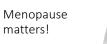


Womans Health: Managing Menopause in Women with a **Cancer Diagnosis** 

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 A normal life transition for women • But harder during cancer More abrupt (surgical menopause)
Earlier (induced by surgery or chemo)

Fewer treatment options for some women with cancer





#### Menopausal Consequences: Short and Long term

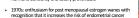
- ≻ Hot flashes can lead to disturbed sleep → which can contribute to weight gain, which can impact self image,
   > Sleep impairment may impact cancer itself; can also →
- Steep impairment may impact carter itself, car also y fatigue which reduces sexual desire
   Long term impact of menopause more CVD and
- cong term impact of menopause more CVD an osteoporosis; potential impact on brain

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#### A Brief History of Hormone Therapy:

> 1942: Premarin approved by the FDA

> 1966: Feminine Forever by Dr. Robert Wilson "menopause is a hormone deficiency and totally preventable"



- 1980:s doctors recommend all women be treated with estrogen and progestin to prevent heart disease, Alzheimer's and osteoporosis
- 2002: Women's Health Initiative –large NIH study of combined hormone therapy – stopped early due to increased risk of breast cancer, heart attacks, and strokes



## A Brief History of Hormone Therapy continued:

Of course, women like "Premarin

- ≥2015: all cause mortality reduced by 39% when women initiate hormone therapy at ages 50-59 compared with women ages 70-79
- ➢ Reduced risk of heart disease if hormone therapy begun within 10 years of menopause

Manson JE, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health initiative randomized trials. JAMA. Sept 2017

## Reasons to take (avoid) hormones Menopausal symptoms Bone health Vaginal health Urethral health **Colon Cancer Prevention** (Increases risk of Breast Cancer)

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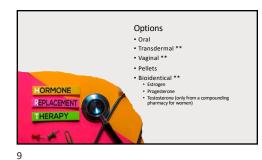
However...  $\succ$  Case control study to evaluate whether  $\uparrow$  risk of breast cancer is dependent on the formulation of menopausal hormone therapy

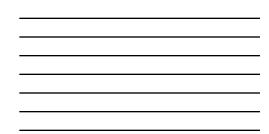
- Population-based case-control study of women >50 using data from the U.K. Clinical Practice Research Datalink

- 43,183 cases of breast cancer were identified (1995 2014) and matched to 431,830 women
   Compared with women who never used HT, its use was associated with an increased risk of breast cancer (OR 1.12, 95% CI 1.09-1.15).

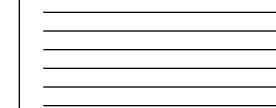
- cancel (vn 112, 95% Cl 109-115);
   Compared with hereast cancer (bioidentical: OR
   104, 95% Cl 100-109; animal-derived: OR 101, 95% Cl 0.96-1.06; both: OR 0.96, 95% Cl 0.89 103);
   Progestogens appeared to be differentially associated with breast cancer (micronized
- progesterone: OR 0.99, 95% CI 0.55-1.79; synthetic progestin: OR 1.28, 95% CI 1.22-1.35; both OR 1.31, 0.30-5.73).
- > Conclusion: While menopausal HT appears to be associated with an increased risk of breast cancer, this risk appears predominantly mediated through synthetic
- progestins. Abennaim HA, et al. Menopausal Hormone Therapy Formulation and Breast Cancer Risk. Obstet Gynecol. 2022

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#### Sexual dysfunction is more common after a cancer diagnosis 60% of women have some sexual problems after cancer treatment • loss of desire for sex (39%) • vaginal dyness (24%)

- vaginai dryness (24
   dyspareunia (9%)
- difficulty feeling excitement and pleasure (21%)
- difficulty achieving orgasm (15%)
- ➤ In 50% of women the problems are chronic
- Esmat Hosseini S, et al. Prevalence of sexual dysfunction in women with cancer: A systematic review and meta-analysis. Int J Reprod Biomed. 2022 Feb 18;20(1):1-12

Goldstein I. et al. The role of sex steroid hormones in female sexual function and dysfunction. Clinical Obstetrics & Gynecology. 47(2):471-84, 2004 Jun.



#### Antidepressant associated sexual dysfunction

- 2163 adult patients treated with antidepressants >8 weeks with a history of normal sexual functioning prior to the antidepressant 20% exclusions choused sexual divergencing. 44% moderate cause caused
- 79% patients showed sexual dysfunction, 64% moderate-severe sexual dysfunction; no differences between men and women.
   Treatment with a serotonergic antidepressant and having a severe mental ilness were associated with the highest likelihood of sexual
- dysfunction. • Sexual dysfunction was spontaneously reported by 838 (41%) of the

2066 evaluable patients.

Montejo, AL et al. A Real-World Study on Antidepressant-Associated Sexual Dysfunction in 2144 Outpatients: The SALSEX I Study. Arch Soc Behov 48, 923–933 (2019)

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#### How you ask the question matters: "Do you have any sexual problems or concerns?"

Yes: 1/10 women and 1/7 men

"In the past 12 months, has there ever been a period of 3 months or more when you experienced any sexual problems or concerns, such as, you had no interest in sex, your vagina felt to dory (women), you had erection difficulties (men), you had pain during or after sex, you had difficulty having an orgasm, you felt anxious about having sex, or you did not enjoy sex?"

Yes: 1/2.5 women and 1/3 men

Flynn, KE et al. Development and Validation of a Single-Item Screener for Self-Reporting Sexual Problems in U.S. Adults. J Gen Intern Med 30(10):1468–75 2015

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#### A better question:

"Most women at menopause start to experience problems with sexual activity. What concerns or problems are you having?"

#### Vaginal dryness: (GSM) Nonhormonal treatment

- ≻ Moisturizers (use regularly)
- Available over the counter Replens - studied in breast cancer survivors: as effective as estrogen. But, contains parabens.
- Vitamin E capsules prick capsule and apply oil
- >Lubricants (use during intercourse)
- Available over the counter YES - plant derived from flax, guar, locust bean, xanthan gum
- Pre-Seed isosmotic

Loprinzi CL. Phase III randomized double-blind study to evaluate the efficacy of a polycarbophil-based vaginal moisturizer in women with breast cancer. J Clinic Onc. 1997

Biglia N. (2010) Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study, Gynecological Endocrinology, 26:6, 404-412



### Lubricant Research 245 women ages 18-68 who purchased lubricants > 96% greater sexual comfort > 94% greater sexual pleasure Overall: increased ease of orgasm Jozkowski KN, et al. Women's perceptions about lubricant use and vaginal wetness during sexual activities. J Sex Med. 2013;10(2):484-92. Kennedy CE et al. Lubricants for the promotion of sexual health and well-being: a systematic review. Sex Reprod Health Matters. 2021;29(3):2044198.

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#### Vaginal dryness: Hormonal treatments

- Intravaginal Estrogen
   Estradiol (synthetic, biodentical 17 beta estradiol):

   creans
   tablet (Vagifem)
   vaginal ring that gradually emits and has the lowest systemic absorption (Estring)
   Estriol (from compounding pharmacy)
- Premain (natural, equine)
   > DHEA
   From a compounding pharmacy or Prasterone (EMA approved 2018)
   > Testosterone Cream from compounding pharmacy
- Ospemifene (oral medication)
   Activates vaginal estrogen receptors (European Medicines agency approved 2015)

Labrie F et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women Menopause: 16:5. 2009



Meneses-Echávez JF, et al. Effects of supervised exercise on cancer-related fatigue in breast cancer survivors: a systematic review and meta-analysis. *BMC Concer*. 2015 Feb 21;15:77. 21

But does not typically help vasomotor symptoms...

#### Can you prescribe vaginal estrogen to cancer survivors?

- $\succ$  Vaginal estrogen may be contraindicated for women on AIs as may counteract AI induced estrogen suppression
- > The American College of Obstetrics and Gynecology 2020 Committee Opinion: for women with a history of breast cancer, "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."

Krause M et al. Systemic Effects of Vaginally Administered Estrogen Therapy: A Review. Female Pelvic Med Reconstr Surg. 2010 May; 16(3): 188–195.

Kendall A. et al. Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. Ann Oncol. 2006;17:584–587.

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Additional treatment options Pelvic floor PT

· International consensus paper on testosterone in menopausal women Flibanserin (oral, for hypoactive sexual desire disorder (HSDD) Vyleesi (injectable medication for HSDD – not approved by European

 Trazadone increases dopamine and lowers serotonin • Buspirone – anti-anxiety agent. Prosexual (in women with anxiety) Buproprion – anti-depressant – at high doses can boost desire Davis SR, et al., Global Consensus Position Statement on the Use of Testosterone Therapy for Women, The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 10, October 2019, Pages 4660–4666.

CBT (when anxiety about pain with intercourse)

- Exercise for menopausal symptoms Prevents weight gain Reduces risk of cancer
  Strengthens bones Reduces risk of other diseases Boosts mood Helps cancer related fatigue

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Medicines agency) Other medications:



Cannioto RA, et al. Physical Activity Before, During, and After Chemotherapy for High-Risk Breast Cancer. J Natl Cancer Inst. 2021;113(1):54-63.

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#### Precautionary Principle

"If there is good scientific information that an action or policy may harm the public or the environment, then even in the absence of conclusive proof that the action or policy is harmful, the burden falls upon those taking the action to demonstrate that it will not be harmful."

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#### 2015 Endocrine Society Position:

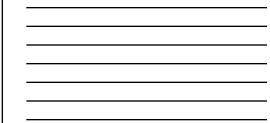
The evidence is strongest for:

 obesity and diabetes; 2) female reproduction; 3) male reproduction; 4) hormonesensitive cancers in females; 5) prostate; 6) thyroid; and 7) neurodevelopment and neuroendocrine systems.

Practical recommendations:

- Careful history talking about the onset of reproductive disorders, occupational and environmental exposure
- Consider possible exposure to endocrine disrupting chemicals when a geographical or community subgroup presents with an unexpectedly high prevalence of disorders associated with EDCs.
- >Advise patients about exposures, minimizing risks, and abiding by the precautionary principle to preserve their reproductive health
- Gore AC et al. The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev. 2015. Diamanti-Kandarakis E et al. 2009 Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. Endocrine Reviews





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#### On the horizon:

#### Fezolinetant

- Oral medication for the treatment of moderate to severe hot flashes in menopausal women
- FDA approved May 2023
- Dose is 45 mg daily
- A NK3 (neurokinin) receptor antagonist
- Being evaluated by EMA

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6/26/23



