Primary care Guidance for Hormone Replacement Therapy (HRT) in women at increased risk of breast cancer (BC)

Writing group: See appendix 1

Introduction

This document summarizes our current understanding of breast cancer risk associated with HRT use. It aims to assist in communication about HRT use and shared decision-making between primary and secondary care providers and women at increased risk of breast cancer. A more comprehensive discussion about HRT and other risks and benefits can be found here: https://cks.nice.org.uk/topics/breast-cancer-managing-fh/management/breast-cancer-managing-fh/.

There is no absolute contra-indication to HRT in women at increased risk of BC but information on potential risks may help in decision making and help to tailor type and duration of HRT treatment.

HRT and Breast Cancer Risk – the principles

There is now considerable evidence supporting the association between HRT use and an increased risk of developing breast cancer. Some broad principles for HRT and breast cancer risk are:

- The longer HRT is used the greater the risk of BC. There is very little if any increase in risk with < 1 year of use suggesting a short trial of HRT to determine reversibility of menopausal symptoms is safe.
- combined estrogen and progestogen containing HRT increases the risk of breast cancer more than estrogen alone
- The relative risk of breast cancer with HRT increases proportionally, independent of baseline risk. There is thus a greater absolute increase in risk with HRT the higher the woman's underlying risk of breast cancer.

Most HRT is initiated when women develop menopausal symptoms during the perimenopause around the age of 50 thus most calculations in this document use a starting age of 50. It is reasonable to assume that HRT taken up to the age of 50 will not increase the risk of BC above that of a woman with and average age of menopause (~50 years). Such HRT use will likely negate any BC protective effects of an early menopause.

Breast Cancer Risk Classification

Several tools are available for calculating a woman's breast cancer risk but this is done primarily in breast cancer family history clinics or by the genetics service. Several risk assessment models are available, such as CanRisk (https://www.canrisk.org/) and Tyrer-Cuzick (https://ems-trials.org/riskevaluator/), however, it is current NHS practice to assume that women without a family history of BC are at population risk. Research is ongoing to identify those at increased BC risk without a FH.

NICE guidance [https://www.nice.org.uk/Guidance/CG164] defines three risk categories:

- **Population or Near Population risk**:

1 in 8 women will develop breast cancer during their lifetime. For such women the 10-year risk of breast cancer from age 50 is approximately 3% and the 20-year risk approximately 6%.

- **Moderately increased risk**:

In this category, between 1 in 4 to 1 in 7 women will develop breast cancer during their lifetime. For these women the 10-year risk of breast cancer from age 50 is between 5 and 8% (Note the NICE guidance (CG164) giving a moderate 10-year risk of 3-8% is for women aged 40years).

- **High risk**:

Among women in this category, at least 1 in 3 women will develop breast cancer in their lifetime. The 10-year risk from age 50 is greater than 8%.

Types of HRT and Breast Cancer risk

1. Combined Estrogen + Progestogen containing HRT

The type and dose of estrogen and route of delivery (topical vs oral) does not appreciably change the risk of BC. However, the different types of progestogen may result in different levels of risk:

1.1. Synthetic progestins (eg levonorgestrel, norethisterone or MPA)

In tables 1 and 2 the risk increases with estrogen and oral or transdermal synthetic progestogens are presented for durations of use of <5 (table 1) and approximately 10 (table 2) years with follow up to a total of 20 years. Figures are provided for women in each of the three main risk categories. **Number needed to treat** can be a useful tool to discuss with patients as it helps to describe in real terms the impact of HRT ie how many women would need to be treated with HRT at their baseline risk level for 1 to develop BC who otherwise would not have done so.

Table 1. 20-year risks of BC after combined HRT use for **< 5 years ***

Risk Categories (10-year risk aged 50)	**No HRT 20-year BC risk**	**5 years HRT 20-year BC risk**	**Absolute increase in risk with HRT**	**Number Needed to Treat**
Population Risk (2.7% used)**	6.2%	7.7%	1.5%	67
Moderate risk 5-8% (6.5% used)	13.6%	17.4%	3.8%	26
High risk >8% (10% used)	19.8%	25.5%	5.7%	18

* Risk estimates derived from 20 year data from[1] ** from[2]

Table 2. 20-year risks of BC after combined HRT use for **approximately 10 years**

Risk Categories (10-year risk aged 50)	**No HRT 20-year BC risk**	**10 years HRT 20-year BC risk**	**Absolute increase in risk with HRT**	**Number Needed to Treat**
Population Risk (2.7% used)**	6.2%	9.4%	3.2%	31
Moderate risk 5-8% (6.5% used)	13.6%	21.2%	7.6%	13
High risk >8% (10% used)	19.8%	31.1%	11.3%	9

* Risk estimates derived from 20 year data from[1] ** from[2]

1.2. Micronized progesterone (eg Utrogestan)

- The risk of developing breast cancer may be lower with combination HRT containing estrogen and micronized progesterone.
- There are far fewer data from epidemiological studies that have examined this question and risk estimates are less certain.
- Estrogen plus micronized progesterone **taken for less than five years** may not increase the risk of BC.
- Estrogen plus micronized progesterone **taken for more than five years** increases the risk of BC to a similar degree as the synthetic progestogens in Tables 1 and 2 above.[1]
- Therefore, the general principle that the longer the duration of usage the higher the BC risk is likely to apply to micronized progesterone also.[1]
- There is a slightly higher risk with continuous vs intermittent dosing.

1.3. Dydrogesterone (Femoston)

- The risk of developing breast cancer may be lower with combination HRT containing estrogen and dydrogesterone than with HRT containing estrogen and other synthetic progestogens.
- The risk increase is evident with short term use but is approximately one third of that seen with other synthetic progestogens (tables 1 and 2)
- The general principle that the longer the duration of usage the higher the BC risk also applies to dydrogesterone. The risk at 10 years is also approximately 1/3rd of that seen with other synthetic progestogens.

1.4. Levonorgestrel-Releasing Intra Uterine Systems (LR-IUS; eg Mirena/Kyleena)

- In premenopausal women Levonorgestrel can be detected in the blood and breast tissue after LR-IUS insertion, albeit at lower levels than with the LNG POP.
- LR-IUS use in this population is associated with increased breast cancer risk in most, but not all cohort and case control studies.
- Only 2 studies have reported risk of BC with LR-IUS in women over the age of 50 but both show an increase in BC risk of comparable magnitude to the combined oral/transdermal HRT data in tables 1 and 2 above, including with LR-IUS and topical/oral estrogen combined.
- Although these data are not conclusive, and may suffer from confounding, they suggest that estrogen plus LR-IUS may not represent a safer approach to HRT from the perspective of BC risk.

2. Estrogen alone HRT

- The type and dose of estrogen and route of delivery (topical vs oral) does not appreciably change the risk of BC.
- Estrogen alone HRT does not appreciably increase BC risk in obese women (BMI>30kg/m2)
- Estrogen alone HRT increases the risk of breast cancer in a duration dependent manner but by a lesser amount than combined estrogen and progestogen HRT (Tables 3 and 4).

Table 3. 20 year risks of BC after estrogen alone HRT use for **< 5 years**

Risk Categories (10-year risk)	**No HRT 20 year BC risk**	**5 years HRT 20 year BC risk**	**Absolute increase in risk with HRT**	**Number Needed to Treat**
Population (2.7% used)**	6.2%	6.9%	0.7%	143
Moderate Risk 5-8% (6.5% used)	13.6%	15.3%	1.7%	59
High Risk >8% (10% used)	19.8%	22.4%	2.6%	38

* Risk estimates derived from 20 year data from[1] ** from[2]

Table 4. 20 year risks of BC after estrogen alone HRT use for **approximately 10 years**

Risk Categories (10-year risk)	**No HRT 20 year BC risk**	**10 years HRT 20 year BC risk**	**Absolute increase in risk with HRT**	**Number Needed to Treat**
Population (2.7% used)**	6.2%	7.3%	1.1%	91
Moderate Risk 5-8% (6.5% used)	13.6%	16.1%	2.5%	40
High Risk >8% (10% used)	19.8%	23.5%	3.7%	27

* Risk estimates derived from 20 year data from[1] ** from[2]

References

1. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019:394:1159-1168.
2. Huntley C et al. Breast cancer risk assessment for prescription of menopausal hormone therapy in women with a family history of breast cancer: an epidemiological modelling study. Br J Gen Pract. 2024;74:e610-e618.

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