JAMA Insights | WOMEN'S HEALTH

Medications for Primary Prevention of Breast Cancer

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Breast cancer is the most common non–skin cancer and the second-leading cause of death from cancer among women, with an estimated 276 000 new cases diagnosed each year in the US.[1] Breast cancer screening leads to early detection, but does not prevent the development, of breast cancer. Several medications are effective at reducing breast cancer incidence. For instance, randomized trials have shown that taking tamoxifen for 5 years reduces breast cancer risk for 20 years, but the adverse effects stop after the medication is stopped.[2] Despite this, use of medications for primary prevention of breast cancer has been low.[3] Reasons for low uptake include women's low perceived need for preventive therapy and their concerns about the harms of treatment.[3] This article provides an overview of the risks and benefits of medications for breast cancer risk reduction to promote their appropriate use.

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Audio and Supplemental content

Identifying Candidates for Risk Reduction

Careful risk assessment is required to ensure that the benefits of primary prevention outweigh the harms. Several breast cancer risk models have been developed and validated in the general US population (Supplement). These models include the Breast Cancer Risk Assessment Tool, the Breast Cancer Surveillance Consortium Risk Calculator, and the International Breast Cancer Intervention Study risk assessment tool. A 2019 study at a large mammography center found that the Breast Cancer Risk Assessment Tool and Breast Cancer Surveillance Consortium Risk Calculator were better calibrated (predicted risk in a population matches the observed risk) than the International Breast Cancer Intervention Study model, and that the Breast Cancer Surveillance Consortium Risk Calculator had the highest discrimination (risk in women developing cancer is greater than the risk in women not developing cancer).[4] The US Preventive Services Task Force has indicated that the benefits of risk-reducing medications generally outweigh the risks in women with an estimated 5-year breast cancer risk of at least 3%.[5]

Medications

Two classes of medications are used for breast cancer risk reduction, selective estrogen receptor modulators (SERMs), which include tamoxifen and raloxifene, and aromatase inhibitors (AIs), which include anastrozole and exemestane. The US Preventive Services Task Force recommended SERMs for breast cancer prevention in 2013 and reaffirmed their recommendation in 2019 with the addition of AIs.[5] Only SERMs have US Food and Drug Administration approval for breast cancer risk reduction.

SERMs have the strongest evidence supporting their effectiveness (Supplement). Meta-analyses report that the absolute risk reduction with SERMs is 7 to 9 fewer invasive breast cancers for every 1000 women treated over 5 years compared with women who were not treated. In a randomized trial that compared raloxifene with tamoxifen, the drugs were not significantly different at 6 years (relative risk [RR], 1.02 [95% CI, 0.82-1.28]). After 9.7 years, raloxifene, compared with tamoxifen, was associated with a higher risk of invasive cancer (RR, 1.19 [95% CI, 1.04-1.37]), but a lower risk of overall mortality (RR, 0.87 [95% CI, 0.75-1.00]).[6] SERMs increase bone density and their use is associated with a decreased risk of fractures in postmenopausal women.[7]

There are several differences in the adverse effects of tamoxifen and raloxifene (eTable in the Supplement). Both increase the risk of venous thromboembolism, but raloxifene has a lower RR for venous thromboembolism compared with tamoxifen (0.75 [95% CI, 0.60-0.93]; absolute risk difference, 4 per 1000 women treated for 5 years). Additionally, tamoxifen is associated with an increased risk of uterine cancer (5 more cases per 1000 women over 5 years).[7] Raloxifene is not associated with an increased risk of uterine cancer. Both SERMs can cause hot flashes, but tamoxifen causes more menstrual abnormalities, sexual dysfunction, and vaginal discharge.

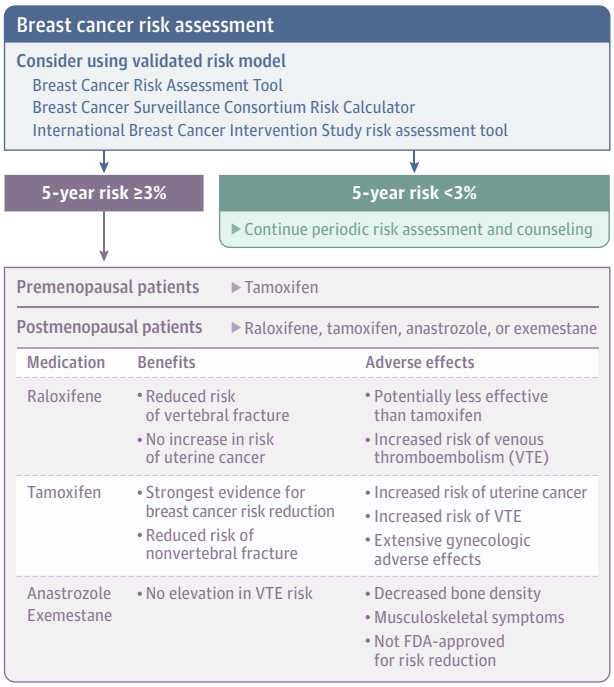
AIs may reduce breast cancer risk by 16 cases per 1000 women over 5 years (eTable in the Supplement).[7] However, these estimates are based on single trials of anastrozole (RR, 0.53 [95% CI, 0.40-0.71])[8] and exemestane (RR, 0.35 [95% CI, 0.18-0.70]).[7] The primary adverse effects of AIs are arthralgias, myalgias, and decreased bone mineral density. AIs can also cause hot flashes, although these symptoms are generally less severe than with SERMs.

Practical Considerations

Several professional society guidelines recommend shared decision-making about breast cancer screening at 40 years of age.[5] Clinicians can use this opportunity to assess a woman's breast cancer risk and identify candidates for risk reduction. Clinicians should also consider risk assessment in younger women with a strong family history of breast cancer or results of a breast biopsy showing atypical hyperplasia or lobular carcinoma in situ. A suggested approach to choosing a medication for breast cancer risk reduction is shown in the **Figure**. Starting a risk-reducing medication at a younger age optimizes the risk-benefit tradeoff for 2 reasons. First, the risk reduction effect of SERMs extends for at least 15 to 20 years, so younger women may have a longer time to benefit. Second, the incidence of venous thromboembolism and uterine cancer increases with age, so the excess harms due to treatment with SERMs will be lower in younger women.

The choice of medication should be guided by individual patient characteristics, including menopausal status, prior hysterectomy, and comorbidities (Figure), although this approach has not been evaluated and validated in rigorous clinical studies. Tamoxifen is the only medication that has been studied and approved for use in premenopausal women. In postmenopausal women, tamoxifen or raloxifene are first-line options. Raloxifene is associated with lower rates of significant harms, but tamoxifen has stronger evidence of long-term benefit and may be preferred in women who have

Figure. Suggested Approach to Choosing Medication for Breast Cancer Risk Reduction



FDA indicates US Food and Drug Administration.

had a hysterectomy because they are no longer at risk for endometrial cancer. Clinicians may consider AIs for postmenopausal women with elevated venous thromboembolism risk who are not at high risk for osteoporosis.

The recommended duration of treatment is 5 years.[5] Women taking risk-reducing medications should continue guideline-based breast cancer screening. Importantly, risk-reducing medications do not decrease the incidence of estrogen receptor–negative breast cancers. For women taking AIs, clinicians could consider obtaining a baseline bone density measurement followed by periodic surveillance.

Future Directions

Integrating breast cancer risk models into the electronic medical record could allow automated risk assessment and facilitate the identification of candidates for breast cancer risk reduction through panel management. Genetic variants improve the performance of breast cancer risk models and may help to refine clinical decision-making. Changes in intermediate markers of risk, such as breast density, may identify women who are not responding to and should stop therapy. There is active work to identify other risk-reducing medications with greater benefits and fewer harms.

Conclusions

Four medications have been shown in randomized trials to reduce the risk for invasive breast cancer. Primary care physicians should consider the risks and benefits of these medications when offering them to women at high risk for breast cancer (5-year risk ≥3%).

ARTICLE INFORMATION

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