

# HRT AND BREAST CANCER RISK

Miss Jo Marsden

Medical Advisory Committee, The British Menopause Society  
President-Elect, The British Association of Day Surgery

## Conflicts of Interest:

Lectures for Mylan 2015-to date, Member of Council of British Menopause Society, Advisory Board for Novo Nordisk, Publications Editor British Association of Day Surgery, Member of Capita Healthcare Knowledge Systems Advisory Board, Chief Investigator of the national UK trial of HRT in symptomatic women with early breast cancer

# HRT AND BREAST CANCER

- This is a controversial topic:
  - Risk is poorly communicated
  - HRT discussed in isolation of its benefits and other lifestyle breast cancer risk factors
- Two recent publications:
  - 2019: Collaborative Group on Hormonal Factors in Breast Cancer
  - 2020: Long-term follow-up of the Women's Health Initiative Study
    - Compare with outcomes with previous evidence
    - Should they change current clinical advice?
- Most women *will not be* diagnosed as a result of their exposure

# HRT AND BREAST CANCER

## EVIDENCE PRECEDING THE 2019 CGHFBC and 2020 WHI study

- Clinical advice based the following studies

1997 CGHFBC

- Re-analysis of 51 observational studies, mostly unopposed oestrogen

2002 to date  
Women's Health Initiative  
(WHI)

- Randomised, controlled trial
- Unopposed or combined HRT vs placebo

2003 to date  
Million Women Study  
(MWS)

- Large, observational study

2015 UK NICE  
Menopause Guidance  
(NG23)

- Meta-analysis of 28 studies
- 27 observational, 1 randomised (WHI)

Individual observational  
studies

- Specific questions relating to HRT exposure not covered by the above

# EVIDENCE PRECEDING THE 2019 CGHFBC and 2020 WHI study

- Risk estimates from studies were small (i.e.  $RR < 2$ )
  - Little or no risk associated with unopposed HRT<sup>1,2</sup>
  - Duration-dependent increased risk associated with combined HRT<sup>1,2</sup>
- Degree of risk is similar to delaying the onset of the menopause<sup>3</sup>
- Risk is restricted to lean women and falls after HRT cessation<sup>2,3</sup>
- No clear evidence of a dosage effect<sup>1,3</sup>
- No additive effect in women with a family history or a benign breast condition<sup>4</sup>
- In women with POI – start counting years of HRT exposure from 50<sup>5</sup>
- No consistent evidence for an increase in breast cancer mortality<sup>2,6</sup>

<sup>1</sup>Cheblowski RT et al JAMA 2015; <sup>2</sup>NICE guideline [NG23], 2015 [www.NICE.org.uk](http://www.NICE.org.uk); <sup>3</sup>CGHFBC, *The Lancet* 1997;

<sup>4</sup>Marsden J. *J Post Reprod Health* 2016; <sup>5</sup>Ewertz M et al *Br J Cancer* 2005; <sup>6</sup>Manson JE et al JAMA 2017

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

- 2019 CGHFBC<sup>1</sup>
  - Re-analysis of 58 observational studies (published *and* unpublished)
  - Main analysis restricted to 24 prospective studies, which contributed 75% of the cases
  - Half of these women were participants in the [Million Women Study](#), which has been widely criticised<sup>2</sup>
- 2020 WHI<sup>3</sup>
  - Long-term follow-up of the placebo-controlled randomised studies
  - Unopposed oestrogen arm, median follow-up 16.9 years
  - Combined HRT arm, median follow-up 18.9 years

<sup>1</sup>CGHFBC, *The Lancet* 2019; <sup>2</sup>Whitehead M, *Endocrine* 2004 <sup>3</sup>Chlebowski et al, *JAMA* 2020

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

- When interpreting results from clinical studies remember:
  - A large observational cohort may provide statistical precision but reliability is limited due inherent bias in methodology
  - Placebo-controlled data provides more accurate risk estimates but only if the study is adequately powered

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

## UNOPPOSED HRT

- 2019 CGHFBC
  - Similar outcomes to the NG23
  - Little or no increased risk with unopposed oestrogen
- 2020 WHI showed a *reduction* in risk
- Most women *will not be* diagnosed as a result of their exposure

Absolute excess risk of breast cancer diagnosis per 1000 women aged 50 to 59*				
	Duration of use	Excess risk	Diagnosed	Not diagnosed
<b>No HRT</b>		-	13	987
<b>Oestrogen</b>				
WHI 2020 <sup>1</sup>	4.6 (median) years	-3	10	990
NICE 2015 <sup>2</sup>	Up to 5 years	+2	15	985
CGHFBC 2019 <sup>3</sup>	< 5 years	+2	15	985
NICE 2015	5-10 years	+3	16	984
CGHFBC 2019	5-9 years	+3	16	984

\*Based on a baseline risk of 13/1000 in women aged 50 to 59 over 5 years.

<sup>1</sup>Chlebowski et al, *JAMA*, 2020; <sup>2</sup>NICE guideline [NG23], 2015 [www.NICE.org.uk](http://www.NICE.org.uk); <sup>3</sup>CGHFBC, *The Lancet* 2019

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

## UNOPPOSED HRT

- Other 2019 CGHFBC findings:
  - No evidence of a dosage effect with unopposed oestrogen
  - Risk of diagnosis does not appear to be increased with vaginal oestrogen
- Women using unopposed oestrogen and low and ultra-low dose vaginal oestrogen can be reassured about their risk



# HRT AND RISK OF BREAST CANCER DIAGNOSIS

## COMBINED HRT

- 2019 CGHFBC and 2020 WHI

- Similar outcomes to the NG23
- Duration dependent increased risk of diagnosis with combined HRT
- Most women *will not* be diagnosed as a result of their exposure

Absolute excess risk of breast cancer diagnosis per 1000 women aged 50 to 59*				
	Duration of use	Excess risk	Diagnosed	Not diagnosed
<b>No HRT</b>		-	13	987
<b>Combined HRT</b>				
WHI 2020 <sup>1</sup>	4.6 (median) years	+3	16	984
NICE 2015 <sup>2</sup>	Up to 5 years	+7	20	980
CGHFBC 2019 <sup>3</sup>	< 5 years	+7	20	980
NICE 2015	5-10 years	+12	25	975
CGHFBC 2019	5-9 years	+13	26	974

\*Based on a baseline risk of 13/1000 in women aged 50 to 59 over 5 years.

<sup>1</sup>Chlebowski et al, *JAMA*, 2020; <sup>2</sup>NICE guideline [NG23], 2015 [www.NICE.org.uk](http://www.NICE.org.uk); <sup>3</sup>CGHFBC, *The Lancet* 2019

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

## COMBINED HRT – PATTERN OF PRESCRIPTION

- 2019 CGHFBC similar finding to previous meta-analysis<sup>2</sup>
  - Continuous combined HRT confers a greater risk than sequential HRT
  - The *absolute* difference in risk between the two types of regimen is small (10 additional cancers with 14 year's use)
  - However, risk of endometrial cancer is significantly decreased by longer-term use of continuous but not sequential HRT prescription<sup>3</sup>

<sup>1</sup>CGHFBC, *The Lancet* 2019; <sup>2</sup>Yang Z et al *Gynecol Endocrin* 2017; <sup>3</sup>Jaakkola S et al *Int J Cancer*, 2011

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

## COMBINED HRT – PROGESTOGEN TYPE

- Prior to CGHFBC

- Risk increased with synthetic progestogens but *not* with progesterone-derived progestogens, dydrogesterone or micronized progesterone

- 2019 CGHFBC contradicts this

- Increased risk with long-term use of micronized progesterone
- However, based on a small number of events so inconclusive

- 2020 Q Research and CPRD database cohort study

- Combined dydrogesterone regimens associated with a lower risk than those with synthetic progestogens<sup>2</sup>

Yang Z et al *Gynecol Endocrin* 2017, CGHFBC *Lancet* 2019,  
Vinogradova et al *BMJ* 2020

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

## COMBINED HRT – PATTERN OF PRESCRIPTION *AND* PROGESTOGEN TYPE

- 2019 CGHFBC and 2020 WHI study did not evaluate this
- 2018 cohort study
  - Suggests *pattern* of prescription most relevant<sup>1</sup>
  - Continuous combined greatest risk irrespective of progestogen type
  - No separate analysis for dydrogesterone and micronized progesterone regimens

\*Baseline risk of 26/1000 per 1000 women aged 50 to 59 <sup>1</sup>Brusselaers N et al *Ann Oncol* 2018  
MPA was the most commonly prescribed progesterone-derived progestogen at this time

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

## COMBINED HRT

- Overall:

- Duration-dependent increased risk of diagnosis
- Risk is greater with continuous combined regimens but this needs to be weighed up against a greater reduction in endometrial cancer diagnosis
- Further study is needed to determine whether pattern of progestogen prescription is more important than progestogen type in determining risk

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

## TIMING OF HRT INITIATION

- 2019 CGHFBC
  - Women who start HRT soon after menopause have an increased risk compared with those commencing HRT years after their menopause
- WHI study (2013, 2020)
  - Does not support the CGHFBC findings<sup>1,2</sup>  
(probably underpowered for reliable assessment of this outcome)
- Current evidence is *insufficient* to recommend time from menopause should influence decision-making about when to commence HRT

<sup>1</sup> Manson JE, et al *JAMA*, 2013 <sup>2</sup>Chlebowski R t al, *JAMA* 2020

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

## 2019 CGHFBC

- HRT use in postmenopausal women younger than 50 increases risk<sup>1</sup>
  - Contradicts previous advice to start counting years of HRT exposure in women with a premature menopause from the age of 50<sup>2</sup>
  - However, the CGHFBC *control group* consisted of women with a premature menopause *not* taking HRT, whose risk of breast cancer is reduced
  - The control group *should* have been age-matched, normally cycling premenopausal women
- The recommendation that years of HRT exposure should be counted from 50 in women with POI should *not* be changed

<sup>1</sup>CGHFBC *Lancet* 2019; <sup>2</sup>Webber L et al *Human reproduction open*, 2017(2), hox007.  
<https://doi.org/10.1093/hropen/hox007>

# HRT AND RISK OF BREAST CANCER DIAGNOSIS

## RISK IN PREVIOUS HRT USERS

- 2019 CGHFBC

- Risk is increased long-term in past users of any HRT

- 2020 WHI

- Long-term risk was not statistically significant from placebo

20-year absolute risk per 1000 women using HRT for up to five years from the age of 50				
	Evidence Source	Absolute Excess Risk	Women diagnosed	Women not diagnosed
<b>No HRT</b>	ONS Cancer Registrations 2017	-	36	964
<b>Past use of oestrogen</b>	WHI study 2020	-9	27	973
<b>Past use of oestrogen</b>	CGHFBC 2019	+5	41	959
<b>Past use of combined HRT</b>	WHI study 2020	+15	51	949
<b>Past use of combined HRT</b>	CGHFBC 2019	+10	46	954

- The absolute excess risk is small in past users
- Most women will not be diagnosed due to past use



# HRT AND BREAST CANCER

- Unopposed oestrogen
  - Small increased risk in 2019 CGHBC but reduced in 2020 WHI study
- Increased risk in past HRT users
  - Significant in 2019 CGHFBC but not in 2020 WHI study
- Differences can be explained by the effect of HRT on occult, hormone sensitive breast cancers, already present in the breast at the time of HRT initiation<sup>1</sup>
  - In western countries, it is estimated 7% of women aged 40 to 80 have occult breast cancers, which are too small for diagnosis by established methods

<sup>1</sup>Santen RJ, *Climacteric* 2019

# HRT AND BREAST CANCER

- Oestrogen-deprived breast cancer cells undergo apoptosis (cell death) when re-exposed to oestrogen, resulting in slower cancer growth
  - **Unopposed HRT** use slows occult cancer growth so it takes longer to reach the threshold size for diagnosis compared with placebo
  - WHI study 'incidence is reduced'
  - **Withdrawal of unopposed HRT** stops oestrogen-induced apoptosis
  - Occult cancer growth begins to increase
  - This results in a late-onset increase in diagnosis years after cessation when the occult cancers finally reach the threshold size for diagnosis

# HRT AND BREAST CANCER

- Combined HRT has a proliferative effect on occult breast cancer growth
  - **Combined HRT** use speeds occult cancer growth so it takes a shorter time to reach the threshold size for diagnosis compared to placebo
  - Accounts for increased incidence of diagnosis in studies
  - **Withdrawal of combined HRT** reduces occult cancer growth
  - Occult cancer growth slows and it will take longer to reach the threshold size for diagnosis
  - Results in a late-onset increase in diagnosis years after cessation

# HRT AND BREAST CANCER

- Excess risk due to past HRT use is small

**Absolute excess risk of breast cancer diagnosis over 10 years per 1000 women starting HRT at age 50 with previous HRT exposure of 5 years**

	Time since last use	Absolute Excess Risk	Women diagnosed	Women not diagnosed
<b>No HRT</b>		-	26	974
<b>Past use of oestrogen</b>				
WHI <sup>1,2</sup> , CGHFBC 2019 <sup>3</sup>	2.8 years (median) < 5 years	-6 +1	17 27	983 973
WHI <sup>4</sup> , CGHFBC 2019 <sup>3</sup>	13.8 years (median) > 10 years	+2 0	28 26	972 974
<b>Past use of combined HRT</b>				
WHI <sup>1,2</sup> , CGHFBC 2019 <sup>3</sup>	2.8 years (median) < 5 years	+3 +2	29 26	971 974
WHI <sup>4</sup> , CGHFBC 2019 <sup>3</sup>	15.3 years (median) > 10 years	+3 +1	29 27	971 973

<sup>1</sup> Manson J et al, *JAMA* 2013; <sup>2</sup> Chlebowski R et al, *JAMA* 2015;

<sup>3</sup> CGHRBC *Lancet* 2019; <sup>4</sup> Chlebowski R et al *JAMA*, 2020

# HRT AND BREAST CANCER

## LNG-IUS AND TESTOSTERONE REPLACEMENT

- Not addressed by the CGHFBC 2019 or 2020 WHI
- LNG-IUS
  - Assumption this is 'breast safe' as there is low systemic absorption
  - Meta-analysis of observational data suggests an increased risk in all users, which is greater in women over 50<sup>1</sup>
- Testosterone
  - Available observational studies variable quality and inconclusive
  - RCTs: no increased risk but underpowered and too short in duration for definite conclusions

<sup>1</sup>Conz L et al, *Acta Obstet Gynecol Scan* 2020; Bitzer J et al, *Maturitas* 2008, Kabat GC et al, *Maturitas* 2014, Elraiyah T et al, *J Clin Endocrinol Metab* 2014, Achilli C et al, *Fertil Steril* 2017

# HRT AND MAMMOGRAPHY

## Current UK guidance in women at population risk

- “ A ‘baseline’ mammogram is not routinely required prior to commencing HRT”
- “Women receiving HRT over the age of 50 years are offered screening every three years as part of the NHSBSP as a matter of routine. In this age group, there is no evidence to support more frequent screening” *(including addition of ultrasound – Jo Marsden addition!)*

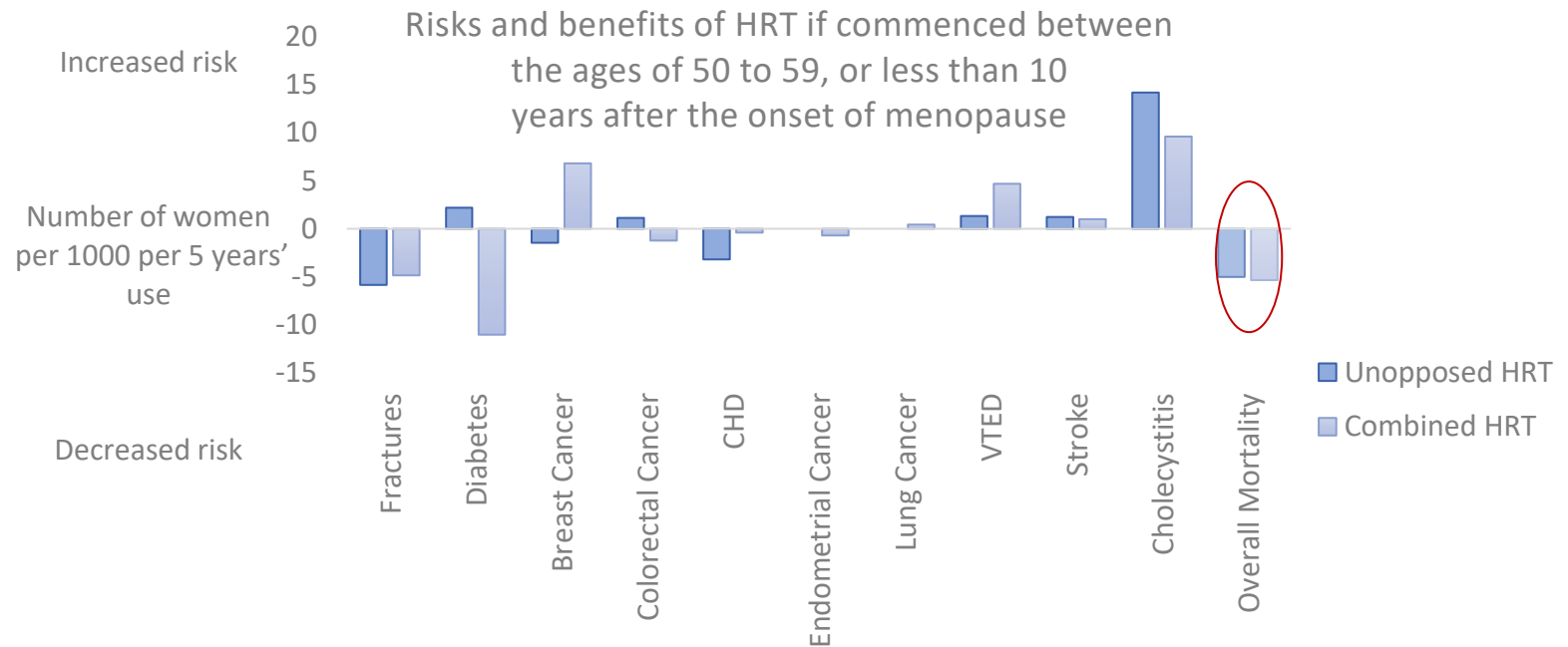
# HRT AND BREAST CANCER MORTALITY

- 2015 NICE Menopause Guidance did not find a significant association<sup>1</sup>
- 2019 MWS reported an increased breast cancer mortality<sup>2</sup>
- 2020 WHI reported a reduction with unopposed oestrogen and no increased with combined HRT (small event numbers)<sup>3</sup>
  - No information about disease stage, treatment or mode of diagnosis, all of which can have a significant impact on prognosis
- Long-term follow-up suggests time-specific differential associations in cause of death associated with HRT, which don't affect overall mortality<sup>4</sup>
  - Slightly higher breast cancer mortality
  - Opposed by lower CVD mortality, mainly in the short-term and lower colorectal cancer mortality in the long-term

<sup>1</sup> NG23 2015 [www.NICE.org.uk](http://www.NICE.org.uk); <sup>2</sup> Beral V et al, *The Lancet* 2019, <sup>3</sup> Chlebowski R et al *JMA* 2020.

<sup>4</sup> Holm H et al, *BJOG*, 2019

# DISCUSSING HRT RISK: COMPETING OUTCOMES



- A risk factor for one condition may protect against another<sup>1</sup>
- Decline in unopposed HRT use since 2002 in the USA resulted in a significant increase in premature mortality for hysterectomized women aged 50 to 59 years<sup>2</sup>

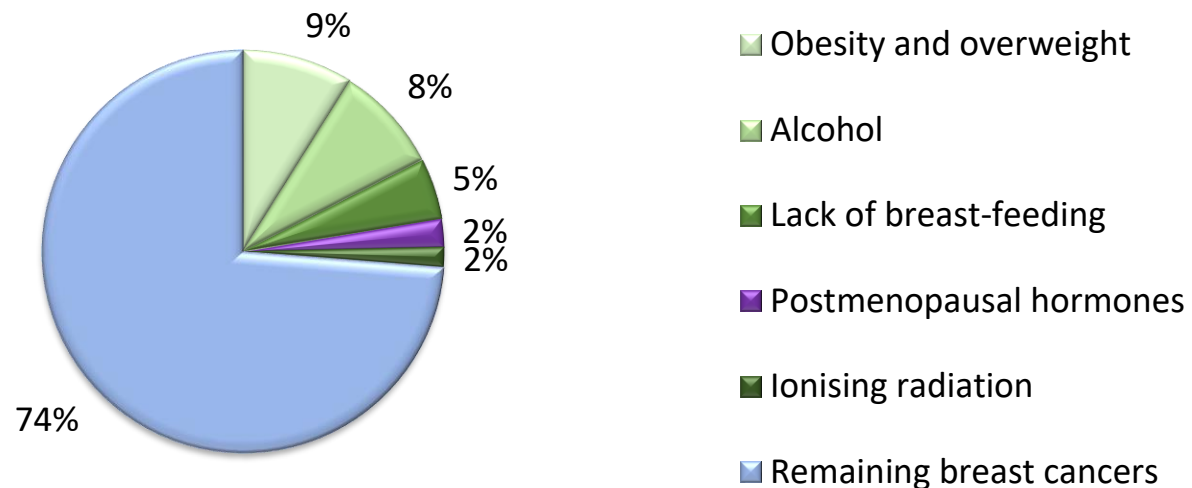
<sup>1</sup>Santen RJ et al *JCEM*, 2010: <sup>2</sup>Sarrel PM et al. *Am J Pub Health*, 2013



# BREAST CANCER AND WOMEN AT POPULATION RISK LIFESTYLE, REPRODUCTIVE AND ENVIRONMENTAL RISK FACTORS

- Accounts for up to 26% of breast cancer diagnoses annually in the UK<sup>1</sup>
- For women at population risk the risk conferred is similar and small (including current and past users of HRT)

**Percentage of breast cancers attributable to modifiable risk factors in the UK**



<sup>1</sup>Brown MF et al. *Br J Cancer*, 2015

# THE ROLE OF HRT IN WOMEN AT ELEVATED BASELINE RISK

- Benign breast conditions
- Family history of breast cancer
  
- There *may not be an additive* effect of HRT in women at high risk due to a high risk benign breast condition or family history
  
- In clinical practice
  - Assume risk estimates are similar to women at population risk
  - Advice should take account of the degree of individual risk
  - Absolute impact is determined
    - By a woman's individual baseline risk
    - Increases as baseline risk grows

# BENIGN BREAST CONDITIONS AND BREAST CANCER RISK

- Encompass a diverse range of conditions
- Classification is histological, based on biopsy findings
  - Used to predict subsequent risk of a breast cancer diagnosis
  - Most *are not* associated with a significant increase in risk (i.e. RR <2)
- Diagnosis of a specific benign breast condition based on symptoms and signs alone may be inaccurate

# BENIGN BREAST CONDITIONS AND BREAST CANCER RISK

Histological classification	Pathology	Common symptoms	Baseline breast cancer risk
Non-proliferative change	Fibroadenoma Duct ectasia Solitary cysts	Lump (+/- pain), nipple discharge or inversion, can be an incidental finding	1
Proliferative disease without atypia	Multiple cysts Ductal papilloma Sclerosing adenosis Usual hyperplasia	Lump (+/- pain), nipple discharge or inversion, can be an incidental finding	2
Atypical hyperplasia	Atypical ductal or lobular hyperplasia	None. Usually an incidental biopsy finding	4
<u>Lobular Carcinoma in Situ</u>	LCIS		10

# BENIGN BREAST CONDITIONS AND BREAST CANCER RISK

## 'Low risk' pathology (up to two-fold increased risk)

- Non-proliferative change
- Proliferative change without cellular atypia
  - Reassure and discharge once the diagnosis is confirmed
  - Can use HRT

## 'High risk' benign breast change (> fourfold risk)

- Atypical hyperplasia
- LCIS
  - Both are considered markers for future risk rather than precursor lesions
  - Annual mammograms are usually recommended for 5 years
  - Avoid HRT

# FAMILY HISTORY OF BREAST CANCER

- Breast cancer and genetic risk factors

- Most breast cancers are sporadic, occurring in women at population risk without significant genetic predisposition
- Annually ~ 55000 cancers are diagnosed in the UK
- Only a minority of these are familial
  - High risk mutations (e.g. BRCA1, BRCA2) account for ~2% (1100) of cancers diagnosed annually
  - Moderate risk mutations account for ~10-15% (5500 to 8200) of cancers diagnosed annually

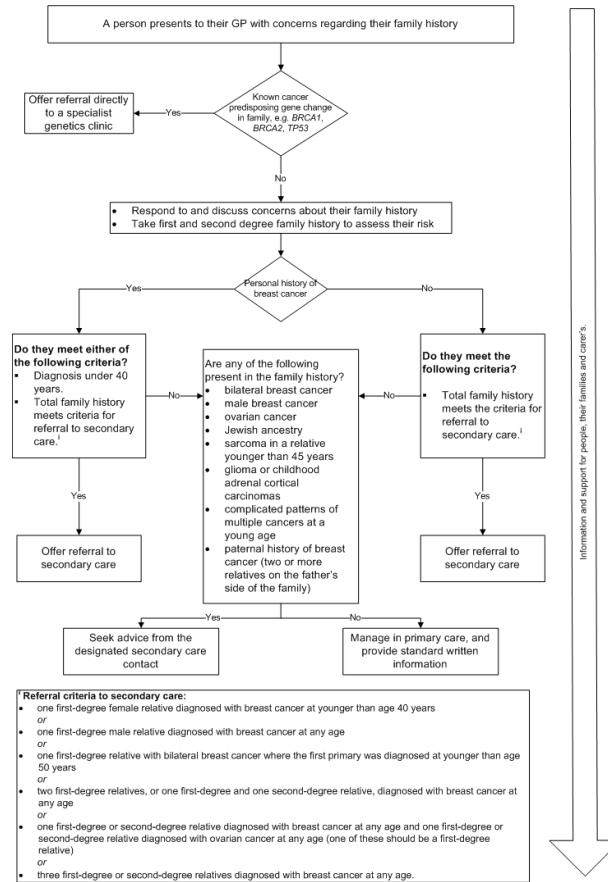
# FAMILIAL BREAST CANCER AND RISK

- In women with an affected first degree relative and no other relevant family history, overall risk is approximately doubled
- However, risk varies with age at diagnosis
  - If the diagnosis was after age 40, the unaffected relative is assumed to be at near population risk and can be managed / advised in primary care
  - If diagnosed at age <40, the unaffected relative is considered to be in a moderate high risk group and should be referred to secondary care for formal risk assessment

# FAMILIAL BREAST CANCER AND RISK

## Assessing risk

- Refer to NICE familial breast cancer guidance (CG164)
- Algorithms for risk assessment and management (pp 40-42)
  - Primary care
  - Secondary care (breast clinic, family history clinic)
  - Tertiary care (cancer genetics)
- It is not expected moderate or high risk patients are given precise risk or carrier probability in 1<sup>0</sup>/2<sup>0</sup> care





# THE ROLE OF HRT IN WOMEN AT ELEVATED BASELINE RISK

Risk Category	Suggested Approach to HRT <sup>1</sup>
Normal, or near population risk	HRT OK
Intermediate	Advise caution
High	Avoid*

- \*BRCA1 and BRCA2 mutation carriers, who have had prophylactic BSO:
  - There is no evidence HRT for symptom relief reduces the protective effect of BSO in reducing breast cancer risk
  - Offer HRT until the age of 50, after which, manage symptoms with lifestyle changes and non-hormonal alternatives<sup>2,3</sup>

<sup>1</sup>Santen RL et al *J Clin Endocrinology and Metab* 2020; <sup>2</sup>The 2017 hormone therapy position statement of the North American Menopause Society. *Menopause* 2017; <sup>3</sup>NICE guideline [NG23], 2015 [www.NICE.org.uk](http://www.NICE.org.uk)

# SYSTEMIC HRT AND TOPICAL OESTROGEN IN BREAST CANCER PATIENTS

## Hypotheses

- They will be safe in women with ER-ve breast cancer
- They should be safe in women with ER+ve cancer being treated with tamoxifen  
(tamoxifen has > 99% binding affinity for the oestrogen receptor)
- They may attenuate the efficacy of aromatase inhibitors, which reduce endogenous oestrogen synthesis

# HRT, TOPICAL OESTROGEN AND TIBOLONE IN WOMEN WITH PREVIOUS BREAST CANCER

## Caveats

- In women with ER+ve cancer
  - The risk of late recurrence (after 5 years) is significant
  - Is HRT initiated years after diagnosis without risk and safe?
- In women with ER-ve cancer
  - Up to 30% of new contralateral primaries are ER+ve
  - Up to 8% of local or distant recurrence is ER+ve (phenotypic shift)
- In women with DCIS
  - Recurrence can be further DCIS (50%) or invasive cancer (50%)
  - The phenotype of recurrence (DCIS or invasive cancer) is usually similar to the primary lesion

# SYSTEMIC HRT AND TIBOLONE IN WOMEN WITH PREVIOUS BREAST CANCER

- All randomised trials were stopped following initial interim analyses of the HABITS and LIBERATE trials where increased recurrence risk was reported
  - All were underpowered at cessation so no firm conclusions can be made about overall findings or or sub-group analyses

Trial	Median duration of use	Median follow-up	Current tamoxifen use	Recurrence (HR, 95% CI)
<b>HRT</b>				
HABITS <sup>1,2</sup>	1.9 years	4 years	21%	2.40 (1.30-4.20)
Stockholm <sup>3,4</sup>	2.6 years	10.8 years	52%	1.30 (0.90-1.90)
UK Trial <sup>5</sup>	1.9 years	11.9 years	69%	1.02 (0.56-1.84)
<b>Meta-analysis<sup>5</sup></b>	-	-		1.45 (0.93-2.26)
<b>Tibolone</b>				
LIBERATE <sup>6</sup>	2.7 years	3.1 years		1.40 (1.14-1.70)

Statistically significant results are in red

<sup>1</sup>Holmberg L et al, *Lancet* 2004; <sup>2</sup>Holmberg L et al, *JNCI* 2008; <sup>3</sup>von Schoultz E et al, *JNCI* 2005; <sup>4</sup>Fahlen M et al, *Eur J Cancer* 2013; <sup>5</sup>Marsden J et al, *Maturitas*, 2017; <sup>6</sup>Kenemans P et al, *Lancet Oncol* 2009

## RISK OF RECURRENCE WITH TOPICAL OESTROGEN

- No increase in risk reported but limited observational evidence
  - Small number of breast cancer events
  - ? safe with concurrent tamoxifen
  - Use in women taking aromatase inhibitors is not recommended

Study	Tamoxifen use	Events	Risk ratio (95% CI)
Durna et al <sup>1</sup> - Estriol cream / pessary (0.5µg) - Estradiol tablet (25 µg)	Unknown	4	0.18 (0.04-0.75)
Dew et al <sup>2</sup> - Estriol cream / pessary (0.5µg) - Estradiol tablet (25 µg)	48% of patients	6	0.57 (0.20-1.58)
Le Ray et al <sup>3</sup> - Vaginal cream or tablet (dose unspecified)	Current	19	0.83 (0.51-1.34)
	Previous	2	0.95 (0.22-4.14)

<sup>1</sup>Durna EM et al, *Med J Aust* 2002; <sup>2</sup>Dew JW et al, *Climacteric* 2003; <sup>3</sup>Le Ray I et al, *Br Cancer Res Treat* 2012

## RISK OF RECURRENCE WITH THE LNG-IUS (MIRENA DEVICE)

The assumption the LNG-IUS may be 'safe' for the management of gynaecological symptoms is not supported due to lack of evidence

- **Prevention of tamoxifen-associated endometrial cancer (RCTs)<sup>1</sup>**
  - Reduction in benign endometrial polyps and hyperplasia but *not* endometrial cancer
  - Underpowered to detect an impact on breast cancer recurrence rates
- **Management of menorrhagia, endometrial thickening or contraception<sup>2</sup>**
  - One small cohort (N=79) reported an increased recurrence with a longer duration of use but these patients had worse prognosis disease

<sup>1</sup>Dominick S et al, *Cochrane Database Syst Rev* 2015; <sup>2</sup>Trinh XB et al, *Fertil Steril*, 2008

# RISK OF RECURRENCE WITH TESTOSTERONE

- Women with a prior breast cancer excluded from RCTs of transdermal testosterone for hypoactive sexual desire disorder/dysfunction
- Small RCT (N=44) of low-dose intravaginal testosterone in women with early breast cancer treated with an aromatase inhibitor associated with significant improvements in vaginal dryness, dyspareunia, overall sexual satisfaction
  - No evidence of systemic testosterone absorption, E<sub>2</sub> not elevated
- 2019 Global Consensus Position Statement on the use of testosterone for women
  - Recommends caution for testosterone use in ER+ve cancer

# VASOMOTOR SYMPTOM MANAGEMENT IN WOMEN WITH A BREAST CANCER DIAGNOSIS<sup>1,2</sup>

- Counsel women about early menopause risk and iatrogenic symptoms
- Refer to a healthcare professional with expertise in the menopause
- In women with vasomotor symptoms provide information about:
  - All management options, including lifestyle changes
  - Avoid paroxetine and fluoxetine in women taking tamoxifen
  - Paucity of evidence and quality of some complementary therapies
  - Offer HRT only if severe, refractory symptoms, with informed, documented consent
  - Avoid HRT in women treated with an aromatase inhibitor

<sup>1</sup>Menopause: diagnosis and management (NG23) 2015; <sup>2</sup>Early and locally advanced breast cancer: diagnosis and management (NG101) 2018 [www.NICE.org.uk](http://www.NICE.org.uk)



# MANAGEMENT OF VULVO-VAGINAL ATROPHY IN WOMEN WITH A BREAST CANCER DIAGNOSIS<sup>1,2</sup>

- Vaginal moisturizers should be first-line management
- If refractory symptoms, consider low-dose topical oestrogen
- Do not use topical oestrogen in the presence of an aromatase inhibitor
- Laser therapy, DHEA, ospemiphene need further clinical evaluation
- **Additional advice** (not in NICE guidance, discuss with breast specialist)
  - Switching to tamoxifen from an aromatase inhibitor, may relieve symptoms but it can take up to three months to do so
  - Consider addition of low-dose topical oestrogen if no benefit (theoretically safe as tamoxifen has high binding affinity to the ER and is not displaced with 'add-back' topical oestrogen)

## SUMMARY

- In women with a low underlying risk of breast cancer (i.e. most of the population), the benefits of HRT will exceed potential harm
  - Unopposed HRT is associated with little or no change in the risk
  - Combined HRT can be associated with an increased risk
- In past HRT users, degree of risk is no greater, or less than other breast cancer lifestyle risk factors
- Don't discuss HRT risk of breast cancer diagnosis in isolation
- In women at elevated risk, refer to breast or menopause specialist for advice

# HRT AND BREAST CANCER

## Information from The British Menopause Society

- Consensus statements

1. Risks and benefits of HRT before and after a breast cancer diagnosis
2. The diagnosis of the menopause and management of oestrogen deficiency symptoms and arthralgia in women treated for breast cancer

- Tools for clinicians

1. HRT and breast cancer, fast facts

- Available online for BMS members ([www.thebms.org.uk](http://www.thebms.org.uk))
- All published in the Journal of Post Reproductive Health