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American Society of Clinical Oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction⋆

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Context

To update ASCO's Clinical Practice Guideline on the use of pharmacologic interventions to reduce the risk of breast cancer, ASCO convened an Update Committee of the Breast Cancer Risk Reduction Expert Panel. ASCO published the first version of this guideline in 1999 and last updated it in 2002. This 2009 updated guideline addresses the roles of tamoxifen, raloxifene, aromatase inhibitors, and fenretinide in reducing the risk of breast cancer. The recommendations the guideline update makes are listed in Table 1. All of the trials that provide evidence for this guideline update used breast cancer incidence as an endpoint and were published between 2002 and 2007. This guideline update addresses the following clinical questions:

- In women who were not previously diagnosed with breast cancer, do tamoxifen, raloxifene, aromatase inhibitors, and/or fenretinide reduce the risk of developing breast cancer (invasive or non-invasive) compared to no pharmacologic intervention?
- What is the comparative, efficacy of tamoxifen, raloxifene, aromatase inhibitors, and fenretinide for breast cancer risk reduction?
- What constitutes effective and responsible communication by physicians of issues regarding breast cancer risk reduction to women eligible to consider use of these agents?

Women at risk are defined as those with:

- a five-year projected breast cancer risk ≥1.66% (according to the National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool),[1] OR

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Conflict of interest statement
No conflict of interest.

[1](available at: [http://www.cancer.gov/bcrisktool]).

- lobular carcinoma in situ (LCIS).

Recommendations

TAMOXIFEN

This recommendation is based on the review of results of four phase III randomized clinical trials that compared five years of tamoxifen to placebo. All of the women were at increased risk for breast cancer. Tamoxifen is approved by the US Food and Drug Administration (FDA) for reducing the risk of invasive breast cancer for women who are at increased risk of breast cancer and either premenopausal or postmenopausal.

Tamoxifen (20 mg/d), taken for five years, may reduce the risk of developing estrogen receptor (ER) positive invasive breast cancer for up to 10 years. In a 2003 meta-analysis of these trials, the risk of ER-positive breast cancer was decreased by 48% (Note: The meta-analysis included data available an average of three years after last entry year of major trials and therefore, did not include some subsequently released data considered in the guideline). There are now follow-up data from one of the studies that the decrease in risk lasted for up to 10 years, but overall, the data on tamoxifen use for more than five years in the setting of risk reduction are limited. Therefore, it is recommended that the duration of tamoxifen be limited to five years outside of a clinical trial setting.

The greatest clinical benefit and the fewest adverse effects were derived from the use of tamoxifen by: younger (premenopausal) women 35 to 50 years of age who are unlikely to experience thromboembolic sequelae or uterine cancer, women without a uterus, and women at high risk of breast cancer.

Tamoxifen is not known to have an effect on overall or breast cancer-specific mortality, but a reduction in diagnoses of breast cancer should be considered an important health outcome in and of itself, even in the absence of ultimate reduction in breast cancer mortality. A possible benefit to taking tamoxifen is reduced risk of fractures, primarily in women who are postmenopausal, based on the result of one trial.

Concurrent hormone therapy is not recommended with tamoxifen used, for breast cancer risk reduction, since the safety of the combination has not been established.

Adverse events—Serious adverse events may result from tamoxifen use. Tamoxifen is not recommended in women with a prior history of deep venous thrombosis, pulmonary embolus, stroke, or transient ischemic attack. Tamoxifen use in the prevention setting may increase the risk of ischemic stroke, particularly in women 50 years of age or older. Follow-up data indicate that the risk of serious adverse events, such as thromboembolism, decreases after active treatment.

Two meta-analyses found the risk of uterine/endometrial cancer nearly doubled with tamoxifen use. In the largest individual clinical trial, the elevated risk of endometrial cancer was only for women 50 years of age and above. In all of the trials, the majority of uterine cancers were successfully treated Stage 1 adenocarcinomas. The guideline recommends that women receiving tamoxifen have a baseline gynecological examination before starting

tamoxifen and annual follow-up continuing after treatment ends, with a timely thorough work-up for abnormal vaginal bleeding. Routine endometrial biopsy is not needed in the absence of abnormal vaginal bleeding. Women with abnormalities on endometrial biopsy performed because of abnormal vaginal bleeding may consider stopping tamoxifen use, in consultation with their gynecologist or primary care physician.

A meta-analysis found the risk of thromboembolic events increased 1.9 fold with tamoxifen use; pulmonary emboli were the most common events. The risk of superficial thrombophlebitis was three fold higher. Therefore, tamoxifen is not recommended for women with a prior history of thromboembolic events, stroke, or transient ischemic attack. Two trials found that the risk decreased after the course of active treatment. Tamoxifen may increase the incidence of cataracts, particularly in older women.

Vaginal discharge and hot flashes were commonly reported adverse effects. However, some trials reported that the gynecological and vasomotor symptoms were greatest during active treatment and did not increase post-treatment. Leg cramps and bladder control problems were also reported by women in the tamoxifen arms. Clinicians should help women become aware that such symptoms may arise with tamoxifen use. Reported effects of tamoxifen on cognition are inconsistent and inconclusive.

Risks and benefits associated with tamoxifen use should be carefully considered during the decision-making process.

RALOXIFENE

This recommendation is based on evidence from four phase III randomized clinical trials. Three trials were placebo-controlled and one trial compared raloxifene to tamoxifen. Not all of the women in the raloxifene trials were at elevated risk of breast cancer. Raloxifene is FDA approved (and label indicated) for treating and preventing osteoporosis in women who are postmenopausal, and for reducing the risk of invasive breast cancer in women who are postmenopausal and at increased risk of breast cancer.

A reduction in risk was observed across the trials, primarily for ER-positive invasive breast cancer. Raloxifene has equal efficacy to tamoxifen in reducing breast cancer risk for women who are postmenopausal. Raloxifene did not reduce non-invasive breast cancer as much as tamoxifen, but this finding was not statistically significant.

Raloxifene (60 mg/day), taken for five years, may be offered as an option to reduce the risk of ER-positive invasive breast cancer for women who are postmenopausal and at increased risk of breast cancer, and for women who are postmenopausal with osteoporosis in whom breast cancer risk reduction is a secondary benefit. The optimal duration of the use of raloxifene is not defined, but safety information for randomized trials is limited to eight years. The guideline recommends the duration of no longer than five years for primary breast cancer prevention. Women who are postmenopausal and for whom breast cancer risk reduction is a secondary outcome (to addressing osteoporosis) may take raloxifene for more than five years.

Raloxifene is not recommended for breast cancer risk reduction in premenopausal women. Raloxifene does not have demonstrated activity against established breast cancer and should not be used to treat breast cancer or prevent its recurrence.

Raloxifene is not known to have an effect on overall or breast cancer-specific mortality, but a reduction in diagnoses of breast cancer should be considered an important health outcome in and of itself, even in the absence of ultimate reduction in breast cancer mortality. For women with osteoporosis at risk for breast cancer, breast cancer risk reduction is an additional potential benefit. Fracture does not appear to be a risk of raloxifene, so women with a prior history of fractures or osteoporosis should not be excluded from considering raloxifene.

Adverse events—Raloxifene is not recommended for women with a prior history of deep venous thrombosis, pulmonary embolus, stroke, or transient ischemic attack. In the three trials comparing raloxifene to placebo, thrombolic events increased with raloxifene, but in two trials, the increase was not statistically significant.

Reported adverse effects included venous thromboembolism, vasomotor symptoms, gynecological symptoms, musculoskeletal problems, dyspareunia, hot flashes, leg cramps, bladder control problems, and peripheral edema.

Risks and benefits associated with raloxifene use should be carefully considered during the decision-making process.

ADVERSE EFFECTS: A COMPARISON OF TAMOXIFEN AND RALOXIFENE

Based on the Study of Tamoxifen and Raloxifene (STAR) trial comparing raloxifene and tamoxifen, there appears to be a more favorable adverse effect profile with raloxifene use. There was a lower risk of deep vein thrombosis, pulmonary embolism, benign uterine complaints, gynecologic symptoms, and cataracts among women who were postmenopausal and taking raloxifene. It is likely that both tamoxifen and raloxifene increase arterial vascular events to a similar degree, especially for older women and those with risk factors for these events. The incidence of cataracts appears increased with tamoxifen use, compared to raloxifene. Overall quality of life was similar in the raloxifene and tamoxifen arms, but the incidence of dyspareunia, weight gain, hot flashes, and musculoskeletal complaints was higher with raloxifene use, whereas the incidence of vasomotor symptoms, bladder incontinence, gynecologic symptoms, and leg cramps was higher with tamoxifen use. Tamoxifen and raloxifene have a similar favorable effect on fracture incidence.

AROMATASE INHIBITORS AND RETINOIDS

Use of aromatase inhibitors or retinoids is not recommended as breast cancer risk reduction agents outside of a clinical trial. Unlike tamoxifen and raloxifene, they are not currently approved by the FDA for breast cancer risk reduction. At the time of the guideline update, there were no completed phase III randomized trials of aromatase inhibitors for breast cancer risk reduction; such trials are ongoing. In the single completed phase III trial of a retinoid, fenretinide, for secondary prevention, there was not a reduction in breast cancer incidence. Fenretinide is now being studied in combination with tamoxifen for the risk

reduction of breast cancer in women at high risk. Ongoing risk reduction trials with aromatase inhibitors and retinoids will provide more important evidence about their risks and benefits in the context of breast cancer risk reduction.

Risk Assessment and Risk Communication

The guideline includes a commentary on risk assessment and risk communication and a brief review of risk assessment models. The greater an individual's risk of developing breast cancer, or the lower risk of incurring side effects from chemoprophylaxis (e.g., prior hysterectomy for tamoxifen use); the more favorable the risk/benefit ratio from chemoprevention is likely to be. Models to assess the risk of developing breast cancer include the Breast Cancer Risk Assessment Model of the NCI [1], based on the Gail model; the Women's Contraceptive and Reproductive Experiences; the Claus and the Tyrer–Cuzick; and Women's Health Initiative models. Each risk model is intended for use within a specific target population; they have not been validated in all populations. Detailed information on the limitations of each risk model is available from the NCI's PDQ breast cancer prevention website (http://www.cancer.gov/cancer_information), and in published literature. The Women's Contraceptive and Reproductive Experiences model is recommended for use by African American women to assess the risk of breast cancer. This model is available at (http://www.cancer.gov/bcrisktool). The guideline notes risk estimates should be calculated periodically, since a woman's risk of breast cancer changes throughout her lifetime.

If a clinician identifies a woman as being at elevated risk for breast cancer, an informed discussion of risk reduction strategies, including risks and benefits, should be initiated while being sensitive to her personal needs and values–including race, culture, and socioeconomic status. The guideline recommends that health care providers present women with both the risks and benefits in absolute and relative terms, which will help to avoid emphasizing the benefits or harms of medical approaches.

Health Disparities

Because this clinical practice guideline represents expert recommendations on the best practices in breast cancer risk reduction, it notes that many women have limited access to medical care and that racial and ethnic disparities are often a reflection of limited access to health care in the United States. White women with health insurance other racial/ethnic groups. Evidence suggests that white women were more than three times as likely as African American and Hispanic women, and insured women were twice as likely as uninsured women, to have had a breast biopsy. In addition, racial/ethnic differences appear to influence risk for breast cancer. Health care providers and researchers should consider these disparities in their assessments of risk, discussions with women at risk, chosen interventions, and when recruiting women for breast cancer risk reduction trials.

In Addition

The guideline includes a section on allelic variants of the *CYP2D6* gene. The guideline does not recommend testing for variants in the risk reduction setting at the present time.

There is a need to develop agents that prevent ER-negative breast cancer, as the benefit of tamoxifen and raloxifene appears limited to reducing the risk of ER-positive invasive breast cancers.

The guideline reviewed literature regarding risk reduction agents and women with *BRCA1* and *BRCA2* mutations and found there were insufficient data on the preventive effect of tamoxifen, raloxifene, and aromatase inhibitors specifically in women who carry the *BRCA* mutation.

Methodology

The ASCO Update Committee reviewed searches of MEDLINE and the Cochrane Collaboration Library and conducted a systematic review of the literature published between January 2002 and July 2007.

Additional Resources

Journal of Clinical Oncology published a full-text version of this guideline on May 26,2009. The full-text is available at www.asco.org/guidelines/bcrr, along with a slide set and Decision Aid. Patient information is available at www.cancer.net.

References

1. Visvanathan K, Chlebowski RT, Hurley P, et al. American Society of Clinical Oncology Clinical Practice Guideline Update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. J Clin Oncol. 2009; 27:3235–58. [PubMed: 19470930]
2. National Cancer Institute. Breast Cancer Risk Assessment Tool. http://www.cancer.gov/bcrisktool

Table 1

Summary of Recommendations.

AGENT	2009 RECOMMENDATION	DOSAGE
Tamoxifen	May be offered to reduce the risk of estrogen receptor(ER) positive invasive breast cancer for premenopausal women with a 5-year projected breast cancer risk ≥1.66%(according to the NCI Breast Cancer Risk Assessment Tool), or with lobular carcinoma in situ (LCIS). Risk reduction benefit continues for at least 10 years. Impact on breast cancer mortality is unknown. May be offered to reduce the risk of ER-positive invasive breast cancer for postmenopausal women with a 5-year projected breast cancer risk ≥1.66% (according to the NCI Breast Cancer Risk Assessment Tool), or with LCIS. Risk reduction benefit continues for at least 10 years. Impact on breast cancer mortality is unknown. Not recommended for women with a prior history of deep venous thrombosis, pulmonary embolus, stroke, or transient ischemic attack. Combined use of tamoxifen for breast cancer prevention and hormone therapy is currently not recommended. Follow-up should include a baseline gynecological examination prior to initiation of treatment and annually thereafter, with a timely work-up of abnormal vaginal bleeding. Risks and benefits should be given careful consideration during the decision-making process.	20 mg/d for5 years
Raloxifene	May be offered to reduce the risk of ER-positive invasive breast cancer to postmenopausal women with a 5-year projected breast cancer risk ≥1.66% (according to the NCI Breast Cancer Risk Assessment Tool), or with LCIS. Impact on breast cancer mortality is unknown. May be used longer than 5 years in women with osteoporosis, in whom breast cancer risk reduction is a secondary benefit. Should not be used for breast cancer risk reduction in premenopausal women. Not recommended for use in women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack. Risks and benefits should be given careful consideration during the decision-making process.	60 mg/d for5 years
Fenretinide	Use is not recommended outside of the clinical trial setting to lower breast cancer risk.	NA
Aromatase Inhibitors	Use is not recommended outside of the clinical trial setting to lower breast cancer risk.	NA

NA=not applicable.