BMS | Consensus Statement

Risks and Benefits of HRT before and after a Breast Cancer Diagnosis

Introduction

The risk of breast cancer diagnosis associated with hormone replacement therapy (HRT) is often assumed by health care professionals and the lay public alike to be very high, which may adversely influence decisions about its initiation and continuance.[1] This is despite the fact the risk conferred by HRT is of a similar degree to other postmenopausal lifestyle risk factors for breast cancer (e.g. obesity, alcohol), irrespective of phenotype.[2] There appear to be several reasons why HRT garners such adverse attention. Media reporting accompanying the publication of some clinical trials has often over emphasised the risks of HRT whilst studies not showing the adverse risks get little attention. The impact of HRT on breast cancer diagnosis is often discussed in isolation of its benefits and there is no or little simultaneous reference to the other lifestyle risk factors for breast cancer, to provide context when counselling women about its use.

HRT and the risk of being diagnosed with and dying from breast cancer

Numerous, mostly uncontrolled, observational studies have evaluated the association between HRT and outcomes from breast cancer with varying conclusions. However, clinical advice and prescribing habits have been largely influenced by findings from the 1997 Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) re-analysis of fifty-one world-wide observational studies and initial publications from the placebo-controlled, randomised Women's Health Initiative Study (WHI) and observational Million Women's Study (MWS) in 2002 and 2003 respectively.[3-6] The collaborative group re-analysis established a duration-dependent association of HRT with risk of diagnosis, emerging after 5 years' exposure (an overall risk ratio of 1.35). This appeared greater with combined rather than unopposed HRT and fell following cessation. The degree of risk with any HRT exposure was estimated to be equivalent to the impact of a delayed menopause (2.3% vs 2.8% per year respectively).[3] The WHI and MWS confirmed risk was greater with combined HRT but whilst the degree of estimated risk was in keeping with that from previous clinical studies (reported as an up to twofold increase), the results caused such concern that HRT prescribing fell significantly world-wide and this persisted regardless of subsequent studies also estimating associated risk was similar and small.[4-7] The WHI and MWS investigators placed emphasis on use of risk ratios and percentage change in risk, whose mis-interpretation spawned considerable, negative publicity. This could have been avoided by presenting findings using absolute excess or attributable risk.[8]

Taken as a whole, clinical studies to date have shown that where risk is increased, it is limited to lean women, there does not appear to be a dosage effect and there is no additive effect in women at elevated personal risk due to a family history or high-risk benign breast condition.[3,9] Overall, with use up to five years, exposure to any unopposed oestrogen (i.e. conjugated equine oestrogen [CEE], oestradiol or oestriol) is associated with minimal or no increased risk.[5,7] This appears to be unaffected by oestrogen type or route of administration (excepting implants where there is no clinical data). Some studies suggest risk might be increased with long-term use (that is for more than ten years) but this requires further confirmation.[7] For combined HRT, a duration-dependent increase in risk is associated with sequential and continuous preparations and appears elevated, regardless of route of administration, including delivery of progestogen via the levonorgestrel intra-uterine system (LNG-IUS).[7,9] There is some evidence suggesting risk may not be elevated if dydrogesterone or micronized progesterone are used in preference to synthetic progestogens in combined preparations.[7] In women with premature ovarian insufficiency (POI), in whom HRT is effective for the management of vasomotor symptoms and likely to lower the long-term risk of cardiovascular disease, prevent osteoporosis and have a beneficial effect on cognitive function, it is recommended that years of HRT exposure should be counted from the age of fifty and not at the age of HRT commencement (i.e. when POI is diagnosed).[3,10]

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In 2015, The National Institute for Health and Care and Excellence (NICE), published its menopause guidance (NG23).[11] This evidence-based review included evaluation of the short-term outcomes of HRT, with use for up to 5 years for the treatment of menopausal symptoms on breast cancer outcomes. The clinical studies eligible for review were mostly observational and ranged from low to moderate quality at best. Of randomised trials, only the WHI study was sufficiently powered for inclusion. Overall the findings did not differ significantly from those of previous evidence and it was recommended to base discussion of HRT around the following statements:

1. HRT with oestrogen alone is associated with no or little change in risk.
2. HRT with oestrogen and progestogen 'can be associated with an increase in the risk.'
3. Risk of diagnosis is not elevated in past users of HRT.
4. Any increase in risk 'is related to treatment duration and reduces after stopping HRT.'
5. No significant increase in breast cancer mortality was found. This has been confirmed subsequently with long-term follow-up of the WHI study and a large meta-analysis, where use of unopposed or combined HRT was not associated with any adverse effect on all cause, total cancer or breast cancer mortality.[12,13]

One of the strengths of the guidance is that findings related to risk of diagnosis were presented using absolute excess risk as recommended for enhancing patient experience in adult NHS services.[11] Doing so illustrates that most women, if exposed to HRT will never be diagnosed with breast cancer and is even more apparent and least biased if absolute risk is framed, which shows the number of women who could be diagnosed and those who would not be diagnosed if exposed to HRT (Table 1).

NICE also recommended HRT counselling should be individualized, accounting for non-modifiable factors that determine baseline breast cancer risk and exposure to modifiable lifestyle risk factors. It has been estimated just under a quarter of breast cancer diagnoses in the UK may be preventable by minimizing modifiable risk factor exposure where the proportion of breast cancers attributable to HRT exposure is estimated to be the same as that associated with lack of exercise (i.e. 3%) and less than those attributed to alcohol (6%) or postmenopausal overweight and obesity (9%).[14] Whilst risk factor modification will therefore have benefit for the population as a whole in reducing breast cancer diagnosis, it is not possible to predict on an individual level who will benefit or not as most women exposed to known risk factors, including HRT, are never diagnosed with breast cancer during their lifetime (Table 2).

Finally, in women at population risk for breast cancer, the overall risk: benefit ratio for both unopposed and combined HRT is favourable with overall reductions in all-cause mortality. It is factitious to discuss HRT without consideration that a risk factor for one health condition may protect against another.

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]

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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]

Summary

In women with a low underlying risk of breast cancer (i.e. most of the population):

1. The benefits of HRT in the short-term (up to 5 years' use) for symptom relief will exceed potential harm

2. The risk of breast cancer diagnosis associated with HRT is equivalent to, or less that of other lifestyle risk factors for breast cancer

3. Communicating risk in terms of absolute excess risk with framing, minimizes bias and misinterpretation

4. The potential risk of breast cancer diagnosis associated with unopposed or combined HRT should not be discussed in isolation of its other short and long-term benefits and risks

5. In women at high risk, if the use of HRT is considered, this should only be for the management of oestrogen deficiency symptoms

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Table 1: Adaptation of NICE menopause guidance reference table 3 with insertion of negative and positive framing of absolute risk [11]

	Absolute excess risk of breast cancer diagnosis per 1000 women aged 45 to 79*					
	Observational studies			Randomised studies		
	Excess	Diagnosed	Not diagnosed	Excess	Diagnosed	Not diagnosed
No HRT	–	23	977	–	23	977
Oestrogen only						
Past use	–	23	977	–	–	–
Current use	+6	29	971	-4	19	981
Duration of use < 5 years	+4	27	973	–	–	–
Duration of use 5 to 10 years	+5	28	972	–	–	–
Time since last use > 5 years	-5	18	982	-5	18	982
Combined HRT						
Past use	-3	20	980	–	–	–
Current use	+17	40	960	+5	28	972
Duration of use < 5 years	+12	35	965	–	–	–
Duration of use 5 to 10 years	+21	44	956	–	–	–
Time since last use > 5 years	-9	14	986	+8	31	969

* The absolute number of events has been calculated using a baseline risk population risk of 23/1000 women aged 45 to 79 years with 7.5 years of follow-up as estimated by NICE from 2010 Office of National Statistics data.[11] The duration of use selected (i.e. up to 5 years) reflects the average duration of HRT exposure in women in the UK prior to publication of the MWS.[6]

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Table 2: The impact of lifestyle risk factors on the absolute risk of breast cancer diagnosis in women at population risk; comparison of HRT with other lifestyle risk factors with negative and positive framing[9]

	Absolute risk of diagnosis per 1000 women aged 45 to 79*		
	Cancers diagnosed	Cancers not diagnosed	Excess risk
No exposure	23	977	–
Risk Increased			
Postmenopausal obesity or overweight	27-40	960-973	+4 to +17
Combined HRT (NICE observational studies)	40	960	+17
Alcohol (regular intake ≥ 6 g/day)	29	971	+6
Unopposed HRT (NICE observational studies)	29	971	+6
Combined HRT (NICE randomised studies)	29	971	+6
Smoking (current smoker)	26	974	+3
Risk reduced			
Unopposed HRT (NICE randomised studies)	17	983	-6
Physical activity (> 9 MET-h/wk)	13	987	-10

* The absolute number of events has been calculated using a baseline risk population risk of 23/1000 women aged 45 to 79 years with 7.5 years of follow-up as estimated by NICE from 2010 Office of National Statistics data.[11]