Medications to lower the risk of breast cancer

CLINICIAN GUIDE

Clinical Oncology Society of Australia

Introduction

There are a number of medications that lower the risk of primary breast cancer in women who have **not** previously been diagnosed with breast cancer. The two most commonly prescribed risk reducing medications[1] are tamoxifen and raloxifene. Both are selective oestrogen receptor modulators (SERM).

Who? Balancing the Potential Benefits and Harms

A woman's personal risk of breast cancer depends on many factors including current age, life style factors, family history, genetic mutations and breast factors including high mammographic breast density and presence of atypical ductal or lobular hyperplasia. The higher the personal risk of breast cancer the greater the potential benefit of SERM.

The ideal candidate for SERM is a woman who is aged 35 years or older and has a higher than average risk of breast cancer, is willing to accept the small risk of potential side effects, and does not have contraindications (see below). This document focuses on information about SERM only; information about breast cancer risk assessment should be sought elsewhere.

SERM is **not** recommended for women at standard (population) risk of breast cancer where the potential harms are likely to out-weigh the potential benefits.

Before prescribing SERM, discuss other management options such as screening and (if appropriate) risk-reducing surgery; taking into account the woman's individual risk category, age, stage of life and preferences; balance the potential benefits with the potential for harm.

The key information
Tamoxifen is effective at lowering the risk of primary invasive and non-invasive breast cancer in women level of confidence: high
Raloxifene is effective at lowering the risk of primary invasive breast cancer in women level of confidence: high
Both tamoxifen and raloxifene lower the risk of osteoporotic fracture in women level of confidence: high
Tamoxifen and raloxifene have **not** been shown to lower breast cancer-specific or all-cause mortality level of confidence: medium
Tamoxifen and raloxifene both **increase** the risk of thromboembolic events (DVT and PE) level of confidence: high
Tamoxifen **increases** the risk of endometrial cancer, but the risk reverses after the treatment is stopped level of confidence: high
The levels of confidence in this document are derived from a review of the literature and expert opinion. **High**: There are consistent results from good quality studies. Further research is unlikely to change the conclusions. **Medium**: Findings are supported by published studies, but further research could change the conclusions. **Low**: Expert opinion only. There are very few studies or existing studies are flawed.

[1] The aromatase inhibitor group is also used to lower the risk of breast cancer. This document does **not** cover this group of medications.

The details: Tamoxifen[2, 3]

(prescriber information https://www.tga.gov.au/search/artg)

BREAST CANCER
Tamoxifen daily for 5 years lowers the relative risk of primary estrogen-receptor (ER)-positive invasive breast cancer by at least one-third in both premenopausal and postmenopausal women, with the benefit lasting for at least 20 years level of confidence: high
Tamoxifen taken daily for 5 years lowers the relative risk of ductal carcinoma in situ (DCIS) by one-third in both premenopausal and postmenopausal women level of confidence: medium
For an individual woman the absolute risk reduction depends on her baseline breast cancer risk level of confidence: high
Tamoxifen does **not** lower the relative risk of ER-negative breast cancer level of confidence: high
MORTALITY
Tamoxifen has **not** been shown to lower all-cause mortality or breast cancer-specific mortality level of confidence: medium
ADVERSE EFFECTS
Symptoms of menopause are common (e.g. hot flushes, night sweats, vaginal dryness or discharge)
Ocular symptoms include eye dryness (common), cataracts (uncommon), retinal deposits (rare)
SERIOUS ADVERSE EFFECTS
Tamoxifen **increases** the risk of endometrial cancer, however, this risk is small in premenopausal women[4] level of confidence: high
Tamoxifen **increases** the risk of thromboembolic events (DVT and PE), although the absolute risk is low particularly in pre-menopausal women level of confidence: high The risk is higher in women who smoke or have a past history of thromboembolic events level of confidence: medium
CONTRAINDICTIONS
not recommended for women who have had thromboembolic events (DVT, PE or thrombotic stroke)
not recommended for women who have been diagnosed with endometrial cancer
not recommended for women who smoke
not recommended for women younger than age 35 due to lack of data in this specific group
not recommended for women who are pregnant, breast-feeding, or planning a pregnancy within the next 5 years
not recommended for women taking anticoagulants, hormone replacement therapy or combined oral contraceptive
caution in women taking medications that interact with tamoxifen http://www.drugs.com/drug_interactions.html
OTHER BENEFITS
Tamoxifen lowers hip and other non-vertebral fractures level of confidence: medium
There is insufficient data to determine whether tamoxifen lowers vertebral fractures

The details: Raloxifene[2]

prescriber information https://www.tga.gov.au/search/artg)

BREAST CANCER
Raloxifene daily for five years, lowers the relative risk of primary estrogen-receptor (ER)-positive invasive breast cancer by about one-third in post-menopausal women level of confidence: high
For an individual woman the absolute risk reduction depends on her baseline breast cancer risk level of confidence: high
Raloxifene does **not** lower the relative risk of ductal carcinoma in situ (DCIS) level of confidence: medium
Raloxifene does **not** lower the relative risk of ER-negative breast cancer level of confidence: high
MORTALITY
Raloxifene has **not** been shown to lower all-cause mortality or breast cancer-specific mortality level of confidence: medium
ADVERSE EFFECTS
Symptoms of menopause are common (e.g. hot flushes, night sweats, vaginal dryness or discharge)
Leg cramps are common
SERIOUS ADVERSE EFFECTS
Raloxifene **increases** the risk of thromboembolic events (DVT and PE), although the absolute risk is low level of confidence: high The risk is higher in women who smoke or have a past history of thromboembolic events level of confidence: medium
Raloxifene does **not** increase the risk of endometrial cancer level of confidence: high
CONTRAINDICTIONS
not recommended for women who have had thromboembolic events (DVT, PE or thrombotic stroke)
not recommended for women taking anticoagulants, hormone replacement therapy or combined oral contraceptive
not recommended for women who smoke
not recommended for premenopausal women due to lack of data in this specific group
caution in women taking medications that interact with raloxifene http://www.drugs.com/drug_interactions.html
OTHER BENEFITS
Raloxifene lowers vertebral fractures level of confidence: medium
Raloxifene does **not** lower hip or other non-vertebral fractures. level of confidence: medium

Prescribing

PRE-TREATMENT CHECKLIST
1. Take a family cancer history If you are concerned about the family history of breast cancer consider referral to a breast specialist or your local clinical genetics service
2. Ensure patient has had a normal mammogram or breast MRI within the last 12 months
3. Full medical history: including current medication use (any contraindications - see link below)
4. Clinical examination: including breast examination
5. Medication history A wide range of medications interact with tamoxifen, especially antidepressants. A wide range of medications interact with raloxifene Detailed information about interactions is available at http://www.drugs.com/drug_interactions.html
6. Record menopause status and symptoms
7. For premenopausal women: check childbearing plans and if appropriate give advice on non-hormonal contraceptive methods while on tamoxifen
PRESCRIBING
Tamoxifen: 20mg daily for 5 years (oral) for either pre-menopausal or post-menopausal women
Raloxifene: 60mg daily for 5 years (oral) for post-menopausal women
Cost – considerable variation between pharmacies; suggest "ring around for best price"
MONITORING
Usually done by the prescribing clinician
Ask women to report any symptoms promptly
Schedule: minimum annual review until treatment stopped Record: 1. current symptoms, including vaginal bleeding for post-menopausal women 2. any side effects 3. result of routine mammograms 4. ensure clinical breast examination has been performed

Cancer Australia Consumer FAQ sheet:
https://canceraustralia.gov.au/sites/default/files/publications/rrm-risk-reducing-medication-for-women-at-increased-risk-of-breast-cancer-due-to-family-history_504af03f31630.pdf

Information for women about risk reducing medications (on UpToDate):
http://www.uptodate.com/contents/medications-for-the-prevention-of-breast-cancer-beyond-the-basics?source=see_link

Further information
If you would like further information about these guidelines or would like to contact COSA or the COSA Familial Cancer Group please email us at cosa@cancer.org.au or phone (02) 8063 4100.

[2] See the 2013 US Preventive Services Task Force meta-analysis. Nelson et al Ann Intern Med 2013;158(8):604.
Tamoxifen: reduces the risk of invasive breast cancer (risk ratio [RR] 0.70, 95% CI 0.59-0.82)
reduces the incidence of non-vertebral fractures (RR 0.66, 95% CI 0.45-0.98)
increases the risk of endometrial cancer; no difference in breast cancer-specific or all-cause mortality.
Raloxifene: reduces the risk of invasive breast cancer (RR 0.44, 95% CI 0.27-0.71)
reduces the incidence of vertebral fractures (RR 0.61, 95% CI 1.41-2.64)
no increased incidence of endometrial cancer; no difference in breast cancer-specific or all-cause mortality.

[3] Lancet Oncol 2015;16:67-75 (primary article); Lancet Oncol 2015;16:7-9 (editorial); JAMA Oncol 2015;1:1033-4

[4] The risk of endometrial cancer associated with Tamoxifen use was observed in the first 5 years of treatment (odds ratio [OR] 3.76, 95% CI 1.20-15.56), but not after 5 years (OR 0.64 with 5-10 year follow-up, 95% CI 0.21-1.80). As the risk of endometrial cancer increases with age, the absolute risk of endometrial cancer associated with Tamoxifen depends on the current age of the individual woman.