

Introduction

Risk reducing medication is an efficacious breast cancer prevention option. It is an option for high-risk women who do not wish to undergo (or who wish to postpone) risk-reducing mastectomy. It is also an option for women whose risk is increased, but is not high enough that surgery would be considered appropriate^{1,2}. Risk-reducing medications are **not** recommended for women at standard (population) risk of breast cancer, where the potential harms are likely to outweigh the potential benefits. Risk-reducing medications should **not** be given for longer than 5 years.

There are a number of medications that have been shown, in placebo-controlled randomised trials, to lower the risk of breast cancer in women who have not previously been diagnosed with the disease. They fall into two main categories:

Selective Estrogen Receptor Modulators (SERMs) - tamoxifen and raloxifene
Aromatase inhibitors (AIs) - anastrozole and exemestane.

All of these reduce the risk of estrogen receptor positive breast cancer, which is the most common type; they have not been shown to reduce the risk of estrogen receptor negative breast cancer.

When reviewing the tables below on each agent it is important to consider that there have been multiple randomised controlled trials of tamoxifen 20mg daily versus placebo for breast cancer prevention, and one of these (IBIS I) has very long-term follow-up data available (20 years). Long-term data (10 years) are also available for anastrozole. The quality of the evidence is less robust for the other agents and for low dose (5mg daily) tamoxifen. The efficacy of raloxifene for primary breast cancer prevention has been compared directly with tamoxifen in a randomised trial with 8 years follow-up, so the comparative efficacy and side effects are reasonably well understood. Conversely the AIs, exemestane and anastrozole, have not been compared directly either to each other or to a SERM in the primary breast cancer prevention setting, and only short-term follow-up data are available regarding exemestane (3 years). Short term follow-up in prevention studies tends to overestimate long-term efficacy (presumably due to treatment of occult cancers) and to underestimate long-term side-effects. The reader should also keep in mind that the side-effects listed in the tables on exemestane and anastrozole below are a guide only and should not be compared with each other, as the 2 studies that assessed these agents against placebo had different study populations and different reporting requirements which could account for the apparent differences seen.

Who? Balancing the Potential Benefits and Harms

A woman's personal risk of breast cancer depends on many factors including her current age, reproductive and life style factors, cancer family history, genetic mutations and single nucleotide polymorphisms, and breast factors (such as high mammographic breast density, prior therapeutic breast irradiation, and presence of atypical ductal or lobular hyperplasia). The higher the personal risk of breast cancer the greater the potential benefit of risk-reducing medications.

It is important to formally assess a woman's absolute breast cancer risk in order to be able to inform her of the likely absolute risk reduction with risk-reducing medication and to be able to balance that against the absolute risk of harm. The iPrevent tool (www.petermac.org/iprevent)^{3,4,5} can help with this process. It utilises two of the most accurate risk estimation algorithms⁶, Tyrer-Cuzick and

BOADICEA and provides estimates of the expected absolute reduction in risk with each of the SERMS, as well as the absolute risk of serious side-effects. It also discusses the benefits and risks of the AIs. Women can use it before or after a consultation and print out the results. Alternatively, clinicians can use published tables to help identify groups of postmenopausal women for whom the benefits of tamoxifen and raloxifene outweigh the risks⁷.

Women prescribed risk-reducing medication should continue to undergo breast cancer screening appropriate to their age and risk. Risk-reducing medications, should be discussed in the context of other risk reducing strategies such as modifying lifestyle factors (exogenous estrogen and progesterone, alcohol intake, weight, exercise, breastfeeding), and, for high risk women, risk-reducing bilateral mastectomy.

THE KEY INFORMATION
Tamoxifen is effective at lowering the risk of breast cancer in pre-menopausal women ⁸
Tamoxifen, raloxifene, exemestane and anastrozole are effective at lowering the risk of breast cancer in post-menopausal women ⁸⁻¹²
Tamoxifen 20mg daily for 5 years reduces breast cancer risk for at least 20 years ¹³
Anastrozole 1mg daily for 5 years reduces breast cancer risk for at least 10 years ¹²
Raloxifene is less effective than tamoxifen at lowering the longer-term risk of breast cancer, but may be preferred for some women due to differences in the risk of serious side-effects ⁹
The relative effectiveness of exemestane and anastrozole in lowering the risk of breast cancer, compared to each other and to tamoxifen or raloxifene is not known
The long-term effectiveness of exemestane in reducing breast cancer risk is unknown
Tamoxifen, raloxifene, exemestane and anastrozole only reduce risk of estrogen receptor positive breast cancer ⁸⁻¹²
No breast cancer risk-reduction drug has been shown to lower breast cancer-specific or all-cause mortality
Both tamoxifen and raloxifene reduce age-related bone loss and lower the risk of osteoporotic fracture in post-menopausal women ¹³
Exemestane and anastrozole worsen age-related bone loss ^{10,11}
Tamoxifen and raloxifene both increase the risk of thromboembolic events (DVT and PE). Absolute risk varies with age and other underlying risk factors for thrombosis. On average, the excess risk is 1 in 250 for tamoxifen over 5 years and 1 in 330 for raloxifene ¹³ . The risk for premenopausal women is lower.
Exemestane and anastrozole do not increase the risk of thromboembolic events ^{10,11}
Tamoxifen increases the risk of endometrial cancer in post-menopausal, but not in pre-menopausal women. On average the excess absolute risk is 1 per 250 post-menopausal women over 5 years ¹³ . The risk reverses after the treatment is stopped
Raloxifene, exemestane and anastrozole do not increase the risk of endometrial cancer ^{10,11, 12} .

The details: Tamoxifen

BREAST CANCER RISK REDUCTION
Tamoxifen 20mg daily for 5 years lowers the relative risk of breast cancer by at least one-third in both premenopausal and postmenopausal women, with the benefit lasting for at least 20 years ⁸

Tamoxifen 5mg daily* for 3 years also **lowers** the risk of breast cancer and may be an option for women who cannot tolerate 20mg daily¹⁵, although long-term benefits of the shorter lower dose regimen are unknown.

For an individual woman the **absolute risk reduction** depends on her baseline breast cancer risk

Tamoxifen **does not** lower the relative risk of ER-negative breast cancer⁸

Tamoxifen **has not** been shown to lower all-cause mortality or breast cancer-specific mortality

OTHER BENEFITS

Tamoxifen **lowers** risk of fractures in postmenopausal women¹⁴

Tamoxifen **reduces** breast complaints such as breast tenderness¹⁶

Tamoxifen often makes menstrual periods lighter and/or irregular and can cause amenorrhoea, but **does not** induce menopause/ovarian failure

Tamoxifen **reduces** mammographic density¹⁹

ADVERSE EFFECTS

Tamoxifen **increases** vasomotor and gynaecologic symptoms (e.g. hot flushes, night sweats, vaginal discharge). On average an extra 1 in 10 women have vasomotor symptoms when on tamoxifen^{16,17}

Tamoxifen may **increase** cataracts. On average an extra 1 in 250 women may develop a cataract due to tamoxifen^{14,18}

SERIOUS ADVERSE EFFECTS

Tamoxifen **increases** the risk of endometrial cancer, in **post-menopausal**, but not in pre-menopausal women. On average the excess absolute risk is 1 per 250 post-menopausal women over 5 years¹⁴. The risk reverses after the treatment is stopped

Tamoxifen **increases** the risk of thromboembolic events (DVT and PE). Absolute risk varies with age and other underlying risk factors for thrombosis. On average the excess risk is 1 in 250 women over 5 years¹⁴. The risk for premenopausal women is lower

CONTRAINDICATIONS

not recommended if lifetime breast cancer risk <1.5 times the population risk

not recommended if previous bilateral mastectomy

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 who are pregnant, breast-feeding, or planning a pregnancy within the next 3 years

not recommended for women taking anticoagulants, hormone replacement therapy or combined oral contraceptive

not recommended for women taking strong CYP2D6 inhibitors (e.g. some antidepressants - consider changing the CYP2D6 inhibitor). Caution in women taking other medications that interact with tamoxifen http://www.drugs.com/drug_interactions.html

** 5mg tablet is not available. The 10mg tablet is not PBS subsidised for prevention, but can be prescribed as a non-PBS prescription and given every second day (the 10mg tablet is difficult to halve and 10mg every second day is reasonable given the long half life of tamoxifen)*

The details: Raloxifene

BREAST CANCER RISK REDUCTION

Raloxifene 60mg daily for five years, **lowers** the risk of breast cancer in post-menopausal women to a similar extent as tamoxifen in the short-term but is less efficacious in the longer term^{9,20}

For an individual woman the **absolute risk reduction** depends on her baseline breast cancer risk

Raloxifene should **not** be used for premenopausal women as there are no data on its efficacy in that setting

Raloxifene **does not** lower the relative risk of ER-negative breast cancer^{9,20}

Raloxifene has **not** been shown to lower all-cause mortality or breast cancer-specific mortality
level of confidence: medium

OTHER BENEFITS

Raloxifene **lowers** risk of fracture¹⁴

ADVERSE EFFECTS

Raloxifene and tamoxifen result in **similar** quality of life, but women on raloxifene report **worse** sexual function²¹

Raloxifene **increases** musculoskeletal problems, dyspareunia and weight gain compared with tamoxifen, but **decreases** gynaecologic problems, vasomotor symptoms, leg cramps and bladder control issues²¹

Raloxifene causes **fewer** cataracts than tamoxifen¹⁴

SERIOUS ADVERSE EFFECTS

Raloxifene **increases** the risk of thromboembolic events (DVT and PE). Absolute risk varies with age and other underlying risk factors for thrombosis. On average the excess risk is **less** than with tamoxifen, i.e. about 1 in 330 women over 5 years¹⁴.

Raloxifene does **not** increase the risk of endometrial cancer¹⁴

CONTRAINDICATIONS

not recommended for premenopausal women due to lack of specific data in this group

not recommended if lifetime breast cancer risk <1.5 times population risk

not recommended if previous bilateral mastectomy

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

caution in women taking medications that interact with raloxifene

http://www.drugs.com/drug_interactions.html

The details: Exemestane

BREAST CANCER RISK REDUCTION

Exemestane 25mg daily for five years, **lowers** the relative risk of breast cancer in the short-term in post-menopausal women by 63%¹⁰. There are **no** data on longer term efficacy

For an individual woman the **absolute risk reduction** depends on her baseline breast cancer risk

Exemestane should **not** be used for premenopausal women as it is not expected to have efficacy in that setting

Exemestane **does not** lower the relative risk of ER-negative breast cancer¹⁰

Exemestane has **not** been shown to lower all-cause mortality or breast cancer-specific mortality

ADVERSE EFFECTS

Exemestane **increases** vasomotor symptoms with, on average, an extra 1 in 12 women experiencing hot flushes when on exemestane¹⁰

Exemestane **increases** diarrhoea and nausea with, on average, about 1 in 25 women experiencing these when on exemestane¹⁰

Exemestane **increases** joint and muscle pain with, on average, an extra 1 in 30 women experiencing these symptoms while on exemestane¹⁰

SERIOUS ADVERSE EFFECTS

Exemestane does **not** increase endometrial cancer or thromboembolic risk¹⁰

Exemestane did **not** increase fractures or osteoporosis in the short-term in the one primary breast cancer prevention trial¹⁰, but is known to reduce bone density with 5 years of daily use in other settings

CONTRAINDICTIONS

not recommended for pre-menopausal women

not recommended if lifetime breast cancer risk <1.5 times population risk

not recommended if previous bilateral mastectomy

not recommended if taking hormone replacement therapy

not recommended if osteoporosis on bone density assessment less than 2 years prior (care in women with osteopaenia)

caution in women taking medications that interact with exemestane

http://www.drugs.com/drug_interactions.html

The details: Anastrozole

BREAST CANCER RISK REDUCTION

Anastrozole 1mg daily for five years, **lowers** the relative risk of breast cancer over 10 years in post-menopausal women by 49%¹¹.

For an individual woman the **absolute risk reduction** depends on her baseline breast cancer risk

Anastrozole should **not** be used for premenopausal women as it is not expected to have efficacy in that setting

Anastrozole does **not** lower the relative risk of ER-negative breast cancer

Anastrozole has **not** been shown to lower all-cause mortality or breast cancer-specific mortality

ADVERSE EFFECTS

Anastrozole **increases** vasomotor symptoms with, on average, an extra 1 in 12 women experiencing hot flushes when on anastrozole¹¹

Anastrozole **increases** vaginal dryness with, on average, an extra 1 in 30 women experiencing this¹¹

Anastrozole **increases** dry eyes with, on average, an extra 1 in 50 women experiencing this¹¹

Anastrozole can **increases** carpal tunnel syndrome with, on average, about 1 in 100 women experiencing this when on anastrozole¹¹

Anastrozole **increases** joint and muscle pain with, on average, an extra 1 in 50 women experiencing these symptoms while on anastrozole¹¹

SERIOUS ADVERSE EFFECTS

Anastrozole **does not** increase endometrial cancer or thromboembolic risk¹¹

Anastrozole did **not** increase fractures or osteoporosis in the short-term in the one primary breast cancer prevention trial, but **does** reduce bone density with 5 years of daily use in other settings

CONTRAINDICATIONS

Not recommended for pre-menopausal women

Not recommended if lifetime breast cancer risk <1.5 times population risk

Not recommended if previous bilateral mastectomy

Not recommended if taking hormone replacement therapy

Not recommended if osteoporosis on bone density assessment less than 2 years prior (care in women with osteopaenia)

caution in women taking medications that interact with anastrozole

http://www.drugs.com/drug_interactions.html

The details: Adverse Effect Summary Comparison*

		Potentially serious side effects:			Less serious side effects:			
	Drug	Blood clots (Thrombosis)	Endometrial (uterine) cancer	Osteoporosis (thin bones)	Hot flushes - sweats	Vaginal changes	Joint/muscle aches	Cataracts
Selective Estrogen Receptor Modulators (SERMS)	Tamoxifen	Rare	Rare	May help prevent	Common	Common (discharge)	-	Rare
	Raloxifene	Rarer	-	May help prevent	Common	Common (discharge)	-	Rarer
Aromatase Inhibitors (AIs)	Anastrozole	-	-	Rare	Common	Common (dryness)	Common	-
	Exemestane	-	-	Rare	Common	Common (dryness)	Common	-

*Note, not all adverse effects are included in this table

Prescribing

Tamoxifen is approved by the Therapeutic Goods Association (TGA) and the 20mg dose is also listed on the Pharmaceutical Benefits Scheme (PBS) for reduction of breast cancer risk in women with a lifetime risk that is at least 1.5 times the population risk. Tamoxifen 10mg is not PBS listed. Raloxifene is TGA approved for the reduction of breast cancer in post-menopausal women at high risk of the disease (defined as previous breast biopsy showing lobular carcinoma in situ or atypical hyperplasia, or one or more 1st degree relatives with breast cancer, or a 5-year predicted risk of

breast cancer of $\geq 1.66\%$ based on the modified Gail model), but has not been submitted for PBS listing. Neither of the AIs have been submitted for TGA or PBS listing for a primary breast cancer risk reduction indication, but they can be prescribed “off-label”. The cost of filling a private (non-PBS) prescription for tamoxifen 10mg, raloxifene, exemestane and anastrozole can vary considerably between different pharmacies.

PRE-TREATMENT CHECKLIST

1. **Formally assess breast cancer risk** using iPrevent or other validated tool. If you are concerned about the cancer family history consider referral to your local clinical genetics service

2. **Full medical history:** including current medication use (check for any possible interactions at http://www.drugs.com/drug_interactions.html and focussing on possible contraindications. For premenopausal women: check childbearing plans and if appropriate give advice on non-hormonal contraceptive methods while on tamoxifen

3. **Determine menopausal status.**

Consider post-menopausal only if:

Aged 60 or older or

Bilateral oophorectomy or

Younger than 60 yo with uterus in situ but with amenorrhoea for >12 months in the absence of another explanation such as continuous pill use, Mirena IUD, pregnant or breastfeeding or

Aged <60 without a uterus and with FSH level >30IU/L

4. **Clinical examination:** ensure breast examination is normal

5. **Imaging:** If appropriate age for imaging, ensure normal bilateral breast MRI or mammogram within the last 12 months

PRESCRIBING

Consider initial trial of 6-8 weeks and then assess and manage side-effects or cease as necessary. Women who don't tolerate one type of risk-reducing agent, may tolerate a lower dose (in the case of tamoxifen) or change to a different agent (in the case of post-menopausal women)

Tamoxifen: 20mg daily for 5 years (oral), 30 tablets and 5 repeats (i.e. PBS listed version for prevention) or 10 mg every second day for 3 years, (note: not-PBS listed for prevention), if 20mg daily not tolerated. Instruct premenopausal women to commence tamoxifen on day 1 of the menstrual cycle to ensure they are not pregnant. Encourage prompt reporting of any post-menopausal vaginal bleeding. Educate regarding symptoms and management of thrombosis. Advise to cease tamoxifen 4-6 weeks prior to any planned elective surgery. Emphasise requirement for effective mode of non-hormonal contraception, potential for “morning after pill” if emergency post-hoc contraception needed, and early reporting if pregnancy suspected. Advise premenopausal women of the need to cease tamoxifen at least 3 months prior to conception.

Raloxifene: 60mg daily for 5 years (oral) Educate regarding symptoms and management of thrombosis

Exemestane 25mg daily for 5 years (note: not PBS listed for prevention). Provide advice on maximising bone health including smoking cessation, calcium and Vitamin D, sunlight, weight-bearing exercise

Anastrozole 1mg daily for 5 years (note: not PBS listed for prevention). Provide advice on maximising bone health including smoking cessation, calcium and Vitamin D, sunlight, weight-bearing exercise

Cost – considerable variation between pharmacies for non-PBS scripts; suggest “ring around for best price”

MONITORING

To be done by the prescribing clinician

Schedule: minimum annual review until treatment stopped

Reassess breast cancer risk especially if new genetic testing performed in family or new cancer family history

Review side-effects, especially post-menopausal vaginal bleeding. Actively manage side-effects.

Consider referral to gynaecologist or menopause clinic if necessary

Review adequacy of contraception (if pre-menopausal)

Re-check contraindications, in case of changed medical history

Annual breast imaging (if age-appropriate)

Breast examination

Reassess bone density every 2 years if on AI

Cease medication after a total of 5 years

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.

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