately one-third compared with tamoxifen (relative risk for exemestane or anastrozole versus tamoxifen 0.67, 95% CI 0.46-0.98) [26]. However, these conclusions were based on low-quality evidence and derived from indirect, cross-trial analyses rather than head-to-head comparisons.

Although AIs are not associated with the increased risks of thromboembolic events observed with SERMs, they may be associated with a loss of bone density. It is therefore important to obtain a baseline bone density and evaluate fracture risk prior to starting an AI [5], as well as routinely during treatment. (See "Evaluation and management of aromatase inhibitor-induced bone loss".)

PREMENOPAUSAL WOMEN

Tamoxifen — For premenopausal women at high risk for breast cancer, we suggest tamoxifen for five years rather than observation, which is consistent with the recommendations of the American Society of Clinical Oncology and the United States Preventive Services Task Force [2,31]. AIs are contraindicated in women with intact ovarian function. There are no data on the efficacy of raloxifene for breast cancer prevention among premenopausal women.

In general, the relative risk reduction observed in trials of tamoxifen versus placebo is comparable between postmenopausal and premenopausal women. For example, in IBIS-I, which enrolled approximately 50 percent premenopausal women, the breast cancer event rate was 4.2 per 1000 woman-years versus 6.25 per 1000 woman-years in the placebo group, for a relative risk of 0.67 (95% CI 0.47-0.95) [14]. By comparison, among postmenopausal women, the relative risk for tamoxifen versus placebo was 0.77.

SPECIAL CONSIDERATIONS

BRCA carriers — The use of tamoxifen in patients with pathogenic breast cancer susceptibility gene (*BRCA*) variants is discussed elsewhere. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Tamoxifen'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary breast and ovarian cancer" and "Society guideline links: Breast cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Medications for the prevention of breast cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- A major public health focus is the prevention of breast cancer. Among women at high risk for breast cancer, endocrine therapy can reduce the risk of the development of invasive and/or in situ breast cancers. (See 'Introduction' above.)
- For women at an increased risk for developing breast cancer, we suggest endocrine therapy rather than observation (**Grade 2B**). (See 'Indications' above.)
  - Our criteria include age 35 years or older with a life expectancy of at least 10 years and one of the following:
    - A history of thoracic radiation administered prior to 30 years of age.
    - A history of lobular carcinoma in situ. (See "Atypia and lobular carcinoma in situ: High-risk lesions of the breast".)
    - A ≥1.7 percent five-year risk for breast cancer. (See "Screening for breast cancer: Strategies and recommendations", section on 'Clinical use of risk prediction models'.)
    - Atypical hyperplasia.

- For **postmenopausal** women, our approach is as follows (see 'Postmenopausal women' above):

  - For women **with normal bone mineral density**, either a selective estrogen receptor modulator (SERM) or an aromatase inhibitor (AI) are appropriate, with a choice between them driven by patient preferences regarding toxicity profiles.

    - SERMs and AIs have not been directly compared in this setting, but indirect comparisons suggest modestly improved outcomes with AIs, and potentially better risk-benefit ratio in older patients. Baseline risk of thromboembolism, cataracts, and uterine cancer increases with advancing age. Thus, for older women (>60 years), especially those with intact uterus, an AI may be more appealing compared with a SERM. However, a SERM is an acceptable alternative for those who wish to avoid the risks of an AI (eg, arthralgias, osteoporosis).

    - We monitor bone mineral density in patients on treatment with AI. (See 'Aromatase inhibitors' above.)

  - For postmenopausal women with **baseline osteopenia/osteoporosis**, we suggest a SERM rather than an AI alone (**Grade 2C**). However, some women who would prefer to avoid the risks of a SERM (eg, thromboembolic disease and endometrial cancer) may reasonably opt for an AI instead, with appropriate treatment for their loss of bone density. (See 'SERMs' above.)

  - When using an AI, both anastrozole and exemestane appear to be comparably effective. (See 'Aromatase inhibitors' above.)

  - When using a SERM, we offer raloxifene if patients are more concerned about uterine cancer and thromboembolic risks than their risk of breast cancer. By contrast, for women who are more concerned about breast cancer prevention or have had a hysterectomy, we offer tamoxifen. (See 'Tamoxifen versus raloxifene' above.)

- For **premenopausal** women at high risk of breast cancer, we suggest tamoxifen rather than observation (**Grade 2B**). These women are not candidates for an AI or raloxifene. (See 'Premenopausal women' above.)

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Contributor Disclosures

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