Menopause after cancer

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Disclosure statement

Expert panel & consultant in last 5 years
• Besins
• Pfizer
• Flordis

Director
• Jean Hailes for Women’s Health

Acknowledgement
• A/Prof Amanda Vincent for slides
Menopause after cancer

- Childhood / adolescent cancer survivors
- Cancers not suitable for MHT
- Breast cancer survivors
- Treatment of vasomotor symptoms
- Treatment of GSM

Menopause after cancer

- Childhood / adolescent survivors
  - >70% long term
  - 6.3% ovarian failure during/immediately after therapy
    - Childhood cancer survivor study
      - Green D J Clin Onc 2009
  - Longer term risk of premature menopause <40 years
    - Euro2K cohort solid cancers survivors study
    - 6% <40 spontaneous PM
      - Thomas-Teinturier C Human Reprod 2013
Cytotoxic agents according to risk of gonadotoxicity

• High risk
  Alkylating agents: cyclophosphamide, ifosfamide, busulphan, chlorambucil, melphalan, chloromethine, procarbazine
• Medium risk
  Platinum agents: cisplatin, carboplatin
  Anthracyclic antibiotics*: doxorubicin (adriamycin)
  Taxoids: paclitaxel, docetaxel
• Low risk
  Vinca alkaloids: vincristine, vinblastine
  Anthracyclic antibiotics*: bleomycin
  Antimetabolites: methotrexate,
  5-fluorouracil, mercaptopurine
  *Anthracyclic antibiotics do not have a strict group effect and therefore the effect depends on the particular antibiotic used.

MHT

• Standard high dose MHT for premature menopause in childhood and adolescent survivors
• Routine screening
Menopause after cancer

- Cancer types unsuitable for MHT
  - Breast cancers?
  - Endometrial stromal cell sarcoma
    - Respond to high dose MPA/no ERT
  - Recurrent uterine cancers
    - Respond to high dose MPA/no ERT

MHT after cancer

- Ovarian cancers –
  - Epithelial
    - No evidence of negative effect
    - Small S Afr. Study showed trend to improved outcome/survival
  - Endometroid
    - No evidence of adverse effect
- Granulosa cell tumour
  - Watch inhibin levels very closely if on MHT
Breast cancer and menopause

- More severe symptoms experienced by women with BC\textsuperscript{1,2}
- Common and persist
  - 6 year follow- up of Australian BC cohort (n=843) no AET\textsuperscript{1}
    - Vasomotor symptoms: 50% <50 years; 73% age 50-59; 51% age 60-69 and 30% age ≥70 years
- Most women have several symptoms
- Negative impact on quality of life\textsuperscript{2}
- Up to 40% women with BC discontinue endocrine treatment due to menopausal symptoms\textsuperscript{3}


Effect of adjuvant endocrine therapy

- Tamoxifen vs Aromatase Inhibitors
  - Tamoxifen: 33-48% effect
  - Aromatase Inhibitors: 7-36%
  - Vaginal dryness: 19%
  - Joint pain: 20-36%

Figure 3: A comparison of the effects of tamoxifen and the aromatase inhibitor anastrozole. Tamoxifen can have both oestrogenic and anti-oestrogenic effects on tissues (see text). However, anastrozole inhibits oestrogen, so is purely anti-oestrogenic. Induces unknown but theoretically possible toxicity with anastrozole.
Bone loss with cancer therapies

- Late menopausal women
- Early menopausal woman
- Aromatase inhibitor (AI) therapy
- AI plus gonadotropin-releasing hormone agonist
- Ovarian failure secondary to chemotherapy

Milat and Vincent, Climacteric 2015

Risk of Cardiovascular disease

- Study comparing predicted risk of BC recurrence and CVD risk
- 415 women with Stage I-III ER+ BC
- average age 60 years

Bardia et al., 2011 Breast Cancer Res Treat
Increased recurrence BC with MHT

Kenemans et al. Lancet Oncology 2009

Non-hormonal pharmacologic therapies for vasomotor symptoms

- Limitations of studies
  - Short term—majority 3 months or less
    - Long term safety/efficacy?
  - Methodological problems
    - Hot flush measurement
    - Sample size
    - Sample participants
    - Loss of follow-up
  - Limited “head to head studies” between agents/with oestrogen
  - Recurrence of symptoms after cessation of therapy
Perception of response

- 2.40-3.20 reduction in number of daily HF with Oestrogen therapy

Wywich et al., Menopause 2008; Nelson et al., JAMA 2004, 2006

“First –line” non-hormonal therapies

- 30-70% reduction in vasomotor symptoms depending on agent
- Clonidine (only PBS listed agent) –second line therapy
Choice of non-hormonal therapy?

- Consider potential additional effect on mood/ sleep
- Meta-analysis rated escitalopram as most effective SSRI
- Gabapentin/ venlafaxine equivalent to low dose oestrogen
- Consider using combined therapy

Non-hormonal therapy: practical tips

- Start low and titrate dose upwards to avoid side effects
- Most treatments work within 4-6 weeks
- Limitations of SSRIs/SNRIs:
  - Do not use paroxetine/fluoxetine with tamoxifen-CYPD6 inhibition
  - Side effects: 20% cease due to adverse effects
  - Discontinuation syndromes- stop gradually
  - Lack of efficacy: about 30% of women get worse
- Limitations of Gabapentin/ Pregabalin
  - Side effects of excessive drowsiness/ dizziness occur in up to 50% but often resolved in 4 weeks


Hickey et al., Oncologist 2008; Vincent Climacteric 2015
Alternative therapies for VMS

<table>
<thead>
<tr>
<th>Agents</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents with inconsistent reports of benefit</td>
<td></td>
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<tr>
<td>Genistein</td>
<td>Purified isoflavone</td>
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<tr>
<td>Daidzein</td>
<td>Breast safety not established</td>
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<tr>
<td>S-equol</td>
<td>Breast safety not established</td>
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<tr>
<td>Nonpurified isoflavones</td>
<td>Breast safety not established</td>
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<tr>
<td>Red clover</td>
<td>Breast safety not established</td>
</tr>
<tr>
<td>High-dose extracted or synthesized phytoestrogen</td>
<td>Agreement about breast safety</td>
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<tr>
<td>Dietary soy</td>
<td>100% benefit in some studies</td>
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<tr>
<td>Vitamin E</td>
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<td>Black cohosh</td>
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<td>Omega-3 fatty acids</td>
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<td>Acupuncture</td>
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<tr>
<td>Exercise</td>
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<tr>
<td>Other complementary approaches</td>
<td></td>
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<tr>
<td>Agents requiring further study</td>
<td></td>
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<tr>
<td>Dietetic sodium block</td>
<td>Need further RCTs to establish lack of complications</td>
</tr>
<tr>
<td>Guided relaxation</td>
<td>Stress management, deep breathing, paced respiration, guided imagery, mindfulness training</td>
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<tr>
<td>Hypnotherapy</td>
<td>Recent studies suggest efficacy with trained practitioners</td>
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NAMS Position statement - Menopause 2015
Cognitive Behavioural Therapy (CBT)

- Studies in menopausal women with/ without breast cancer
- >50% reduction in the impact of hot flushes
- Improvements in sleep, anxiety and quality of life.
- 4 two hour sessions once a week in small group or guided self help CBT over weeks equally effective

Mann et al., 2012; Ayers et al., 2013

Incidence of VVA symptoms

The incidence of VVA symptoms has been estimated at approximately 60%.
- Symptoms increases with age,
  - 50% of women aged 50 to 60 years
  - 72% of women older than 70 years.
- WHI study,
  - Two thirds of women had physical evidence
  - Only 10% declared symptoms.
  - Estimated that only 7% of women are treated.

Archer D et al Menopause 2015
- The incidence increases with time from perimenopause to postmenopause.
  - 47% at 3 years

Dennerstein et al 2000
Menopause after breast cancer

- More severe symptoms with menopause
- Younger age
- Surgery, chemotherapy and radiotherapy
  - Breast cancer surgery +/- risk reduction BSO
  - After chemotherapy develop vulval and vaginal burning due to inflammation
  - Adjuvant therapy – aromatase inhibitors > tamoxifen
    - GSM symptoms
- Impact on QOL
GSM Management after breast cancer

Depends on symptoms
- Age, type of cancer, prognosis and response to management of her cancer
- Combination of GSM + VMS or GSM alone
- Severity of symptoms
- Impact on functioning (e.g. sleep deprivation, persistent UTI, severe dyspareunia, body image)
- Partner response; understanding and flexible or inflexible & demanding
- Health professional team and their attitudes/beliefs

Urogenital symptoms: management
- Need to exclude infection/dermatological problem
- Lifestyle modification
  - Avoid scented soaps/chemicals, panty liners
  - Stop smoking
- Vaginal moisturisers/lubricants
  - Some lubricants can increase vaginal dryness but may be useful for sexual intercourse
- Vaginal oestrogen
  - Most effective treatment for urogenital symptoms
  - Conflicting evidence re safety with AI use
  - Vaginal oestriol preferable to oestradiol?
- Consider changing adjuvant endocrine therapy
  - Less vaginal dryness with tamoxifen
GSM after breast cancer

• Distinction between moisturizers & lubricants

  • Optimal balance of both osmolality & pH
  • Physiological similarity to natural vaginal secretions
  • Relieve discomfort & pain with intercourse
  • Reduce friction
  • Different use immediate / longer term
  • WHO – 380mOsm/kg
    • But upper limit 1200mOsm.kg acceptable
    • >1200mOsm/kg – irritation, contact dermatitis, cytotoxicity

Edwards D, Panay N 2016 Climacteric

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GSM after breast cancer

Lubricants

• For relief of dryness and associated pain with penetrative sex
• Water-based-
  – Nonstaining, less side effects cf silicon-based
  – Excipients – humectants, emollients, preservatives
    – Effect osmolality / pH
    – Others – glycerine, propylene glycol, parfum, sweeteners, warming agents, parabens
  – Some no list of ingredients
  – Sylk (877) but KY jelly (2007)

Edwards D, Panay N 2016 Climacteric
GSM after breast cancer

• Vaginal moisturisers;
  • Rehydrate dry mucosal tissue by changing the fluid content of the vaginal endothelium
    – Absorbs and adheres to vaginal skin, last 2-3 days, mimicking vaginal secretions
    – Lowering pH
    – Contains water, plant-based or synthetic polymers for adherence and other excipients (effect osmolality & pH)
  • Replens (2011)

Edwards D, Panay N 2016 Climacteric

GSM after cancer

• OVERcome study to improve sexual problems following breast cancer treatment (Olive Oil, Vaginal Exercise, and MoisturizeR)
  • Improvements in dyspareunia, sexual function, and quality of life over time (all P<0.001).
  • PFM relaxation training was reported to be effective (P≤0.001). Maximum benefits were observed at week 12.
  • Most women rated PFM relaxation exercises (92%), vaginal moisturizer (88%), and olive oil (73%) as helpful, indicating that the intervention was acceptable.
  • Unexpectedly, six cases (11%) of vaginal stenosis were noted during initial screening.

» Juraskova et al J Sex Med 2013
Vaginal oestrogen therapy

- Study in breast cancer survivors
  - ¾ of women would not use oestrogens because of the attitudes of their health practitioners
  - No strong recommendations either supporting or rejecting the use of various vaginal oestrogens in some postmenopausal BC women on AIs
    - AIs reduce plasma estradiol levels from around 20 to 3 pmol/l
    - Increasing use of AIs in hormone-sensitive early breast cancer
    - Increased number of vaginal dryness (16.3%) and dyspareunia (17.8%)

Vaginal oestriol

- Estriol (E3) one of the three major naturally occurring estrogens.
  - Lower estrogenic potency than estradiol
    - Range 1:10 to 1:100
    - 1930 found in pregnant women’s urine
    - Major estrogen of placenta
  - Greater relative affinity for ERβ than ERα
  - Minimizing extravaginal effects
- Estradiol and estrone can be reversibly metabolized
  - Estriol cannot be transformed to estradiol or estrone

Caruso S et al 2015 Menopause
Moegele et al 2012 Arch Gynecol Obstet
Vaginal Oestradiol

- Oestradiol 10ug vaginal tablet (Vagifem low)
  - Annual oestradiol exposure of only 1.14 mg.
  - Minimal systemic E2 absorption,
  - No increased risk of endometrial hyperplasia or carcinoma and
  - Improved management of the symptoms of estrogen deficiency-induced vaginal atrophy
  - Safety in BCSs on AI not established
Vaginal oestrogen therapy

Santen, RJ Climacteric 2014

Figure 3 Levels of estradiol after administration of a 10-µg estradiol tablet on days 1, 14 and 83 measured with highly sensitive and specific GC/MS/MS assay. Day -1 is on the day prior to administration of the estradiol tablet and day 82 is on the day before the next estradiol administration when the patient is on a twice-weekly administration schedule. Figure reproduced from Eugster-Hausmann et al. with the permission of the author and publisher.

Gynoflor

- Gynoflor
- Low dose oestradiol 0.03mg with lactobacillus combined vaginal preparation,
- Improved symptoms in Breast cancer patients on AIs

Donders et al 2014

Fig. 2 Estradiol (E2) pharmacokinetics (PK) on visit E (day 0) and visit C2 (day 28); (PPS, n = 16)
New therapies

**Ospemifene (oral therapy)**
- Non-steroidal estrogen receptor agonist/antagonist
- Nearly full estrogen agonist effect in the vaginal epithelium
- Improved the vaginal maturation index (decreased parabasal cells and increased superficial cells),
- Decreased vaginal pH, and
- Decreased severity of dyspareunia or vaginal dryness compared to placebo.
- Side effect hot flushes 13%
- Safety not known in BCSs.

**Prasterone**
- Daily intravaginal prasterone (DHEA) (0.50%; 6.5 mg) treatment.
- Significant, beneficial effects
  - Lower percentage of vaginal parabasal cells, higher percentage of vaginal superficial cells, vaginal pH,
  - Reduction in moderate to severe dyspareunia
  - No endometrial stimulation
  - No safety data in BCSs
  - No significant drug-related adverse effect

Archer D et al 2015

Simon J Climacteric 2013

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**Laser for GSM**

Microablative CO2 laser
Erbium YAG laser

Both laser types studied in women with symptoms of vaginal dryness, POP, Dyspareunia, stress Incontinence.
All studies report improvement in symptoms
24 month study with Erbium laser shows on going improvement in symptoms

Gambaccini M 2016
1 of 4 papers at IMS 2017
BRCA positive women

Prophylactic bilateral salpingo-oophorectomy:
- BSO reduces the incidence of primary ovarian cancer in BRCA gene mutation carriers by 95%.
- Must remove also the entire fallopian tube.
- BSO also reduces breast cancer risk in women
  - BRCA2 mutations around 70% and
  - BRCA1 around 35%.
- Recommended age for risk-reducing BSO is usually between 35 and 40 years.
- Prophylactic mastectomy:
  - Reduction in breast cancer incidence (>90%) in women with bilateral prophylactic mastectomy (BPM)

Domchek S, Menopause Vol. 23, No. 9, pp. 1026-1027 DOI: 10.1097/GME.0000000000000724 2016

The American College of Obstetricians and Gynecologists makes the following recommendations and conclusions in women with urogenital symptoms or atrophy-related urinary symptoms.

1. **Nonhormonal approaches** first-line choices during or after treatment for breast cancer.
2. In estrogen-dependent breast cancer vaginal estrogen should be reserved for those patients who are unresponsive to non hormonal remedies.
3. The decision to use vaginal estrogen may be made in coordination with a woman's oncologist.
4. An informed decision-making and consent process in which the woman has the information and resources to consider the benefits and potential risks of low-dose vaginal estrogen.

*Data do not show an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer who use vaginal estrogen to relieve urogenital symptoms.*
<table>
<thead>
<tr>
<th>Pharmacological Intervention</th>
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<tbody>
<tr>
<td>Nonhormonal vaginal moisturizers and lubricants (first-line therapy; transient benefit, low compliance)</td>
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<tr>
<td>Low-dose vaginal estrogens (LETs) for BCSs who do not respond to nonhormonal intervention, after discussion of risk and benefits; caution in women receiving Als. Great efficacy, even at ultra-low doses)</td>
</tr>
<tr>
<td>Oral ospemifene (no clinical trials available in BCSs); in healthy women the efficacy is comparable with LETs, no endometrial or breast stimulation after 12 months of therapy)</td>
</tr>
<tr>
<td>Androgen therapy (experimental; concerns regarding possible aromatization of androgens to estrogen in BCSs)</td>
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<table>
<thead>
<tr>
<th>Nonpharmacological Interventions</th>
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</thead>
<tbody>
<tr>
<td>Vaginal laser (no clinical trials available in BCSs; short follow-up for evaluating its efficacy in healthy women)</td>
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<tr>
<td>Couple counseling</td>
</tr>
<tr>
<td>Management of psychosocial distress</td>
</tr>
<tr>
<td>Regular sexual activity</td>
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<tr>
<td>Need for larger clinical trials:</td>
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<tr>
<td>• Vaginal dilators of graduated size</td>
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<tr>
<td>• Pelvic floor physical therapy</td>
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<tr>
<td>• Topical lidocaine</td>
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Abbreviations: AI = aromatase inhibitor; BCS = breast cancer survivor; LET = local estrogen therapy.