P.O. Box 30195
Lansing, MI 48909
Phone: 877-588-6224
FAX: 517-335-9397
www.michigancancer.org

MCC
Michigan Cancer Consortium

POSITION PAPER FOR HEALTH CARE PROVIDERS
Use of Pharmacologic Intervention for Breast Cancer Risk Reduction

Introduction

The American Cancer Society estimates, in 2014, over 232,600 women in the United States will be diagnosed as having invasive breast cancer.[1] Breast cancer is the most frequently diagnosed cancer among Michigan women and, in Michigan, is the second most commonly diagnosed cancer.[1] Its incidence is rapidly increasing due to an aging population, rising socioeconomic status, increases in obesity, and several other lifestyle changes, such as later age at first childbirth, reductions in breastfeeding, and decreases in physical activity. Lifestyle improvements (e.g. exercise, diet, maintaining an optimum weight, limiting alcohol intake, and limiting exposure to exogenous estrogens) are important components of breast cancer prevention. In addition to basic lifestyle changes, women who are identified at an increased risk for developing breast cancer may also benefit from pharmacologic interventions[10-13]. For these women, providers should discuss the risks and benefits associated with specific pharmacologic interventions as an option to supplement lifestyle modifications.[3]

This paper will discuss guidelines set forth by the United States Preventive Services Task Force (USPSTF)[2] and American Society for Clinical Oncology (ASCO)[3] which recommend pharmacologic interventions to reduce the risk of breast cancer in women not previously diagnosed with breast cancer. These recommendations are for use by medical oncologists, surgical oncologists, gynecologists, and all primary care providers.

Identifying Women at Increased Risk for Breast Cancer

Risk of breast cancer can be determined by the National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool (available at http://www.cancer.gov/bcrisktool)[4-5] or other validated risk assessment models[6-9]. Women at increased breast cancer risk are defined as having a 5-year projected absolute risk of breast cancer $\geq$ 1.66% or women diagnosed with lobular carcinoma in situ.[5] (LCIS) (The USPSTF and ASCO both recommend health care providers who identify women at increased risk for breast cancer, engage them in shared, informed decision making, and then consider pharmacologic interventions, specifically selective estrogen-receptor modulators (SERMS) or aromatase inhibitors, to reduce their risk.)

Effectiveness of Medications for Breast Cancer Risk Reduction

In women > 35 years of age, who are at increased risk of breast cancer, tamoxifen should be discussed as an option to reduce the risk of estrogen receptor (ER) positive breast cancer.[10] For *postmenopausal* women, tamoxifen, raloxifene[11-12] and exemestane[13] should be discussed as options for breast cancer risk reduction. Use of other selective ER modulators or other aromatase inhibitors to lower breast cancer risk is not recommended outside of a clinical trial nor are they recommended in women at

low-risk (≤ 1.66%, as determined by the Breast Cancer Risk Assessment Tool or other validated risk assessment tools).

Findings from Breast Cancer Prevention Trials: SERMS

SERMs [13] are drugs that have some anti-estrogen properties and some estrogen-like properties. Their anti-estrogen activity may help reduce the risk of breast cancer by blocking the effects of estrogen on breast tissue. Tamoxifen and raloxifene are SERMS that have been shown in randomized controlled trials to reduce the risk for estrogen receptor (ER) positive breast cancer.

Tamoxifen

A systematic review of clinical trials (NSABP P 1 and2)[11-13] found evidence that treatment with tamoxifen (20 mg/day for 5 years) reduced the incidence of invasive breast cancer in women by 49% (7 fewer cancer events/1000 women over 5 years). The incidence for non-invasive breast cancer was reduced by 50% (8 fewer cancer events/1000 women over 6 years). Non-vertebral fractures were reduced in women taking Tamoxifen (3 fewer events/1000 women). Tamoxifen' s risk reduction benefit continues for at least 10 years.[17] Contraindications: See Table 1.

Raloxifene

Data from clinical trials[18-19] provided evidence that treatment with raloxifene (60 mg/day for 5 years) in post-menopausal women also reduced the incidence of invasive breast cancer by 49%, (9 fewer cancer events/1000 women) over 5 years. There were 8 fewer events/1000 women for ER positive breast cancers. Compared with placebo, raloxifene reduced the incidence of vertebral fractures by 7 events/1000 women whereas tamoxifen reduced the incidence of vertebral fractures by 3 events/1000 women. [14-16] Raloxifene should not be used for breast cancer risk reduction in premenopausal women. Compared to tamoxifen, raloxifene had a significantly lower risk of thromboembolic events (statistically significant only for deep vein thrombosis) and uterine cancer in post-menopausal women and lower incidence of benign uterine hyperplasia, cataracts, and cataract surgery. [20-21] Contraindications: See Table 1.

Effectiveness of Aromatase Inhibitors: Findings from Clinical Trials

Exemestane

Clinical trials[22-23] studying the preventive effects of an aromatase inhibitor in post-menopausal women showed exemestane (25 mg/day for 5 years) significantly reduces the overall risk of invasive breast cancer and the risk of ER positive invasive breast cancer by up to 73%. The data do not show a reduction in the risk of ER negative breast cancer or non-invasive breast cancers with exemestane use. Contraindications and list of adverse events – Table 1

Net Health Benefits

The USPSTF [2]concludes that medications to reduce the risk for breast cancer confers benefit in women who are at increased risk for the disease. Tamoxifen is associated with clear benefit, with adequate evidence for risk reduction of invasive breast cancer. Raloxifene is associated with a similar benefit for breast cancer risk reduction but no increased risk for endometrial cancer. Both tamoxifen and raloxifene were beneficial in decreasing bone fractures. The USPSTF found evidence of small to moderate risk for medication associated venous thrombolic events (VTEs) depending on age, as well as small to moderate

risk for medication-associated endometrial cancer with tamoxifen depending on hysterectomy status and age.

ASCO [3] concludes that the reported findings indicate that exemestane is a reasonable option for reducing the risk of invasive breast cancer in postmenopausal women at increased risk of breast cancer. Clinical trials have shown that exemestane significantly reduced the incidence of invasive breast cancer, was not associated with serious adverse effects, and resulted in only minimal changes in health-related quality of life. ASCO found that the potential for bone loss should be mentioned when discussing the risks and benefits of exemestane for prevention. Women receiving exemestane should undergo bone monitoring and have adequate vitamin D and calcium supplementation.

Patient and Provider Discussion

The potential preventive benefit of tamoxifen, raloxifene and exemestane in women at increased risk of breast cancer has been demonstrated through various clinical trials. In the next decade, it has been estimated that > 2 million women in the United States could potentially benefit from risk reducing pharmacologic agents. However, these medications are infrequently used by women for breast cancer risk reduction, even among those with a favorable risk-benefit profile. In studies[25-26] describing how women decide whether to take medications to reduce their risk for primary breast cancer, women had substantial concerns about potential serious adverse events, especially when they were informed of the medications' risk and benefits. Women who were interested in receiving risk reduction medications often overestimated their own risk for breast cancer (i.e. erroneously thought they were at high risk). When considering pharmacologic options providers should discuss both the risks and benefits (Table 1). This discussion should be tailored to the individual patient. Women placed great emphasis on recommendations from their providers. The following points should be included as part of the discussion:

1. Assessment and discussion of individual risk of developing breast cancer.
2. Options for reducing the risk of developing breast cancer (to include discussion of both lifestyle modifications and pharmacologic interventions).
3. Potential impact of specific pharmacologic agents on the incidence of both invasive and noninvasive breast cancers
4. Potential risks and adverse effects of pharmacologic agents
5. Long-term effectiveness of pharmacologic agents
6. Accessibility, cost, and insurance coverage for risk assessment, counseling, initial treatment and follow-up.
7. Plan for follow-up

Providing information[27] on net health benefits and adverse events of pharmacologic agents, tailored towards the woman's individual risk in developing events/effects such as those described in Table 1 can be helpful in the decision making process.

Table 1: Summary of Clinical Practice Guidelines for Pharmacologic Interventions Approved for Risk Reduction

Drug Name	**Tamoxifen (SERM)**	**Raloxifene (SERM)**	**Exemestane (Aromatase Inhibitor)**
Dose & Interval	20 mg orally daily for 5 years	60 mg orally daily for 5 years	25 mg orally daily for 5 years
Indications	• May be used in both **pre and post-menopausal** women • Used to reduce the risk of ER positive invasive breast cancer or with *LCIS* Other indications: • Used in treatment of endocrine sensitive breast cancer in both the adjuvant and in the metastatic setting	• Used in **postmenopausal women ONLY** • Used to reduce the risk of ER positive invasive breast cancer or with *LCIS* Other indications: • Used in prevention of postmenopausal osteoporosis • Used in treatment of postmenopausal osteoporosis	• Used in **postmenopausal women ONLY** as an alternative to tamoxifen or raloxifene to reduce the risk of ER positive invasive breast cancer or with *LCIS* or *atypical hyperplasia* *Other indications:* • Used in adjuvant treatment of ER positive breast cancer and in women whose disease has progressed after tamoxifen therapy or from therapy with other aromatase inhibitors
BENEFITS			
Breast Cancer Prevention	Invasive Breast Cancer : 49% reduction; 7 fewer events/1000 women Non-Invasive Breast Cancer: 50% reduction Cumulative incidence through 6 years was 8.1 fewer events/1000 women • ER Positive Cancer- 8 fewer events/1000 women • Risk Benefit Reduction continues for at least 10 years	• Invasive Breast Cancer: 49% reduction; 9 fewer events/1000 women • Noninvasive breast cancer – Less efficacy than tamoxifen. Cumulative incidence through 6 years was 11.6/1000 women • ER positive cancer: 8 fewer events /1000 women	• Invasive Breast Cancer: 65% overall reduction 5.5 fewer events/1000 women • Noninvasive Breast Cancer- no reduction • ER positive Cancer: 73% reduction
ADVERSE EVENTS/SIDE EFFECTS			
Bones/Fractures	• Vertebral fractures: no difference • Non-vertebral fractures: 19% reduction; 3 fewer events/1000 women • Premenopausal women: associated with an increased rate of bone loss • Postmenopausal women: 1% increase in bone mass/year	• Vertebral fractured – 7 fewer events/1000 women; bone mineral density of the femoral neck is increased by 2.1% over placebo • Non-vertebral fractures: no difference	• Bone Loss – no data on fracture risk; 8% reduction in the cortical bone thickness
Cataracts	• 13% - 15 events per 1000/women	• No difference	• No difference
Gynecological	• Increased risk of endometrial cancer*; in postmenopausal women 4 more events/1000 women • Abnormal vaginal bleeding requires immediate work-up	• Less risk of uterine cancers (36% fewer) compared to tamoxifen;	• No difference
Drug Name	**Tamoxifen (SERM)**	**Raloxifene (SERM)**	**Exemestane (Aromatase Inhibitor)**

Menopausal Symptoms	Vasomotor symptoms (hot flashes and night sweats)	Vasomotor symptoms (hot flashes and night sweats)	Small increase in menopausal symptoms; hot flashes (40%), joint pain (30%), fatigue, (23%) insomnia (10%), diarrhea (5%) nausea (7%).
Contraindications	Not recommended for use in women: • Taking hormone replacement therapy • History of venous thromboembolism (deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack) • Prolonged immobilization (within prior 3 months) • Body mass index (BMI) of > 25kg/m • Pregnant women or women who may become pregnant, or are nursing mothers	Not recommended for use in women: • Who are Pre-menopausal • History of venous thromboembolism (deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack) • Prolonged immobilization (within prior 3 months) • Body mass index (BMI) of > 25kg/m • Pregnant women or women who may become pregnant, or are nursing mothers.	Not recommended for use in women: • Who are Pre-menopausal

* NOTE: The difference between the treatment groups in non–cancer-related hysterectomies has likely caused an underestimate of the true magnitude of endometrial cancer risk associated with tamoxifen and an underestimate of the true magnitude of difference between the 2 treatment groups for this end point. The large proportion (51.6%) of women in STAR who had already undergone hysterectomy is likely attributable to the fact that such women had no risk for uterine malignancy, which was associated with tamoxifen in the BCPT.

References

1. American Cancer Society Cancer Facts and Figures 2014, p 4- 5, 9.
2. Moyer VA Medications for Risk Reduction of Primary Breast Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement, Annals of Internal Medicine. Downloaded from www.annals.org pp 1-13
3. Visvanathan K, Hurley P, Bantug E et al "Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: American Society of Clinical Oncology Clinical Practive Guideline, Journal of Clinical Oncology 2013; 31(23) 2942-2962
4. National Cancer Institute Breast Cancer Risk Assessment Tool at http://www.cancer.gov/bcrisktool)
5. Gail MH, Brinton LA, Byar DP, et al: Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 81:1879-1886, 1989
6. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer: Implications for risk prediction. Cancer 73:643-651, 1994
7. Gail MH: Discriminatory accuracy from singlenucleotide polymorphisms in models to predict breast cancer risk. J Natl Cancer Inst 100:1037-1041, 2008
8. Amir E, Evans DG, Shenton A, et al: Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme.J Med Genet 40:807-814, 2003.
9. Tyrer J, Duffy SW, Cuzick J: A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 23:1111-1130, 2004
10. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: Report of the national surgical adjuvant breast and bowel project P-1 study. *J Natl Cancer Inst* 1998;90(18):1371-1388.
11. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, et al. Effects of Tamoxifen vs Raloxifene on the Risk of Developing Invasive Breast Cancer and Other Disease Outcomes. The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA 2006; 295. Published online Jun 5 2006.
12. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al; National Surgical Adjuvant Breast and Bowel Project. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res (Phila). 2010;3:696-706. [PMID: 20404000]
13. National Cancer Institute (2006-04-26). "Study of Tamoxifen and Raloxifene (STAR) Trial". U.S. National Institutes of Health. Retrieved July 3, 2007.
14. Gradishar, W, Cella, D. Selective Receptor Modulators and Prevention of Invasive Breast Cancer. JAMA 2006; . Published online Jun 6 2006.
15. Land, S, Wickerham, D, Costantino, J, et al. Patient Reported Symptoms and Quality of Life During Treatment With Tamoxifen or Raloxifene for Breast Cancer Prevention. The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA 2006; . Published online Jun 6 2006.
16. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of Tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91(21):1829-46.
17. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of Tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen-positive tumors. J Natl Cancer Inst 1996;88(21):1529-42.
18. Cummings SR, Eckert S, Krueger KA, et al. The effect of Raloxifene on risk of breast cancer in postmenopausal women. *JAMA* 1999;281:2189-97.

19. Chlebowski RT, Col N, Winer EP, et al. American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including Tamoxifen, Raloxifene, and aromatase inhibition. *Journal of Clinical Oncology* 2002; 20(15):3328–3343.
20. Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, Disch D, et al. Continuing Outcomes Relevant to Evista: Breast Cancer Incidence in Postmenopausal Osteoporotic Women in a Randomized Trial of Raloxifene. J Natl Cancer Inst 2004;96:1751–61.
21. Dickler M, Norton, L ., The MORE Trial: Multiple Outcomes for Raloxifene Evaluation. Breast Cancer as a Secondary End Point: Implications for Prevention, Annals of the New York Academy of Sciences 2001; 949 (1), 134–142.
22. Dunn BK, Cazzaniga M, DeCensi A, Exemestane: One Part of the Chemopreventive Spectrum for ER-positive Breast Cancer. Breast 2013 Jun;22(3):225-37.
23. Cuzick J, Forbes, JF, Dowsett, M., et al. "Anastrozole for prevention of breast cancer in high risk postmenopausal women (IBIS-II): an international, double-blind, randomized placebo-controlled trial.
24. Melnikow, J, Kuenneth, C, Helms, L, et.al. Chemoprevention: Drug Pricing and Mortality. The Case for Tamoxifen. Wiley InterScience. Published online Jul 24 2006.
25. Fagerlin A, Dillard AJ, Smith DM, et al: Women's Interest in taking Tamoxifen and Raloxifene for Breast Cancer Prevention: Response to a Tailored Decision Aid. Breast Cancer Res Treat 127:681-688, 2011
26. Fagerlin A, Zikmund-Fisher BJ, Ubel PA: Helping patients decide: Ten steps to better risk communication. J Natl Cancer Inst 103:1436-1443, 2011
27. American Cancer Society, Medicines to Reduce Breast Cancer Risk http://www.cancer.org/cancer/breastcancer/moreinformation/medicinestoreducebreastcancer/medicines-to-reduce-breast-cancer-risk-toc
28. Agency for Health Care Research and Quality, Reducing the Risk of Breast Cancer with Medicine: A Guide for Women AHRQ Publication Number 09(10)-EHC028-A. http://effectivehealthcare.ahrq.gov/ehc/products/50/389/breast%20cancer%20medications%20consumer%20guide.pdf