



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

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**Menopause
matters!**

- 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



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**Menopausal
symptoms**

On a continuum from "Wow, I haven't had a period in a long time." ---->

Hot flashes, night sweats, sleep disturbance, vaginal dryness or burning, vaginal atrophy with pain on intercourse, mood changes, cognitive challenges, overall misery.



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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 → fatigue which reduces sexual desire
- Long term impact of menopause – more CVD and 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"
- 1970s: enthusiasm for post menopausal estrogen wanes with recognition that it increases the risk of endometrial cancer
- 1980s: 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



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A Brief History of Hormone Therapy continued:

- 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

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Reasons to take (avoid) hormones

- Menopausal symptoms
- Bone health
- Vaginal health
- Urethral health
- Colon Cancer Prevention
- Heart Protection?
- Alzheimer's Prevention?
- (Increases risk of Breast Cancer)

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However...

- Case control study to evaluate whether ↑ 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).
 - Compared with never users, **estrogens were not associated with breast cancer** (bioidentical: OR 1.04, 95% CI 1.00-1.09; animal-derived: OR 1.01, 95% CI 0.96-1.06; both: OR 0.96, 95% CI 0.89-1.03).
 - **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**.

Goodwin ML, et al. Menopausal Hormone Therapy Formulation and Breast Cancer Risk. *Obstet Gynecol.* 2022

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Options

- Oral
- Transdermal **
- Vaginal **
- Pellets
- Bioidentical **
 - Estrogen
 - Progesterone
 - Testosterone (only from a compounding pharmacy for women)

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Body Image

- **Personal challenges**
 - Mastectomy or other breast surgery can lead to loss of pleasure from breast stimulation
 - Pain, numbness, scar tissue, lymphedema
 - Vaginal pain with intercourse
 - Depression and anxiety interfere with sexual function
- **Partner challenges**
 - Discomfort re-surgical changes to the body
 - Fear of hurting partner
 - Communication about sexuality is often difficult

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Sexual Dysfunction is common

- United States probability study of 3000 adults
- **43% of women** report a sexual dysfunction or concern
 - 22% low desire
 - 14-20% arousal disorder
 - 8-25% orgasmic dysfunction
- **31% of men** report a sexual dysfunction or concern
 - 5-10% low desire
 - 5-40% erectile dysfunction
 - 21-30% premature ejaculation
 - 5% delayed ejaculation

Laumann EO, et al. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999 Feb 10;281(6):537-44.

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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 dryness (24%)
 - dyspareunia (9%)
 - difficulty feeling excitement and pleasure (21%)
 - difficulty achieving orgasm (15%)
- In 50% of women the problems are chronic

Eunat Hossain 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):3-12.

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

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Antidepressant associated sexual dysfunction

- > 2163 adult patients treated with antidepressants >8 weeks with a history of normal sexual functioning prior to the antidepressant
 - 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 illness 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 SALSEX1 Study. Arch Sex Behav 48, 323-333 (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 too dry (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?”

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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

Logroni CL. Phase III randomized double-blind study to evaluate the efficacy of a polycarbophil-based vaginal moisturizer in women with breast cancer. *J Clin Oncol*. 1997.
 Biglia N. (2010) Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. *Gynecological Endocrinology*, 26(4), 404-412

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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, bioidentical 17 beta estradiol):
 - creams
 - tablet (Vagifem)
 - vaginal ring that gradually emits and has the lowest systemic absorption (Estring)
 - Estriol (from compounding pharmacy)
 - Premarin (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

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Can you prescribe vaginal estrogen to cancer survivors?

- 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.* 2019;Mar;16(3):188-195.

Kendall J 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
- CBT (when anxiety about pain with intercourse)
- 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 Medicines agency)
- Other medications:
 - Trazadone increases dopamine and lowers serotonin
 - Buspirone – anti-anxiety agent. Prosexual (in women with anxiety)
 - Bupropion – 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.

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Exercise for menopausal symptoms

- Prevents weight gain
- Reduces risk of cancer
- Strengthens bones
- Reduces risk of other diseases
- Boosts mood
- Helps cancer related fatigue
- But does not typically help vasomotor symptoms...



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

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Physical activity and risk of breast cancer mortality

- 1,340 patients – DELCaP Study: prospective re lifestyle and prognosis. Activity before diagnosis, during treatment, and at one-and two-year intervals after enrollment
- Women meeting the Physical Activity Guidelines before and one year after diagnosis experienced a 41% reduction in recurrence (HR=0.59, 95% CI: 0.42-0.82) and 49% reduced mortality (HR=0.51, 95% CI: 0.34-0.77)
- Women meeting Physical Activity Guidelines two years after diagnosis had a 55% reduction in recurrence (HR=0.45, 95% CI: 0.31-0.65) and 68% reduced mortality (HR=0.32, 95% CI: 0.19-0.52)
- The level of exercise matters too: low-active patients had a 59% reduced mortality(HR=0.41, 95%CI: 0.24-0.66), moderate-active patients had a 58% reduced mortality (HR = 0.42, 95% CI: 0.23-0.76), and high-active patients had a 69% reduced mortality (HR=0.31, 95% CI: 0.18-0.53)

Cannoto RA, et al. Physical Activity Before, During, and After Chemotherapy for High-Risk Breast Cancer. *J Natl Cancer Inst.* 2021;113(3):36-43.

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Mind Body tools for vasomotor symptoms

- Breathwork
- Guided Imagery
- CBT
- Mindfulness
- Self Hypnosis
- Group support
- Apps (Insight Timer)



Stefanopoulou E, et al. Mind-body interventions for vasomotor symptoms in healthy menopausal women and breast cancer survivors: A systematic review. *J Psychosom Obstet Gynecol.* 2017; Sep;38(3):210-225

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Acupuncture for menopause

1. Acceptable to health care professionals & breast cancer survivors
2. Widely researched: natural menopause, cancer treatment-related menopause
3. RCTs reveal acupuncture is as effective as Gabapentin or Venlafaxine with <rebound effect, and <adverse effects
4. Addresses many menopausal symptoms including sleep, anxiety, low mood, poor concentration, improved energy, quality of life
5. Safe - few minor adverse effects (bleeding, bruising, transient pain at sites)
6. Lasts for ≥ 3 months



(Fukun et al 2017; Wang et al 2018; Mao et al 2015; Walker et al 2010; Chen et al 2020; de Valois et al 2010, 2012, 2022; Chen et al 2020; Frisk et al 2014)

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There are too many people counting calories and not enough people counting chemicals.



Environmental Chemicals

Grindler NM et al. Persistent Organic Pollutants and Early Menopause in U.S. Women. *PLoS one* Jan 2015.

Horwitz R, Malins V. Environmental sensitivity as a trigger of erythema nodosum and perimenopausal symptoms. *BMJ Case Reports* 2017; bcr.2017.220433.

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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:

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

Practical recommendations:

- Careful history taking 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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Brand	Yes	KY Jelly	Durex Play	Sylk	Astroglide	Boots Jelly	Replens	Ingredient Concern*
Paraben(s)	✗	✓		See GSE	✓		✓	Estrogen mimics, found in breast tumors – avoid if breast cancer history / not wearing WBT; any hormone related concerns.
Glycerine	✗	✓	✓	✓	✓	✓	✓	Mucosal irritant (dehydrates & irritates mucosa above 20%), at < 5% is Considered nutrient, so may "soothe" Trush outbreaks & leaves sticky residue.
Glycols	✗		✓				✓	Cell wall disrupter, called penetration enhancer as pulls other chemicals thru skin into blood stream.
Grapefruit Seed Extract (GSE)	✗			✓				No proven preservative efficacy; banned in Sulfonamide Personal Care products. FDA research shows preservative efficacy due only to those active agents: Methylparaben, Triclosan and Benzothiazolium chloride.
Mineral oil	✗							Called liquid paraffin, petroleum by-product & thought to suffocate skin by coating it.
Certified Organic	✓	✗	✗	✗	✗	✗	✗	Some companies label products "organic" if it only contains 1% organic ingredients, regardless of other non-toxic ingredients. The Soil Association certification guarantees purity and quality of ingredients and assures strict manufacturing standards.

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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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Resources:

- Environmental Working Group – www.ewg.org
- Healthy Living App (free app, created by ewg)
- Program on Reproductive Health and the Environment at UCSF – prhe.ucsf.edu
- Collaborative for Health and Environment www.healthandenvironment.org
- University Arizona – free online course with CME/CE on environmental health: Integrativemedicine.arizona.edu/education/online_courses/eviro-med



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