York Hospitals NHS
NHS Foundation Trust

Use of hormonal medication in patients with an elevated breast cancer risk

Women can have an increased risk of breast cancer due to

- personal history of breast cancer
- family history of breast cancer
- biopsy proven high risk lesions, e.g. LCIS

If your patient has a family history and has not been assessed, please consult the family history referral guidelines first. This guidance applies only to women who have had their risk accurately assessed as being elevated due to one of these three criteria.

The guidance is for the use of hormonal contraceptives and hormone replacement therapy in women with an elevated breast cancer risk.

HRT

In women with elevated breast cancer risk, use of HRT should be used to manage oestrogen deficiency symptoms only (vasomotor symptoms such as hot flushes and sweats or urogenital symptoms such as vaginal dryness). The exception to this is in women with BRCA1/2 mutations who have undergone risk reducing oophorectomy. As a general principle, non-hormonal alternatives should be tried first.

Women with a personal history of breast cancer

Breast multi-disciplinary teams are not best placed to manage and provide the most suitable follow-up for menopausal problems, which can be complex to resolve and are best dealt with by health professionals with an interest in the menopause – consider referral to a practitioner with expertise in gynaecological-endocrinology.

- Systemic HRT is not recommended for women taking an aromatase inhibitor. (NICE)
- Systemic HRT in women taking tamoxifen may not increase risk but evidence is lacking (BMS)
- Avoid progestogens (BMS)
- Switches to endocrine breast cancer treatment (i.e. from one drug to another) may alleviate symptoms of estrogen deficiency and arthralgia (BMS)
- Women on tamoxifen should not use St John's wort, soy or red clover due to potential interactions (BMS)
- Mirena coil – risk of recurrence appears to be elevated with continuous preparations of combined HRT, including levonorgestrel intra-uterine system (LNG-IUS)

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Vasomotor symptoms

- Use lifestyle and non-hormonal alternatives for first-line management of vasomotor symptoms, recognising HRT could be considered if symptoms are refractory (NICE, BMS)
- Clonidine, pregabalin and gabapentin may be used for vaso-motor symptoms but side effects may limit compliance (BMS)
- Women on tamoxifen should not use SSRIs or SNRIs (particularly fluoxetine and paroxetine) to manage vaso-motor effects due to their inhibitory action on the tamoxifen anti-cancer effects (BMS).
- SSRIs and SNRIs can be used in women on aromatase inhibitors and in women with ER negative cancers.

Vulvo-vaginal symptoms

- If treatment with vaginal moisturisers and lubricants (e.g. KY jelly, replens, astroglide) fails to alleviate symptoms, topical oestrogen can be discussed (low and ultra-low dose topical oestrogen), where systemic therapy would not be appropriate (NICE)
- Women with ER negative cancers can use low-dose topical oestrogens e.g Gynest 0.01% cream and are very unlikely to be at increased breast cancer risk (Oxford)
- Women with ER positive cancers on Tamoxifen can use low-dose topical oestrogens e.g. Gynest 0.01% cream and are very unlikely to be at increased breast cancer risk (Oxford)
- Women with ER positive cancers on aromatase inhibitors should use non-hormonal lubricants and consider, if marked problems due to vaginal symptoms, sparing use of low-dose topical oestrogens e.g. Gynest 0.01% cream with an associated theoretical increase in breast cancer (recurrence) risk (Oxford) The BMS advice against using topical oestrogens in women taking aromatase inhibitors.

Women with a moderate to high risk family history of breast cancer

- Lifestyle and non-hormonal alternatives should be used as first-line management of vasomotor symptoms in high-risk women, HRT may be needed for severe, refractory symptoms (BMS)
- In BRCA1/2 gene mutation carriers, after risk-reducing BSO, add-back HRT (combined HRT if they have a uterus, oestrogen-only HRT if they don't have a uterus) can be used until the age of an expected natural menopause (51-52), after which non-hormonal alternatives are used as first-line management for symptom control (BMS, NICE)
- HRT usage in a woman at familial risk should be restricted to as short a duration and as low a dose as possible. Oestrogen-only HRT should be prescribed where possible. (NICE)
- A woman having an early (natural or artificial) menopause should be informed of the risks and benefits of HRT, but generally HRT usage should be confined to women younger than age 50 years if at moderate or high risk (NICE)

Women with biopsy proven high risk lesions (e.g. LCIS)

- Lifestyle and non-hormonal alternatives should be used as first-line management of vasomotor symptoms in high-risk women, HRT may be needed for severe, refractory symptoms (BMS)
- No further guidance available but advise treat as personal history of cancer.

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Hormonal contraceptives

Women with a personal history of breast cancer

- Avoid the oral contraceptive pill (risk of recurrence increased)
- Mirena coil – risk of recurrence appears to be elevated with continuous preparations of combined HRT, including levonorgestrel intra-uterine system (LNG-IUS) – the effects with it's use as a contraceptive are presumably the same. The Dutch guidelines suggest it may be considered for women with ER negative tumours.

Women with a moderate to high risk family history of breast cancer

- Advice to women up to age 35 years with a family history of breast cancer should be in keeping with general health advice on the use of the oral contraceptive pill (i.e. it can be used) (NICE)
- Women aged over 35 years with a family history of breast cancer should be informed of an increased risk of breast cancer associated with taking the oral contraceptive pill (i.e. consider alternatives forms of contraception) (NICE)
- If contemplating OCP use, (cancer.org)
    - Use a low-dose oestrogen OCP – risk of breast cancer appears not to be increased
    - Avoid ethynodiol diacetate (risk increased)
    - Avoid triphasic OCPs with an average dose of 0.75 mg of norethindrone (risk increased)

Women with biopsy proven high risk lesions (e.g. LCIS)

- No guidance available
- Suggest avoiding OCP

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References

Personal communication from Dr N Levitt, Consultant in Medical Oncology, Oxford University Hospitals NHS Trust (see below)

British Menopause Society Consensus Statement: The risks & benefits of HRT before and after a breast cancer diagnosis. https://associationofbreastsurgery.org.uk/media/64949/cancer-care-v3.pdf accessed on 11th September 2019

British Menopause Society Consensus Statement:, The diagnosis of the menopause and management of oestrogen deficiency symptoms and arthralgia in women treated for breast cancer. https://associationofbreastsurgery.org.uk/media/64949/cancer-care-v3.pdf accessed on 11th September 2019

NICE CG164 Familial breast cancer: classification, care and managing breast cancer and related risks in people with
a family history of breast cancer (CG164) -
https://associationofbreastsurgery.org.uk/media/64259/nice-familial-breast-cancer-classification-care-and-managing-breast-cancer-and-related-risks-in-people-with-a-family-history-of-breast-cancer-pdf-35109691767493.pdf accessed on 11th September 2019

Gaffield ME, Culwell KR, Ravi A. Oral contraceptives and family history of breast cancer. *Contraception* 80(4):372-80

Breastcancer.org article on the oral contraceptive and breast cancer risk.
https://www.breastcancer.org/research-news/study-questions-birth-control-and-risk accessed 11th September 2019

Dutch breast cancer guidelines 2012 accessed 11th September 2019

From ABS / BMS consensus statement

HRT in women at high baseline risk of breast cancer In women with a familial risk or a high-risk benign breast condition (i.e. biopsy-proven epithelial atypia or Lobular Carcinoma In Situ), HRT exposure has not been shown to have an additive effect on risk of diagnosis.7,9 Its absolute impact therefore increases as a woman's baseline risk rises. Although it is recommended lifestyle and non-hormonal alternatives should be used as first-line management of vasomotor symptoms in high-risk women, HRT may be needed for severe, refractory symptoms and should be considered on an individual basis following specialist and patient discussion.7,9,11,15 In the absence of data, it would be difficult to justify use of HRT for indications other than symptom relief, where longer duration therapy would be indicated as for example in population-risk women with POI. The exception to this is BRCA1 and BRCA2 mutation carriers, who have undergone risk-reducing bilateral salpingo-oophorectomy (BSO). Here, add-back HRT (unopposed or combined) has not been shown to diminish the risk-reducing benefit of BSO on subsequent risk of breast cancer diagnosis but clinical data is very limited.7,9 The current recommendation is that after risk-reducing BSO, add-back HRT is used until the age of an expected natural menopause, after which non-hormonal alternatives are used as first-line management for symptom control and the prevention of chronic, oestrogen-deficiency health problems.7,15

Use of HRT after breast cancer Women treated for breast cancer may experience multiple symptoms including hot flushes and vulvo-vaginal atrophy as a consequence of a natural menopause or as a side effect of treatment aimed at reducing the activity or synthesis of oestrogen. Iatrogenic

symptoms are not limited to women with hormone sensitive disease as chemotherapy-induced ovarian suppression will occur irrespective of the oestrogen receptor (ER) status of the primary tumour. Systemic HRT and topical (vaginal) oestrogen are the most efficacious treatments but contra-indicated in women with ER positive disease. HRT, however, may not be without risk for those with an ER negative primary. Although there is high concordance in hormone receptor status between first and second primary breast cancers, a minority with an ER negative primary may present with an ER positive contralateral cancer (up to 30%) and approximately 8% may present with ER positive metastatic disease.16,17 It is unknown whether lifestyle risk factors have a part in this. It has been hypothesised risk will not be increased in women taking concurrent tamoxifen due to the very high binding affinity for the oestrogen receptor. However, as aromatase inhibitors reduce oestrogen production it would be counter-intuitive to prescribe concomitant exogenous sex hormones.7,9,11 Despite theoretical predictions, clinical evidence is inconclusive due to the premature closure of all three randomised trials of HRT in breast cancer patients, when all were underpowered. These were stopped when interim analysis of one trial showed an increased risk of recurrence. Overall risk was not increased following interim analysis of the two other trials or meta-analysis of all three (hazard ratio 1.45, 95% confidence interval 0.93- 2.26).18 Tibolone, a synthetic steroid with weak oestrogen, progestogen and/or androgen activity, has been used as an alternative to HRT for symptom relief but a large randomised study in breast cancer patients was also stopped prematurely due to an increased risk of recurrence (hazard ratio HR 1.40, 95% CI 1.14-1.70).19
NICE has taken a pragmatic approach, recommending lifestyle and non-hormonal alternatives for first-line management of vasomotor symptoms, recognising HRT could be considered if symptoms are refractory.11,20 For women with symptoms due to vulvo-vaginal atrophy if treatment with vaginal moisturisers fails to alleviate symptoms, topical oestrogen can be discussed.11 There is generally lower concern about systemic absorption from low and ultra-low dose topical oestrogen, which is minimal and could be acceptable where systemic therapy would not be. Neither systemic HRT nor topical oestrogen are recommended in women taking an aromatase inhibitor and with both, prescription should only take place after discussion between the patient, her primary health care and breast specialist team.11

Advice regarding topical oestrogens for women with vaginal atrophy post breast cancer (from Oxford breast MDT)

Women who have had ER-negative breast cancers can be reassuring that use of topical oestrogens does not put them at increased risk of problems from their breast cancer.

Women with ER-positive breast cancers who are on tamoxifen can be prescribed topical oestrogens. We would recommend trying Gynest 0.01% oestrogen cream first as this contains the lowest concentration. Tamoxifen blocks the oestrogen receptor and should therefore prevent any adverse effects from the oestrogen at other sites in the body. As a result, women can be reassured that topical oestrogens are very unlikely to put them at any increased risk of problems from their breast cancer.

Women on aromatase inhibitors (Anastrozole, Letrozole, Exemestane): Women on these drugs do quite commonly have local effects from vaginal oestrogen deprivation. If non-hormonal lubricants do not work, then it is reasonable to try an oestrogen containing preparation. We would recommend Gynest 0.01% cream as this has the lowest concentration of oestrogen. It's use should be as intermittent and sparing as possible to relieve symptoms. Non-hormonal lubricants can be used in addition. We believe there is a little systemic absorption of the oestrogen; however this is thought to diminish as the vaginal wall repair. Although there is a theoretical risk to such treatment, we feel that it is warranted in women who have marked problems due to vaginal atrophy.

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This statement has been agreed by the Oxford Breast MDT.

Hormone replacement therapy (from NICE CG164)

1.7.10 Women with a family history of breast cancer who are considering taking, or already taking, HRT should be informed of the increase in breast cancer risk with type and duration of HRT. [2004]

1.7.11 Advice to individual women on the use of HRT should vary according to the individual clinical circumstances (such as asymptomatic menopausal symptoms, age, severity of menopausal symptoms, or osteoporosis). [2004]

1.7.12 HRT usage in a woman at familial risk should be restricted to as short a duration and as low a dose as possible. Oestrogen-only HRT should be prescribed where possible. [2004]

1.7.13 A woman having an early (natural or artificial) menopause should be informed of the risks and benefits of HRT, but generally HRT usage should be confined to women younger than age 50 years if at moderate or high risk (see also recommendations 1.7.53 and 1.7.54). [2004]

1.7.14 Alternatives to HRT should be considered for specific symptoms such as osteoporosis or menopausal symptoms (see also recommendations 1.7.53 and 1.7.54). [2004]

1.7.15 Consideration should be given to the type of HRT if it is being considered for use in conjunction with risk-reducing gynaecological surgery.

HRT for women with no personal history of breast cancer who have a bilateral salpingooophorectomy before the natural menopause

1.7.53 When women with no personal history of breast cancer have either a *BRCA1* or *BRCA2* mutation or a family history of breast cancer and they have had a bilateral salpingo-oophorectomy before their natural menopause, offer them:

combined HRT if they have a uterus

oestrogen-only HRT if they don't have a uterus

up until the time they would have expected natural menopause (average age for natural menopause is 51–52 years). [2013]

1.7.54 Manage menopausal symptoms occurring when HRT is stopped in the same way as symptoms of natural menopause. [2013]

Hormonal contraceptives (from NICE CG164)

1.7.4 Advice to women up to age 35 years with a family history of breast cancer should be in keeping with general health advice on the use of the oral contraceptive pill. [2004]

1.7.5 Women aged over 35 years with a family history of breast cancer should be informed of an increased risk of breast cancer associated with taking the oral contraceptive pill, given that their absolute risk increases with age. [2004]

1.7.6 For women with *BRCA1* mutations, the conflicting effects of a potential increased risk of breast cancer under the age of 40 years and the lifetime protection against ovarian cancer risk from taking the oral contraceptive pill

should be discussed. [2004]

1.7.7 Women should not be prescribed the oral contraceptive pill purely for prevention of cancer, although in some situations reduction in ovarian cancer risk may outweigh any increase in risk of breast cancer. [2004]

1.7.8 If a woman has a *BRCA1* mutation and is considering a risk-reducing oophorectomy before the age of 40 years, the oral contraceptive pill should not be prescribed purely for the reduction in ovarian cancer risk. [2004]

Dutch guidelines

Remaining considerations (for women with a personal history of cancer)
The use of hormonal contraception is advised against on the basis of the same arguments as with HRT. A Mirena spiral may be considered in the case of hormone receptor-negative tumours. Substantiating literature is still lacking