Greater Manchester guideline for use of risk-reducing endocrine treatment in women who have never had breast cancer, but have a moderate or high risk of future breast cancer

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Protocol for risk-reducing endocrine therapy

- The NICE guideline on familial breast cancer (CG164) recommends that patients with an increased risk of breast cancer are managed through the use of standardised resources, written protocols and written patient information.
- This guideline is designed for use by advanced nurse practitioners, breast care nurses and GPs with extended roles in breast disease, who have undergone specific training in family history assessment and the use of risk-reducing endocrine therapy.
- The guideline should be used within dedicated family history clinics and in conjunction with the NICE guidelines on breast cancer family history, the Greater Manchester Patient Information documents, the Greater Manchester Breast Cancer Risk Assessment Document and the Greater Manchester Primary Care Prescription Document. All documents can be accessed via the Greater Manchester Cancer Website: https://gmcancer.org.uk/cancer-pathway-boards/breast/endocrine-therapy/
- The protocol below has been developed to facilitate the prescription of preventive medication in primary care. It has been ratified by Greater Manchester Cancer and approved by the Greater Manchester Medicines Management Group.

Implementation of this guideline

- We have developed this protocol to facilitate the prescription of risk-reducing endocrine medications safely and efficiently, so that eligible women have equitable access to risk-reducing medication regardless of where they live.
- Use the *Greater Manchester Breast Cancer Risk Assessment Document* to document the patient's risk assessment and identify any potential contraindications, cautions or drug interactions (link above).
- Use your standard breast cancer risk assessment tool to calculate the patient's future risk of breast cancer.
- Use the algorithms below to assess whether women are eligible for risk-reducing endocrine medication and guide the decision about risk-reducing medication options.
- Use the *Greater Manchester Risk-reducing Endocrine Therapy Prescription Document* to inform the GP of the treatment plan (link above).
- Ensure a shared approach to decision-making with the use of the *Greater Manchester Risk-reducing Endocrine Therapy Patient Information Documents (link above).*

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Use of risk-reducing endocrine medication

- Uptake of risk-reducing endocrine medication is widely reported to be approximately 10%, but recent data suggest that only 1-2% of women within established high risk breast cancer screening services have heard of risk reducing medication including tamoxifen (Phillips et al).
- A recent poll of family history services in Greater Manchester and Mid and East Cheshire, showed that only 2 of 7 family history clinics prescribe risk-reducing endocrine medication for prevention themselves, with 5 of 7 referring on to either the regional centre Manchester University Foundation Trust or Primary Care for further advice and prescription.
- This creates a significant access barrier for eligible women and places an unacceptable burden on GPs to discuss the benefits and risks of risk-reducing endocrine therapy without appropriate training. Indeed, in Phillips et al, 80% of primary care physicians lacked confidence in prescribing tamoxifen for this indication.

Tamoxifen

- Tamoxifen is a selective oestrogen receptor modulator (SERM) that was approved for breast cancer risk reduction by NICE in 2013, for women who do not have an increased risk of thromboembolic disease.
- Tamoxifen was licensed for this indication in 2018.
- Meta-analysis of preventive clinical trials demonstrate a breast cancer **risk reduction of approximately 35%** with tamoxifen 20mg taken daily for 5 years.
- Tamoxifen should be stopped at least 3 months before trying to conceive. Risk-reducing endocrine therapy should be taken for 5 years continuously, therefore, if the patient has not completed her family, consider delaying risk-reducing endocrine therapy until she has completed her family.
- Stop tamoxifen 6 weeks before elective surgery.
- Tamoxifen can cause endometrial cancer in postmenopausal women and is not recommended for breast cancer risk-reduction in post-menopausal women with an intact uterus, in whom anastrozole or raloxifene are preferred.
- Tamoxifen is on the Greater Manchester Medicines Management Group (GMMMG) '*Green (specialist advice) list*'. This means it is suitable for initiation by primary care following written or verbal advice from a specialist service.

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Tamoxifen treatment during the peri-menopause

- If women have had menstrual bleeding (even if irregular) within the last 12 months, they should be treated according to the 'pre and peri-menopausal' algorithm of the Greater Manchester risk-reducing endocrine therapy guideline.
- If women are aged 45-50 years, and are commenced on risk-reducing tamoxifen treatment, they should be advised to contact the family history service once they have been amenorrhoeic for 12 months, for confirmation of menopausal status (serum LH, FSH and oestradiol).
- If blood tests confirm the patient to be post-menopausal, follow the Greater Manchester post-menopausal risk-reducing endocrine medication algorithm to assess if the patient can be switched to anastrozole.
- Anastrozole is the preferred preventive therapy in postmenopausal women unless severe osteoporosis is present.

Anastrozole

- Anastrozole is an aromatase inhibitor (AI), which inhibits the production of oestrogen in post-menopausal women. By reducing oestrogen levels, anastrozole reduces the chance of breast cancer developing.
- Clinical trials have shown anastrozole to **reduce the risk of breast cancer by 50%** when taken for 5 years at a dose of 1mg daily.
- Anastrozole is approved by NICE (CG164) for risk-reducing treatment in post-menopausal women who do not have severe osteoporosis.
- Anastrozole was licensed for this indication in 2023.
- Risk-reducing anastrozole is on the Greater Manchester Medicines Management Group (GMMMG) '*Green (specialist advice) list*'. This means it is suitable for initiation by primary care following written or verbal advice from a specialist service.
- See next page for information about monitoring and managing bone health whilst taking risk-reducing anastrozole.

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Monitoring bone health for patients taking risk-reducing anastrozole

- It is appropriate to request that primary care colleagues monitor a patient's bone health, but general practice should be provided with adequate and specific guidance for women taking risk-reducing endocrine therapy.
- The Greater Manchester Risk-Reducing Endocrine Therapy Prescription Document provides bone health guidance for general practitioners and should be used when recommending risk-reducing endocrine therapy. [add link]
- Patients who are commenced on risk-reducing anastrozole should have a bone density scan within 3 months of commencing treatment.
- If the T-score is within normal limits, no treatment is required and no further bone density scan is needed.
- If the T-score is between -1 and -2, the GP should start vitamin D and calcium supplementation and repeat the bone density scan in 2 years.
- If the T-score is between -2 and -4, the GP should start oral bisphosphonates in addition to vitamin D and calcium, and repeat the bone density scan in 2 years.
- If the T-score is below -4, anastrozole should be discontinued and the patient referred back to the family history clinic for discussion of raloxifene or tamoxifen. The GP should still ensure the patient is prescribed vitamin D and calcium supplementation and bisphosphonates.

Raloxifene

- Raloxifene is a selective oestrogen receptor modulator (SERM)
- Raloxifene is licensed for the treatment of osteoporosis and so is very useful for patients who have a moderate or high breast cancer risk and also have osteoporosis.
- Raloxifene is approved by NICE (CG164) for risk-reducing treatment in post-menopausal women who cannot take anastrozole or tamoxifen due to osteoporosis or endometrial cancer risk.
- As raloxifene was not originally authorized for risk-reduction, this is an 'off-label' or 'unlicensed' use, but NICE is satisfied that there is enough evidence to support its use in this setting.
- Clinical trials have shown raloxifene to **reduce the risk of breast cancer by approximately 25-30%** when 60mg raloxifene is taken daily for 5 years.
- Raloxifene is on the Greater Manchester Medicines Management Group (GMMMG) '*Green (specialist initiation) list*'. This means that it is suitable for ongoing prescribing within primary care, following initiation by a specialist service. The patient's first prescription for Raloxifene must therefore be completed in secondary care.

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Shared approach to decision-making using the Greater Manchester Risk-Reducing Endocrine Therapy Patient Information Documents[1]

Guidance for PRE- and PERI-MENOPAUSAL women[2]

Life time risk from age of 20	Less than 17%
10 year risk between ages of 40 and 50	Less than 3% (less than 5% at age 50)

Population risk

Do **not** offer risk-reducing endocrine treatment.

Discuss life style changes that reduce the risk of breast cancer
- Weight loss
- Reduction in alcohol intake
- Regular exercise
- Stopping smoking

Promote the NHS Breast Screening Programme
- 3 yearly mammograms from the age of 50 to 70
- Self-referral after 70 years of age

Encourage breast awareness
- Discuss regular self-examination of breasts with patient
- Ensure patient is aware of red flag symptoms of breast cancer
  - Lump in the breast or axilla
  - Change to the skin of the breast or nipple
  - New nipple inversion
  - Unilateral, bloody or clear nipple discharge

Life time risk from age of 20	17% or greater, but less than 30%
10 year risk between ages of 40 and 50	3% - <8% (5% - <8% at age 50)

MODERATE risk

OFFER risk reducing endocrine medication

Is the patient 35 years of age or over?

Yes

DVT risk assessment:
- Has the patient had previous DVT or PE?
- Does the patient have a first degree relative with history of DVT/PE (without precipitating factors)?
- Does the patient have a BMI greater or equal to 35?
- Does the patient have significant limitations to her mobility?
- Does the patient have significant cardiac or respiratory co-morbidity?[3]

Endometrial assessment:
- Does the patient have a family history of endometrial cancer?
- Is the patient known to have endometrial hyperplasia?

No to all

TAMOXIFEN
20mg once per day for 5 years[4]

Discontinue tamoxifen 3 months before trying to conceive

Discontinue tamoxifen 6 weeks before surgery

Do not offer risk-reducing endocrine medication to patients who have had bilateral mastectomy

Yes to any

Not for tamoxifen treatment.
Risks of tamoxifen treatment may outweigh benefits for this patient.

For patients with BMI >35, advise weight loss to reduce breast cancer risk.

For patients with other DVT/PE risks, recommend that the patient contacts family history service once post-menopausal to consider an aromatase inhibitor.

Life time risk from age of 20	30% or greater
10 year risk between ages of 40 and 50	8% or greater

HIGH risk

RECOMMEND risk reducing endocrine medication

No

Not for risk reducing endocrine treatment at current age.

Recommend that the patient contacts the family history service at 35 years of age to consider risk reducing endocrine medication

[1]Greater Manchester Risk-Reducing Endocrine Therapy Patient Information Documents can be found via the following link:
https://gmcancer.org.uk/cancer-pathway-boards/breast/endocrine-therapy/

[2]Consider a patient to be post-menopausal if they have had 12 continuous months without menstruation. Women under the age of 55 years, without a uterus but with at least one ovary in situ, or with a hormonal IUD (Mirena coil) in situ, will/may have no menstruation but may be pre-menopausal. In such cases, serum analysis of menopausal status will be required.

[3]Consider a patient to have severe cardiac or respiratory co-morbidity if they have a medical history of: myocardial infarction, angina, cardiac failure, pacemaker, atrial fibrillation, severe COPD or other respiratory disorder that limits the activities of daily living.

[4]Please use the Greater Manchester Risk-Reducing Endocrine Therapy Assessment Document and Primary Care Prescription Document which can be found on the Greater Manchester Cancer Website
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Shared approach to decision-making using the Greater Manchester Risk-Reducing Endocrine Therapy Patient Information Documents[1]

Guidance for POST-MENOPAUSAL women[2]

Life time risk from age of 20	Less than 17%
10 year risk between ages of 40 and 50	Less than 3% (less than 5% at age 50)

Population risk

Do **not** offer risk-reducing endocrine treatment.

Discuss life style changes that reduce the risk of breast cancer
- Weight loss
- Reduction in alcohol intake
- Regular exercise
- Stopping smoking

Promote the NHS Breast Screening Programme
- 3 yearly mammograms from the age of 50 to 70
- Self-referral after 70 years of age

Encourage breast awareness
- Discuss regular self-examination of breasts with patient
- Ensure patient is aware of red flag symptoms of breast cancer
  - Lump in the breast or axilla
  - Change to the skin of the breast or nipple
  - New nipple inversion
  - Unilateral, bloody or clear nipple discharge

Life time risk from age of 20	17% or greater, but less than 30%
10 year risk between ages of 40 and 50	3% - <8% (5% - <8% at age 50)

MODERATE risk

OFFER risk reducing endocrine medication

Life time risk from age of 20	30% or greater
10 year risk between ages of 40 and 50	8% or greater

HIGH risk

RECOMMEND risk reducing endocrine medication

Is the patient under 70 years of age?

No

Not for risk reducing endocrine treatment at current age.

Risks of endocrine treatment may outweigh benefits.

Yes

Is the patient known to have severe osteoporosis[4]?

Yes

ANASTROZOLE
1mg once per day for 5 years[5,6,7]

No

DVT risk assessment:
- Has the patient had previous DVT or PE?
- Does the patient have a first degree relative with history of DVT/PE?
- Does the patient have a BMI greater or equal to 35?
- Does the patient have significant limitations to her mobility?
- Does the patient have significant cardiac or respiratory co-morbidity?[3]

Yes to any

Not for risk reducing endocrine medication.

Risks of endocrine treatment may outweigh benefits.

For patients with BMI >35, advise weight loss to reduce breast cancer risk.

No to all

Has the patient had a hysterectomy?

Yes

TAMOXIFEN
20mg once per day for 5 years[5,6,7]

No

RALOXIFENE
60mg once per day for 5 years[5,6]

[1]Greater Manchester Risk-Reducing Endocrine Therapy Patient Information Documents can be found via the following link:
https://gmcancer.org.uk/cancer-pathway-boards/breast/endocrine-therapy/

[2]Consider a patient to be post-menopausal if they have had 12 continuous months without menstruation. Women under the age of 55 years, without a uterus but with at least one ovary in situ, or with a hormonal IUD (Mirena coil) in situ, will/may have no menstruation but may be pre-menopausal. In such cases, serum analysis of menopausal status will be required.

[3]Consider a patient to have severe cardiac or respiratory co-morbidity if they have a medical history of: myocardial infarction, angina, cardiac failure, pacemaker, atrial fibrillation, severe COPD or other respiratory disorder that limits the activities of daily living.

[4]Severe osteoporosis should be defined as T-score <-4.

[5]Women should have their bone mineral density assessed when commenced on anastrozole treatment. See notes accompanying this algorithm and/or the Greater Manchester Risk-reducing Endocrine Therapy Prescription Document for further details.
https://gmcancer.org.uk/cancer-pathway-boards/breast/endocrine-therapy/

[6]Please use the Greater Manchester Risk-Reducing Endocrine Therapy Assessment Document and Primary Care Prescription Document which can be found on the Greater Manchester Cancer Website
https://gmcancer.org.uk/cancer-pathway-boards/breast/endocrine-therapy/

[7]Do not offer risk-reducing endocrine medication to patients who have had bilateral mastectomy

[8]Discontinue tamoxifen 6 weeks before elective surgery