The specialist authority for menopause & post reproductive health

The benefits and risks of HRT before and after a breast cancer diagnosis

The British Menopause Society (BMS) is the specialist authority for menopause and post reproductive health in the UK. The BMS educates, informs and guides healthcare professionals, working in both primary and secondary care, on menopause and all aspects of post reproductive health.

BMS consensus statements, prepared by specialists from the BMS medical advisory council, address key disorders and controversial topics relating to menopause and post reproductive health. They reflect new studies together with recent medical and scientific information from articles in professional journals, plus informal consensus.

The consensus statements are evidence-based, comprehensively referenced and peer reviewed and they are regularly updated.

Introduction

This is an important and controversial topic. 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 that most women will not be diagnosed in their lifetime and any risk conferred by HRT is comparable or less than that of other postmenopausal lifestyle risk factors for breast cancer (e.g. obesity, alcohol).[2] 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. This consensus statement provides an overview of the association between HRT and breast cancer outcomes in women at low and higher risk of breast cancer. It has been updated in light of a recent meta-analysis in 2019 by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC)[3] and publication in 2020 of the long-term outcomes from the placebo-controlled, randomised Women's Health Initiative study (WHI).[3,4]

A summary of recommendations for clinical practice is provided at the end of this statement.

HRT and the risk of being diagnosed with breast cancer, studies pre-dating the 2019 CGHFBC[3] and 2020 WHI[4] study

To aid interpretation and provide context, the results of these two recent publications are discussed in context with key clinical studies pre-dating them, which have influenced UK HRT prescribing. Those that have largely shaped clinical practice include the 1997 CGHFBC re-analysis of 51 world-wide observational studies, previous publications from the randomised WHI study, the observational Million Women's Study (MWS) and the 2015 UK National Institute for Health and Care and Excellence Menopause Guidance (NG23).[5-9]

1. The 1997 CGHFBC 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).[5]
2. In 2002 and 2004, initial findings from the placebo controlled, randomised WHI study confirmed an overall increased risk of borderline significance with continuous combined HRT (i.e. 0.625mg conjugated equine oestrogen [CEE] plus 2.5mg medroxyprogesterone acetate [MPA]). Risk was not significantly increased, however, when subgroup analysis was performed by age group (i.e. 50 to 59, 60 to 69 and 70 to 79 years).[6] Unopposed oestrogen (i.e. 0.625mg CEE) was associated with a non-significant reduction in risk of diagnosis.[7] These contrasting outcomes can be explained by the effect of HRT on the reservoir of occult hormone sensitive cancers present in the breast at the time of its initiation. When deprived of oestrogen long-term, breast epithelium becomes susceptible to oestrogen-induced apoptotsis upon oestrogen re-exposure. Hence, in hormone naïve postmenopausal women, commencement of unopposed oestrogen reduces the growth of any occult breast cancers so they take longer to reach the size threshold for diagnosis and a decrease in risk of diagnosis is observed. Exposure to combined HRT is hypothesised to stimulate occult breast cancer growth leading to them reaching their size threshold for diagnosis sooner, therefore risk of diagnosis is increased.[10]
3. In 2003, the observational MWS reported risk of diagnosis to be increased with all HRT regimens, the greatest elevation in risk associated with combined preparations. In contrast with all other studies, the impact of HRT was observed with short-term use risk (i.e. 6 months to less than 2 years).[8] This erroneous finding has been attributed to ascertainment bias and underestimation of duration of HRT exposure. Further criticisms of the study methodology have been explained in detail elsewhere.[11]

Unfortunately, whilst the degree of estimated risk with combined HRT from the randomised WHI was between 1.2-1.3 and that of the MWS was in keeping with the 1997 CGHFBC and other observational study risk estimates (i.e. up to twofold increase), the adverse publicity their results generated caused a significant fall in HRT prescribing world-wide. Both study investigators placed emphasis on use of risk ratios and percentage change in risk, which were misinterpreted and could have been avoided by presenting findings using absolute numbers with framing.[12]

4. The 2015 NG23[9] included evaluation of the short-term outcomes of HRT, with use for up to 5 years on breast cancer outcomes.[9] 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.

Taken as a whole, clinical evidence *predating* the 2019 CGHFBC[3] and the July 2020 WHI[4] publication led to the following conclusions:

- HRT with oestrogen alone (CEE, oestradiol, oestriol) is associated with no or little change in risk and may not be increased with low-dose vaginal oestrogen.[9,13]
- Combined HRT, delivered by any route of administration, can be associated with an increased risk, which appears duration dependent.[9,14,15] A recent meta-analysis of observational data suggests an increased risk in all users of the levonorgestrel intra-uterine system (LNG-IUS), which is greater in women over 50.[16] Risk may not be elevated if dydrogesterone or micronized progesterone are used in preference to synthetic progestogens but further confirmatory evidence is needed.[13,14,17]
- Risk of diagnosis is not elevated in past users of HRT[9]
- Risk is limited to lean women (i.e. not overweight or obese)[5]
- There does not appear to be a dosage effect with oestrogen[15]
- There may not be an additive effect in women at elevated personal risk due to a family history or high-risk benign breast condition.[5,15]
- In women with premature ovarian insufficiency (POI), it is recommended that years of HRT exposure should be counted from the age of 50 and not at the age of HRT commencement when POI is diagnosed.[5,18]

The 2019 CGHFBC[3] and long-term follow-up of the WHI study (2020)

The 2019 CGHFBC[3] involved re-analysis of data from 58 published *and* unpublished, worldwide observational studies, however, the main outcomes reported were restricted to data from 24 prospective studies, which contributed 75% of the cases, half of these were from the widely criticised MWS. No results from the placebo controlled, WHI study published prior to 2019 were shown for comparison in the main paper. The most recent report from the randomised WHI study in July 2020 provided risk of diagnosis and mortality data in women allocated to receive unopposed CEE (0.625mg) or continuous combined HRT (CEE 0.625mg plus MPA 2.5mg daily) after a median follow-up of 16.9 and 18.9 years respectively.

When comparing the findings from these two studies and placing them in context of previous clinical evidence, it is relevant to keep in mind that whilst analysis of large patient cohorts such as the 1997 and 2019 CGHFBC[3] re-analyses and 2015 NG23[9] will produce statistical precision, reliability is limited due to the risk of bias and confounding inherent in observational methodology. The WHI placebo-controlled data is likely to provide a better estimate of the relative risk for HRT versus placebo.

The main findings of the 2019 CGHFBC[3] re-analysis are summarised below and interpreted alongside comparable outcomes from the most recent WHI study publication and prior, relevant clinical evidence.

1. The risk of breast cancer diagnosis is greater with combined than unopposed HRT

- Both the 2019 CGHFC[3] and 2020 WHI[4] study findings concur with previous evidence[3,4]
  The duration-dependent increase in risk with combined HRT in the 2019 CBHFBC is associated with sequential and continuous combined preparations, although the risk with the latter is greater and supported by a previous meta-analysis[17] The difference in absolute risk, however, between continuous and sequential combined HRT is small, with up to 14 years exposure an estimated excess difference of 10 additional breast cancer diagnoses per 1000 women aged between 50 to 59 respectively.[3] This should be weighed against the risk of endometrial cancer which is significantly decreased by the long-term use of continuous but not sequential HRT.[19]
- The 2019 CGHFBC[3], in common with previous studies, reported short-term use for up to 5 years of dydrogesterone and micronized progesterone-containing combined regimens were not associated with an increased risk of diagnosis.[3,17] In contrast, the 2019 CGHFBC[3] suggests a longer duration of dydrogesterone or micronized progestogen use, is associated with an increased risk of breast cancer diagnosis.[3] No meaningful conclusions can be drawn, particularly for micronized progesterone, as the number of breast cancer events was too small for reliable estimation.[3]

2. The 2019 CGHFBC[3] concluded unopposed oestrogen to be associated with an increased risk of breast cancer diagnosis but this contrasts with the randomised WHI study, where a decreased risk of diagnosis was reported with unopposed CEE.[4] These apparent opposing effects can be explained by the oestrogen deprivation hypothesis, which states the duration of a woman's endogenous oestrogen depletion determines whether apoptosis of pre-existing, occult breast cancers occurs upon oestrogen re-exposure with unopposed HRT. Short-term oestradiol depletion is not associated with apoptosis upon re-exposure, whereas long-term oestradiol deprivation is.[10]

- The breast tissue in women recently postmenopausal is only short-term oestradiol deprived. Hence initiation of unopposed HRT does not cause apoptosis but stimulates proliferation of pre-existing, occult breast cancers. As this proliferative effect is much less than that of estrogen plus a progestogen, it takes a much longer time to detect an increased risk of breast cancer diagnosis with oestrogen alone. This would explain the CGHFBC finding that women commencing unopposed oestrogen shortly after their menopause appear to have no increase in breast cancer if used over a period of 5 years but with more prolonged use, the risk of diagnosis increases.
- In contrast, older postmenopausal women will have been depleted of oestradiol for longer and exposure to unopposed HRT stimulates apoptosis, slowing the growth of pre-existing occult breast cancers. As the average age of women in the WHI study was 63, this likely accounts for the finding of a protective effect. This appears to be supported by the 2019 CGHFBC[3], as in women over 60 at time of commencing unopposed HRT, the risk of breast cancer diagnosis was either not increased or reduced depending on whether analysis of prospective or retrospective observational studies was undertaken (relative risk 1.03, 95% CI 0.88-1.21 vs 0.56, 95% CI 0.46-0.68).

3. In the 2019 CGHFBC[3] re-analysis, risk with unopposed oestrogen was elevated with oral and transdermal oestrogen administration but unaffected by low and ultra-low dose vaginal preparations that have minimal systemic absorption. This concurs with previous evidence.[13,17,20]

4. In the 2019 CGHFBC[3] re-analysis, there was no evidence of a dosage effect with unopposed oestrogen.

Table 1 compares the absolute excess risk with current HRT use from the randomised WHI, 2019 CGHFBC[3] and 2015 NG23[9]. Overall, the absolute excess risk of breast cancer diagnosis with HRT use is small, regardless of category of current use. Most women exposed to HRT will not be diagnosed with breast cancer as a result of exposure.

Absolute excess risk of breast cancer diagnosis over 5 years per 1000 women starting HRT at age 50

	Duration of HRT use	HR or RR (95% CI)	Absolute Excess Risk (95% CI)	Women diagnosed	Women not diagnosed
No HRT[21]				13	987
Oestrogen alone					
Use up to 5 years					
WHI study 2020[4]	4.6 yrs (median)	0.76 (0.58-0.98)	-3 (-5, 0)	10	990
NICE 2015	Up to 5 years	1.16 (0.95-1.42)	+2 (-1, +5)	15	985
CGHFBC 2019[b]	< 5 years	1.16 (1.10-1.24)	+2 (+1, +3)	15	985
Use up to 10 years					
WHI study	No data	—	—	—	—
NICE 2015	5-10 years	1.23 (0.94-1.61)	+3 (-1, +8)	16	984
CGHFBC 2019	5-9 years	1.22 (1.17-1.28)	+3 (+2, +4)	16	984
Combined HRT					
Use up to 5 years					
WHI study 2020[4]	3.2 years (median)	1.26 (1.02-1.56)	+3 (0, +7)	16	984
NICE 2015	Up to 5 years	1.52 (1.25-1.85)	+7 (+3, +11)	20	980
CGHFBC 2019[a]	< 5 years	1.56 (1.49-1.64)	+7 (+6, +8)	20	980
Use up to 10 years					
WHI study	No data	—	—	—	—
NICE 2015[b]	5-10 years	1.94 (1.41-2.66)	+12 (+5, +22)	25	975
CGHFBC 2019	5-9 years	1.97 (1.90-2.04)	+13 (+12, +14)	26	974

a Risk estimate for less than 5 years category has been calculated by pooling the numbers for < 1year and 1 to 4 years duration of HRT exposure, using inverse variance weighting
b Evidence on observational estimate demonstrated very serious imprecision in the estimate of effect.

5. In the 2019 CGHFBC[3], past users of HRT were reported to have an increased risk of breast cancer diagnosis more than 10 years after cessation. However, most evidence prior to the 2019 CGHFBC[3] showed a fall in risk of breast cancer diagnosis after HRT cessation and the latest follow-up from the randomised WHI study reported no significant increase or decrease in the risk of diagnosis after a median follow-up of 16.2 years or 18.9 years for women allocated unopposed or combined HRT respectively.

- Although the above appears conflicting, the outcomes can still be explained by the impact of changes to HRT exposure on pre-existing, hormone sensitive, occult breast cancers. Withdrawal of unopposed oestrogen stops oestrogen-induced apoptosis, leading to an increase in cancer growth rate. Hence, following cessation, the incidence of diagnosis will begin to increase as the size threshold for diagnosis is eventually reached. After a number of years, this will negate the initial reduction in risk observed in the 2020 WHI[4] study and also account for the increased risk of late-onset diagnosis in the 2019 CGHBFC[3]. Stopping combined HRT will slow the rate of occult cancer growth resulting in an initial fall in diagnosis, followed by a late-onset increase, when the diagnostic size threshold is reached.[10] The 2020 WHI[4] study, suggests the 'rebound' effect of unopposed and combined HRT withdrawal on tumour growth promotion takes longer to become evident and it may not be potentially clinically relevant in a woman's lifetime following cessation of use.
- For both unopposed and combined HRT, however, the absolute excess risk in past users is small and less than that associated with being overweight or drinking 2 or more units of alcohol per day).[3,4,22]

Table 2 shows comparative absolute risks in women with a previous duration of HRT use up to five years from the 2019 CGHFBC[3] and randomised WHI study.

Absolute excess risk of breast cancer in women over 5 years per 1000 women starting HRT age 50 with previous HRT exposure, by duration of use and time since stopping

Prior duration of HRT use, up to 5 years	Time since last use	HR or RR (95% CI)	Absolute Excess Risk (95% CI)	Women diagnosed	Women not diagnosed
No HRT[21]		—	—	**13**	**987**
Past use of oestrogen					
Time since stopping < 5 years					
WHI 2013, 2015[23,24]	2.8 years (median)[a]	0.55 (0.34-0.89)	-6 (-9, -1)	7	993
CGHFBC 2019b	< 5 years	1.05 (0.96-1.16)	+1 (-1, +2)	14	986
Time since stopping 5 to 9 years					
WHI 2013, 2015[23,24]	6.6 years (median)[e]	1.17 (0.73-1.87)	+2 (-4, +11)	15	985
CGHFBC 2019	5-9 years	1.06 (0.97-1.16)	+1 (0, +2)	14	986
Time since stopping > 10 years					
WHI 2020[4]	13.8 years (median)	0.84 (0.59-1.20)	+2 (-5, +3)	15	985
CGHFBC 2019	> 10 years	1.02 (0.95-1.10)	0 (-1, +1)	13	987
Past use of combined HRT					
Time since stopping < 5 years					
WHI 2013, 2015[23,24]	2.8 years (median)[a]	1.23 (0.90-1.70)	+3 (-1, +9)	16	984
CGHFBC 2019[b]	< 5 years	1.13 (1.05-1.21)	+2 (+1, +3)	15	985
Time since stopping 5 to 9 years					
WHI 2013, 2015[23,24]	8.2 years (median)[c]	1.37 (1.06-1.77)	+5 (+1, +10)	18	982
CGHFBC 2019[b]	5-9 years	1.21 (1.14-1.29)	+3 (+2, +4)	16	984
Time since stopping > 10 years					
WHI 2020[4]	15.3 years (median)	1.23 (0.96-1.59)	+3 (-1, +8)	16	984
CGHFBC 2019[b]	> 10 years	1.08 (1.01-1.15)	+1 (0, +2)	14	986

a Duration of the early intervention phase post HRT cessation.
b Risk estimate for less than five years duration of HRT exposure has been calculated by pooling the numbers for <1 year and one to four years categories, using inverse variance weighting accounting for a common reference category.
c Duration of late intervention phase in the estrogen only and combined HRT arms.

Table 3 shows comparative 20-year absolute risks in women using HRT for up to five years from the age of 50 based on the 2019 CGHFBC[3] and randomised 2020 WHI[4] study. Overall, the absolute excess risk of breast cancer diagnosis with HRT use is small. Most women exposed to HRT will not be diagnosed with breast cancer as a result of exposure.

HRT use	Evidence Source	Absolute Excess Risk[a]	Women diagnosed	Women not diagnosed
No HRT	ONS Cancer Registrations 2017[21]	—	61	939
Past use of oestrogen	WHI study 2020[4]	-9	52	948
Past use of oestrogen	CGHFBC 2019	+5	66	934
Past use of combined HRT	WHI study 2020[4]	+15	76	924
Past use of combined HRT	CGHFBC 2019	+10	71	929

a 20-year absolute risk calculated as risk from 5 years of <5 years HRT use, followed by 5 years of <5 years since stopping HRT, followed by 5 years of 5-9 years since stopping HRT, followed by 10 years of >10 years since stopping HRT.

6. The 2019 CGHFBC[3] reported women who start HRT soon after menopause have an increased risk of invasive breast cancer, compared with never users

- Risk of diagnosis was found to be increased in women who commenced HRT nearer to the time of onset of menopause compared with those starting it more than five years since menopause. However, this is relatively weak evidence, not supported by the randomised WHI study, which in itself was underpowered for reliable assessment of this outcome.[4]
- In conclusion, there insufficient evidence currently to recommend that time from menopause should influence decision-making.

7. The CGHFBC also found use of HRT in postmenopausal women younger than 50 to be associated with an increased risk of breast cancer diagnosis, which contradicts advice to date.[3]

- The control group, of age-matched postmenopausal women, however, was inappropriate as an early menopause reduces breast cancer risk. The population for comparison should have consisted of age-matched *normally cycling* women.
- The current recommendation that years of HRT exposure in women with POI should be counted from the age of natural menopause (i.e. 50) should stand. Younger peri and postmenopausal women accrue significant symptom, quality of life, bone and cardiovascular benefits from HRT.[18]

Placing breast cancer risk with HRT in perspective

1. HRT and other lifestyle risk factors for breast cancer

The 2015 NG23[9] recommended HRT counselling should be individualized, accounting for non-modifiable factors that determine a woman's personal, baseline breast cancer risk, such as family history and exposure to modifiable risk factors, which include HRT.[9] Avoidance of modifiable risk factors has been estimated to potentially prevent just under a quarter of breast cancers diagnosed in the UK female population (23%).[22] In women who are overweight or obese, or those whose alcohol intake is elevated, the population attributable risk is 8%, which is greater than that associated with any HRT exposure (including risk in past users), at 5%.[3,22] Unfortunately, it is not possible to predict on an *individual* basis, who will benefit from minimising exposure to these.

Table 4 summarises absolute population risk estimates and population attributable risk fraction (PARF) by for obesity, alcohol intake and HRT. The PARF indicates the percentage of breast cancer diagnoses that are attributable to a given risk factor.

Lifestyle risk factors	HR or RR	Absolute excess risk per 1000 women over 5 years 50-59 years	PARF (%)
Postmenopausal obesity[25]			
Overweight vs healthy weight[a]	1.17	+4	4.8%
Obese vs healthy weight[a]	1.46	+10	14.0%
Alcohol[26b]			
35-44g / day	1.32	+8	6.9%
≥45g / day	1.46	+11	5.8%
Unopposed HRT up to 5 years use			
WHI study[4]	0.76	-6	—
2015 NG23[9]	1.16	+3	2.1%[c]
2019 CGHFBC[3]	1.16	+3	2.1%[c]
Combined HRT up to 5 years use			
WHI study[4]	1.26	+8	3.4%[c]
2015 NG23[9]	1.52	+9	6.5%[c]
2019 CGHFBC[3]	1.56	+10	7.0%[c]

a Normal weight, body mass index (BMI) (<25 kg/m^2, overweight BMI 25–29.9 kg/m^2, obese BMI ≥30 kg/m^2
b Risk with alcohol is unaffected by menopausal status. 1 unit of alcohol = 8g
c HRT use prevalence taken to be 13.5% in women aged 50-59 but may have changed in recent years[27]

2. HRT benefits and risks

For women experiencing menopausal symptoms, with a low underlying risk of breast cancer (i.e. most of the female population), the benefits of HRT in relieving symptoms, improving quality of life and conferring protection against cardiovascular disease and osteoporosis, will exceed potential harms, which include the small increased risk of breast cancer and venous thrombo-embolic disease (VTED) diagnosis.[9] In 2017, postmenopausal female deaths in England and Wales from ischaemic heart disease and osteoporosis combined (20,388) were almost four times that attributed to breast cancer (5,483).[28] HRT-associated risk of VTED can be minimised by the use of transdermal oestrogen and possibly with combined preparations containing micronized progesterone or dydrogesterone.[9]

3. HRT and mortality

a. Breast cancer mortality

The 2019 CGHFBC[3] did not evaluate this relationship with HRT, although an accompanying research letter from the MWS investigators and long-term follow-up of the randomised WHI study (2020) did.[4,29] The MWS investigators reported current and previous HRT use for a duration of more than five years was associated with an increased risk of breast cancer death. Other meta-analysis, the 2015 NG23[9] and the randomised WHI study do not concur with this.[4,9,30,31] The most recent data from the WHI study suggests a reduction in breast cancer mortality with unopposed oestrogen but the number of events is small.[4] All evidence, however, is open to scrutiny as collectively there is failure to provide adequate information about disease stage, treatment and mode of breast cancer diagnosis (i.e. whether screen-detected or symptomatic), which have a significant impact on prognosis. Furthermore, hormone sensitive breast cancer, which is promoted by HRT, has a higher long-term

relapse pattern compared with hormone insensitive disease. Beyond five years from diagnosis, the risk of recurrence is greater and beyond fourteen years, overall survival is worse in oestrogen receptor positive cancer.[32]

b. All-cause mortality

In women at population risk for breast cancer, the overall mortality risk: benefit ratio favours unopposed and combined HRT.[31,33] A recent cohort study with a follow-up of just under 18 years, however showed time-specific differential associations in cause of HRT-associated death with a slightly higher breast cancer mortality, however, this was offset by lower colorectal cancer and cardiovascular deaths.[33] This illustrates how inappropriate it is to discuss HRT association with breast cancer without any consideration that a risk factor for one health condition may protect against another. The decline in unopposed oestrogen use in the USA since 2002, which has resulted in a significant increase in premature mortality for hysterectomized women aged 50 to 59 years, illustrates the relevance of fully informed patient discussion.[34]

HRT in women at high baseline risk of breast cancer

This refers to women with a familial risk or a high-risk benign breast condition (i.e. biopsy-proven epithelial atypia or Lobular Carcinoma in Situ). The latest follow-up from the randomised WHI study shows that unopposed oestrogen is associated with a significant risk reduction in women without a family history (defined as one first degree relative with breast cancer) and those without a history of a benign breast biopsy. In women with a positive family history or previous benign breast biopsy, risk was similar to women allocated to receive placebo.[4] Combined HRT was associated with an increased risk of diagnosis irrespective of family history and in women without a benign breast condition to a similar degree as women allocated to receive placebo but no increase was found in those with a history of the latter.[4] Some of these findings appear to contradict previous conclusions that there is no additive effect of HRT on breast cancer diagnosis in women at high risk. However, event numbers for women with a family history or previous benign breast biopsy were not always large. Furthermore, it is not possible to determine the significance of the degree of risk conferred by the family history or benign breast condition as no details about about associated risk category are available.

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.[9,14,15,35,36] 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 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.[14,15] Further studies are needed to clarify risk with combined compared with unopposed HRT and the optimal duration of use.[37] 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.[14,36]

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.[38] Systemic HRT and low-dose 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.[39,40] 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.[9,14,15] 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).[41] 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).[42]

When is it appropriate to discuss systemic or vaginal HRT in the management of women with diagnosis of a previous breast cancer?

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.[9,38] For women with symptoms due to vulvo-vaginal atrophy if treatment with vaginal moisturisers fails to alleviate symptoms, vaginal oestrogen can be discussed.[9] There is generally lower concern about systemic absorption from low and ultra-low dose vaginal oestrogen, which is minimal and could be acceptable where systemic therapy would not be. Neither systemic HRT nor low-dose vaginal 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.[38]

Summary

The British Menopause Society is of the view that the 2019 CGHFBC[3] re-analysis and 2020 WHI[4] study provides important additional information on the risk of breast cancer diagnosis with HRT. The only findings which should influence clinical advice is that risk does not appear to be elevated with low-dose vaginal oestrogen and that risk may persist after systemic HRT is stopped but this can still be explained by a growth-promoting effect. No arbitrary limits should be placed on the dose or duration of usage of HRT as decisions should be made on an individualised basis after discussing the benefits and risks with each patient. In addition to the potential increased risks of breast

cancer and VTED, they should also be considered in the context of the overall benefits obtained from using HRT including symptom management and improved quality of life as well as the cardiovascular and bone protective effects associated with HRT. From a research perspective, there is need for large, long-term prospective randomised controlled trials using conventionally regulated bio-identical HRT and further research and development of new regimens.

Key points

1. In women with a low underlying risk of breast cancer (i.e. most of the population), the benefits of HRT for up to 5 years' use for symptom relief will exceed potential harm.
   - Unopposed oestrogen is associated with no, or little change in risk but this may be influenced by age at initiation
   - There is no evidence of a dosage effect with oestrogen
   - Vaginal oestrogen is not associated with an increased risk
   - Combined HRT can be associated with an increased risk, which appears duration dependent
   - Whilst risk with continuous combined HRT may be greater that with sequential HRT, the difference in risk is small and may be offset by protection against endometrial cancer
   - Avoidance of synthetic progestogens in combined preparations may minimise risk
   - Risk is limited to lean women
   - Risk associated with HRT (including past users) is less than other lifestyle risk factors for breast cancer
   - In women with POI, years of HRT exposure should be counted from the age of 50
   - Communicating risk in terms of absolute excess risk with framing, minimizes misinterpretation.

2. In women at high risk, or breast cancer survivors.
   - There is no additive effect of HRT exposure in women at elevated personal risk due to a family history or high-risk benign breast condition.[3,9]
   - If the use of HRT or vaginal oestrogen is considered, this should only be for the management of oestrogen deficiency symptoms after discussion with the woman's breast specialist team
   - Vaginal oestrogen can be used in women taking tamoxifen but not aromatase inhibitors.

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