City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Assessing and Addressing Sexual Toxicities in Patients with Cancer

Linda D Bosserman, MD, PhD, AASECT, FACP, FASCO

Professor, Medical Oncology & Research Therapeutics

Value-Based Care, Breast Medical Oncology and Sexual Health Specialist

Director of Protocols & Pathways and Center for International Medicine

City of Hope National Medical Center

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

- I will discuss off-label and non-FDA approved use of Testosterone for women with breast cancer based on evidence
- I will discuss the compounding of Testosterone under FDA 502A and B guidelines, as there is no FDA-approved testosterone for women, which all national guideline committees recommended in a 2019 consensus statement published by many national societies.
- I will discuss the use of compounded estradiol cream, which is very cost-effective in doses recommended for women with breast cancer under FDA 502A and B guidelines, as many insurances do not cover the FDA-approved estradiol vaginal pills and suppositories or have an unaffordable co-pay, and the cash price, even using generics and discount programs is runs $600/month as of 10/24.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Understanding and respecting cultural differences in comfort discussing sexual health and how to address.*
- *Review to avoid biases in addressing patients with diverse sexual desires or practices.*

Sexual Health and Sexuality in Cancer Patients

Sexual Health:

The World Health Organization defines sexual health as a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity.

Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence.

(WHO- 2006a)

Sexuality: Consensual sharing of Physical Body

"…a central aspect of being human throughout life encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. (WHO – 2006a)

Identity, Independence, & Intimacy- all impacted by Cancer and Cancer Therapies

Often focus on Life at diagnosis but

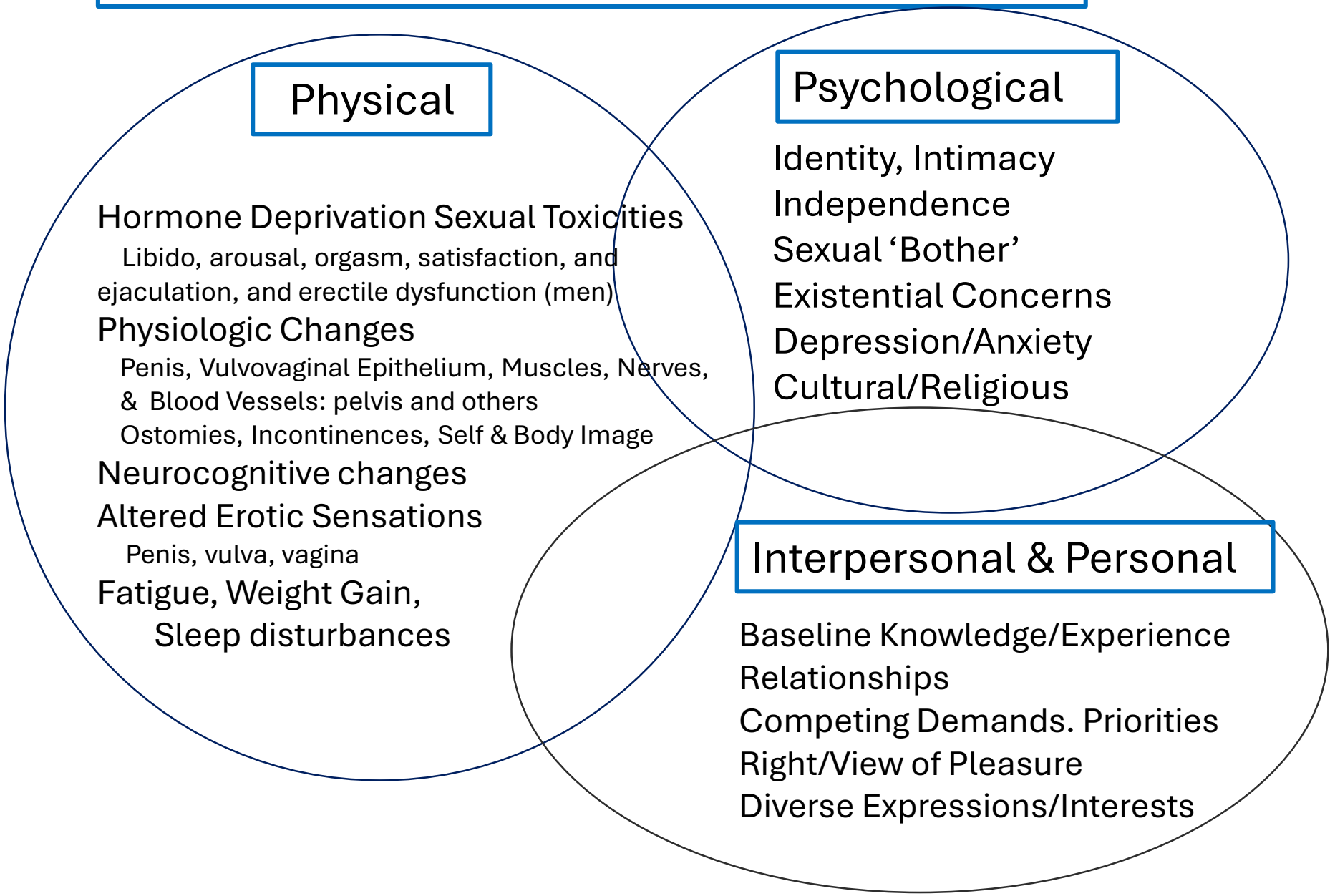
Long-term Quality of Life includes Sexual Health during Diagnosis, Therapy Choices, Care Management, survivorship, and end-of-life care.

80% of cancer patients have sexual health impacts

"Don't Ask, Don't Tell" didn't work in the Military -

and it doesn't work for High Quality Cancer Care

Cancer Impacts Sexual Health Domains



Three Interactive Domains of Sexual Health

All Potentially Impacted by Cancer, Therapies, and Toxicities

Sexual Issues in Patients with a Cancer Diagnosis

- 80% of Cancer Patients have their sexual health impacted by cancer diagnosis and therapies
  - Intimacy: Role changes, psychological, social, financial, physical spiritual impacts of cancer
    - Hormone release during intimacy, from hugging and kissing to sexual pleasuring, intercourse, and orgasm, increases the sense of intimacy, satisfaction, and bonding and lowers the divorce rate.
  - Independence: Sense of self, sense as a vital and purposeful individual impacted by cancer treatments and toxicities with secondary impacts on finances, care needs, and social, work and partner relationship changes.
  - Identity: Sense of self as an individual and as a sexual person varies at baseline and is impacted by physical, financial, social, and emotional impacts of cancer diagnosis, treatment, survival, and end of life.
- IF YOU DON'T ASK about Sexual Concerns and Toxicities: Patients won't tell as they don't want to burden their docs, or they don't think it can be important in perspective to their CANCER, and many have not talked to a doctor about their sexual issues in the past. (Kang, 2018,Reese, 2018, Katz, 2022,

Develop A Sexual Health Agenda as part of your Care

- Understand your Sexual Beliefs, Values, Experiences, and Knowledge of Diversities to become comfortable asking and offering care
- Get Comfortable asking about and Discussing Sexual Toxicities
- Develop a Standardized questionnaire that includes sexual toxicities
- Gain Knowledge of Treatment Toxicities and Options to treat
  - Short and long Toxicity and Options to Prevent and Treat
  - Different Cancer therapies with different sexual toxicities
- Gather or Develop Resources
  - Referral Sources
  - Educational tools
  - Treatment Pathways
  - Treatment details: doses, formulations, uses, monitoring and durations
  - Visit Note Templates and Order Sets

Standardize and Normalize Asking about Sex Life and Toxicities

- Key to Addressing Sexual Health Needs is Getting Comfortable then Normalizing and Standardizing Approach
  - Standardized invitation question(s) as part of intake and PRO questionnaires
    - Asking indicates a willingness and (hopefully) capacity to help patients address the complex impacts of cancer on their sexual health
  - Training of staff at all levels to increase comfort and competency to ask about sexual health toxicities in ways that
    - Respect cultural differences, religious, community, situational, and personal beliefs about the role of sexuality in an individual's life or their life with their partner
    - Education about the diversity of sexual beliefs, practices, needs, preferences and options for sexual activities in patients who have a cancer diagnosis and the partners they share their sex life with
- To Increase Asking about Sexual Health, staff, and clinicians also need to know the common toxicities with different treatments and at least a general idea of the options to prevent or address them. After normalizing the importance of addressing sexual toxicities, patients are more willing to talk about their concerns and to see care to address them.

Practical Approaches to Addressing Sexual Toxicities

- Include Sexual Health question(s) in Standardized PRO or Intake Questionnaires
  - PROMIS has a screening question and others on aspects of sexual health
  - NCCN recommends the Brief Sexual Health questionnaire 6 questions for men or women, not currently validated for transgender and sexual minority patients
  - Other validated questionnaires for men and women, some cancer-specific
  - If not interested or no issues, continue to ask at follow-up visits
- NORMALIZE and VALIDATE patient's sexual health and toxicity issues and questions
  - YOU DON'T have to know all the answers but be willing to ask, acknowledge and refer
- Develop a Referral and Resource Plan for your Practice
  - Sex Therapists, Therapists (couples, individuals), Psychiatrists, Physical Therapists including pelvic floor PTs, GYN, OT, support groups
  - Informational handouts and web-based resources
- Address medical care of sexual toxicities: Arm yourself with knowledge
  - Inform patients accurately of expected toxicities from treatment, treatment options, and options for toxicity therapies
  - Treatment pathways can guide treatment of common sexual toxicities:
    - MEN: Erectile Dysfunction and Sexual Bother are the two most commonly impacted sexual health domains. The next two common sexual health issues are Low Libido and changes in Sexual Experience from ejaculation and orgasm leading to less satisfaction
    - WOMEN: Vaginal dryness to atrophy with painful intercourse and loss of libido are the two most common toxicities, followed by decreased low arousal, lubrication, and orgasm.

Busy Oncology Practices can address sexual toxicities with Pathways and Referral Resources

Cancer & Cancer Treatment Impacts on Men's Sexual Health

Hormone Therapy, Surgery, Radiation, Chemo

- Urinary incontinence
- Sexual incontinence
- Erectile dysfunction
- Loss of libido
- Fatigue
- Difficulty with ejaculation
  - Retrograde/dry ejaculation
- Orgasmic dysfunction
- Climacturia
- Anodyspareunia
- Penile length and girth loss
- Penile curvature

- Loss of body hair
- Depression
- Anxiety
- Mood changes
- Weight gain
- Increase in breast tissue
- Decreased testicular size
- Ostomy appliances

National Cancer Institute, Sexual Health Issues in Men with Cancer, 2022

Sexual Toxicities in Men with Cancer

Erectile Dysfunction

Persistent or recurrent inability to attain or maintain a penile erection sufficient for sexual penetration or satisfaction lasting at least 3 months

Sexual Bother

When a combination of sexual changes has sex felt as “not worth the bother”

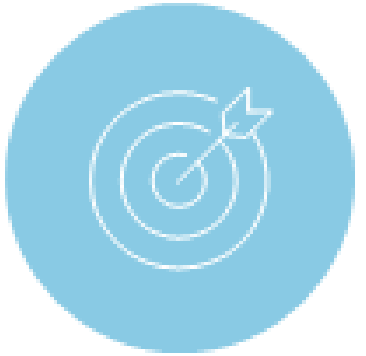
Commonly from embarrassment or shame over interest, erections, ability to reliably satisfy self and/or partner

Low Libido

Loss or distressing lessening of interest in sexual activity.

It can be tied to a man’s sense of masculine identity and self-worth.

Can impact intimacy and satisfaction with partner



Orgasm, Ejaculation & Satisfaction Issues

Intensity or loss of orgasm

Ejaculation stoppage or retrograde

Reduced Penile length

Treatment approaches to improve sexual health for Men with Cancer
Optimal to become familiar with treating common toxicities

- Addressing Baseline Function
- Addressing risks and benefits to sexual health with cancer treatment options
- Addressing Erectile Dysfunction
- Addressing Sexual Bother: in men and their partners
- Addressing low libido in men
- Addressing orgasm, ejaculation, and satisfaction in men

- Details of Treatments for Individual Toxicities beyond this overview talk. If interested, I can share a 1-hour slide talk on this topic for any who are interested: lbosserman@coh.org

Sexual Toxicities in Women with Breast Cancer & Menopause

- Physiologic changes of Estrogen and Testosterone Deprivation
  - Genitourinary Syndrome of Menopause (GSM)
    - Vaginal dryness to atrophy, shortening and constriction, discomfort, itching, inflammation, pain, dyspareunia, decreased sensation and engorgement with stimulation, less lubrication
    - Vulvar dryness to atrophy with potential discomfort, itching, inflammation, pain, decreased sensation and engorgement with stimulation
    - Clitoral shrinkage, decreased sensitivity and engorgement with stimulation
    - Vulvar dryness to atrophy, inflammation, discomfort, itching, rashes
    - Labia minors and majora atrophy to involution, less sensation to pain with touch
    - Urethral retraction, enlargement, discomfort with frequency, incontinence and increased UTIs
  - Functional changes of Estrogen and Testosterone Deprivation- 5 Domains
    - Libido: none to lower baseline, with stimulation or maintained during sexual activities
    - Arousal: none to lower baseline, may require longer and different stimulation, can be less even with stimulation and may be difficult to maintain interest during sexual activities
      - Less lubrication, engorgement of vagina and clitoris
    - Orgasm: none to less, often needs more, different and longer stimulation to achieve, less intense or satisfying
    - Pleasure: decreased to unpleasurable
    - Sexual Satisfaction: lower to none

Sorting out the Diagnostic Components for Rx Considerations

(After eval and treatment of social, relational, educational, emotional issues and pelvic floor health)

- GenitoUrinary Syndrome Of Menopause: with or without distress
  - Need to discuss treatments to prevent and treat physiologic and sexual toxicities and to improve all-cause mortality. Only hormonal therapies heal. Needs individualized and updated risk /benefit assessment
  - Vulvovaginal health develops and is maintained by estradiol, progesterone and testosterone
  - Urethral health develops and is maintained by estradiol and testosterone
- Sexual Domain Impacts causing distress (no distress, discuss prevention, Testosterone is key)
  - Libido
  - Arousal
  - Orgasm
  - Pleasure
  - Satisfaction
- Vaso Motor Symptoms (VSM)- hot flashes: there are hormonal and nonhormonal options
- Birth Control: is an issue for some premenopausal women to consider
- HRT with natural estradiol, micronized progesterone, and testosterone improves all-cause mortality and reduces CVD, bone, brain, breast and other cancers
  - Use in women with hormone-positive cancers deserves a risk/benefit discussion, NOT JUST A NO

Prescription Therapies for GSM & Sexual Domain Toxicities in Women and Women with Breast Cancer

- Vaginal Hormone Therapies for On or Off-Label Prescribing: (safe for women with breast cancer and other women)
  - Estradiol - Low dose pills, ring, gel, suppository, cream: GSM and sex toxicities, not VMS, no progestins needed with vaginal dosing
  - Estriol – treats GSM and sexual toxicities but is only available by compounding in the US, widely used in Europe and Australia
  - Androgens: DHEA (prasterone suppositories) and compounded Testosterone cream or pellets for VMS, GSM, and Sexual Toxicities
- Systemic Hormone Therapies (require risk-benefit assessment and updated review of science for women with hormone-positive cancers)
  - Estrogens as Estradiol NOT CCE: GSM, Sexual Toxicities and VMS. No clotting with oral estradiol in studies to date, only CCE/and synthetic progestins
  - Estrogen as Estradiol plus micronized progestin (not medroxyprogesterone) for women with a uterus: GSM, Sexual Toxicities & VMS
  - Estrogen as Estradiol Plus Testosterone cream by pellet, oral or combination treatment: GSM, Sexual Toxicities and VMS
  - Estradiol -as Femring gets systemic levels, treats VMS but need micronized progestin if women have a uterus
- Non-Hormone Therapies for On or Off-Label Prescribing
  - Ospemifene: can help after completing therapy for breast cancer if local therapies not used or helpful
  - Flibanserin: option if heal VVA first, does not respond to testosterone, and still has low libido. Costly and has toxicities
  - Bremelanotide (not recommended, bad science, toxic)
  - Bupropion: (only if depressed on SSRIs and can change. Tamoxifen contraindication not supported by literature)
  - Lasofoxifene: only in metastatic breast cancer, may help as part of therapy
- Non-hormone therapies with efficacy but only potentially available by compounding
  - Soy Vaginal Gel: need to compound, 6 randomized studies in women with out cancer show efficacy and safety
  - Alprostadil: need to compound for use in women
  - Cannabis vaginal gel: option for those interested
- Many non-prescription therapies can help and support (see appendix slides)

  - SEPARATE talks on these topics can be provided to detail each of these topics, which are beyond the focus of this overview talk)

Addressing Updated Science of HRT for Women with Breast Cancer ISSUE IS WHAT HRT: Hormones are not all the SAME!!

- Estradiol and micronized progesterone do not cause breast cancer
- HRT in long-term studies improves all-cause mortality 40%, reduces cardiovascular disease 30-50%, reduces bone fractures, reduces breast cancer risk 30%, reduces dementia, and improves women's quality of life
- Women with Hormone Positive Breast Cancer can be safely treated with vaginal hormone therapies to prevent and treat physiologic and sexual toxicities
- Women with hormone-positive breast cancer who got systemic HRT in 25 trials:
  - Had no increase in breast cancer mortality in all 25 trials
  - Had no increase and some decreases in breast cancer recurrence in 24 of 25 trials
  - Only one study (Habits) had an increased local recurrence breast cancer recurrence risk BUT women had no pre-study mammograms, the study was terminated early with small numbers that did NOT MEET THE PRESPECIFIED numbers to detect a difference, and the increased local recurrences with the HRT group used the synthetic progestin, NETA (norethindrone acetate) which has been associated with increased breast cancer risks). (Bluming, 2022)
- National leaders have called for studies of estradiol and micronized progesterone in women with breast cancer, which are still needed to provide more comprehensive evidence-based guidelines for treating women with hormone-positive breast cancer as well as other women at menopause with and without symptoms.

Estrogen and Other Hormones HEAL VVA, Dyspareunia & HSDD, AND are Safe and Effective in Women with Breast Cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Survivorship: Hormone-Related Symptoms (Female)

NOT EVIDENCE BASED

Vaginal dryness →

- Non-hormonal treatments
  - Vaginal moisturizers, vaginal gels, oils (category 2B)
- Lubricants for sexual activity[n]
- Local estrogen treatment[o] (ie, rings, suppositories, creams) (category 2B)
  - Limited data in breast cancer survivors suggest minimal systemic absorption with rings and suppositories. Therefore, if estrogen-based treatment is warranted, rings and suppositories are preferred over creams for survivors of hormonally sensitive tumors.
- Other topical hormones (ie, testosterone,[p] DHEA[o,q])
- Consider referral to appropriate specialist for management
- For vaginal pain or discomfort, see SSF-2

Low-Dose Hormone-Based Prescription Therapies for VVA, Dyspareunia, and HSDD

Low-dose estrogen based (80-90% effective)

- **Estradiol (E2)**
  - **Cream, rings, tablets, and capsules**
  - **4,7.5, 10, and 25 µg dosing**
- Estriol (E3)
  - Compounded cream or gel
  - Ultra low-dose: 30-50 µg/dose
  - Low dose: 250-500 µg/dose
- Conjugated estrogens
  - > 200 ingredients, >10 estrogens
  - Do not recommend over pure, bioidentical products

DHEA based

- DHEA vaginal suppositories
  - 6.5 mg dose
- Compounded creams
  - 3.25 mg and 6.5 mg dose options

Testosterone based

- **Low-dose vaginal creams or gels**
  - **300-500 µg/dose**
  - **One study had 5000 µg/dose used**
- Transdermal patch (not in US)
  - 300 µg/day delivery

What do the studies tell us about the safety & efficacy of low-dose vaginal hormone therapies in women with breast cancer?

20 Years of Study Results of Vaginal Estradiol or Estriol in Women with HR+ Breast Cancer on EDT with VVA (cont.)

8 Prospective Trials with Very-Short-Term Follow-up

38 women-years of data

Trial	Median f/u
Kendall 2006	12 wk
Biglia 2010	12 wk
Pfeiler 2011	4 wk
Willis 2012	12 wk
Donders 2014	12 wk
Melisko 2016	12 wk
Hirschberg 2020	12 wk
Streff 2021	16 wk

- **175 women with br ca on EDT got vaginal E2 or E3**
- **51 control women with br ca on EDT without E2 or E3 use**

SYMPTOMS IMPROVED SIGNIFICANTLY ON VAGINAL E2 OR E3

MIXED RESULTS OF E2 SERUM LEVEL RISES, MOST RETURNED TO BASELINE ON SHORT-TERM F/U, NOT TESTED FOR DEGREE OF VVA HEALING, AND SERUM LEVELS RETURNING TO NORMAL

NO EVIDENCE OF INCREASED RECURRENCE RISK; ONLY CONCERNS RAISED ABOUT SOME E2 LEVEL RISES OR FSH/LH CHANGES ON SHORT-TERM F/U

20 Years of Study Results of Vaginal Estradiol or Estriol in Women with HR+ Breast Cancer on EDT with VVA

> 50,000
women-years of data
(estimated from f/u times)

6 Observational Trials with Long-term Follow-up

Trial	Follow-up
Vassilopoulou 1997	7.9 yr (median)
Dew 2003	5.5 yr (median)
Le Ray 2012	3.5 yr (mean)
Cold 2022	9.8 yr (median)
Sund 2023	5.1 yr (median)
McVicker 2023	5.0 & 8.0 yr (median)

- **6,309 women with br ca on EDT used vaginal E2 or E3**
- **76,459 control women with br ca on EDT with no E2 or E3 use**

SYMPTOMS IMPROVED SIGNIFICANTLY ON VAGINAL E2 OR E3

NO INCREASED BREAST CANCER RECURRENCE RISKS IN LONG-TERM F/U*

NO INCREASE IN MORTALITY IN LONG-TERM FOLLOW-UP

*Cold study: 93 women on AI and 729 tam to AI on VET had higher RR vs 2,430 without VET: HR 1.39 but no cofactor control Much larger McVicker study: 1,459 on VET + AI or tam/AI had no increased RR, vs. 20,913 without VET, adjusted HR 0.72 (95% CI, 0.58-0.91)

Even HUGE E2 rises during pregnancy do not increase breast cancer recurrence risks!

E2 levels for women

Pre-puberty:	<10 pg/mL
Ovulating:	30-400 pg/mL
Pregnancy:	188-7,192 pg/mL
Post-meno:	<18 pg/mL
AI:	<10 pg/mL
Tamoxifen	95 pg/mL
AI + OS:	50 pg/mL
Tam + OS:	73 pg/mL

Abbassi-Ghanavati, M et al., 2009, Lum, et al., 1997, Bellet., et al., 2016.

High levels of E2 for 9 months don't increase breast cancer recurrence risks!

- POSITIVE TRIAL
  - 516 women desiring pregnancy
  - Stage I-III breast cancer
  - On EDT 18-30 months
  - TOOK BREAK from EDT up to 2 years
  - 365 babies were born

No increased recurrence risks to interrupting EDT and having high E2 levels with pregnancy!

Partridge, A. H., et al, 2023

Why are 175 women preventing millions from getting safe and effective vaginal hormone therapy?

- **6,309** women with br ca on EDT using vaginal E2 or E3
- **76,459** control women with br ca on EDT without E2 or E3 use

- **175** women with br ca on EDT got vaginal E2 or E3
- **51** control women with br ca on EDT without E2 or E3 use
- Variable to no rises in serum E2 levels

>50,000 women-years of low-dose vaginal estrogen safety

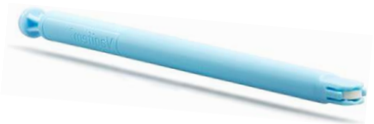
vs.

38 women-years of low-dose vaginal estrogen uncertainty

Local Estradiol (E2) for VVA & Dyspareunia

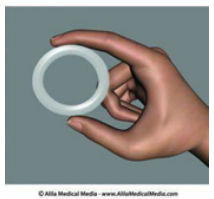
- Use and products: None approved but supported by guidelines for use in women with breast cancer
  - For severe VVA with breast cancer may need to use daily for 2-4 weeks vs 2 weeks and then 1-3x/week ongoing vs 1-2x/week or as needed to control symptoms
  - **Estradiol Cream**: Use applicator or fingers to apply cream to opening of vagina or around vulva. Advantage to treat vulva and vagina but can be messy, FDA approved:
    Estrace Cream, many generics, (Can compound for 10-25ucg dosing or less $$$)

    - Estrace Cream: 0.01% cream (releases 0.1 mg estradiol/gram/use)
    - Cumulative dosing 7 mg/year
    - (Conjugated Estrogens, not recommended, Premarin Vaginal Cream 0.625 mg/g is FDA approved)
  - **Estradiol Vaginal Pills**: 4 µg (0.004 mg estradiol/tablet) or 10 µg pill (0.01mg estradiol/tablet) by applicator into upper vagina (CAN BE $$ and variable insurance coverage, even for generics)
    - FDA Approved: Vagifem 4 µg and 10 µg, Yuvafem 4 µg and 10 µg and many generics, use qhs, #30
    - Cumulative dosing 1 mg/year



  - **Estradiol Gel Capsule**: 4 µg and 10 mcg vaginal inserts
    - FDA Approved: Imvexxy 4 µg suppository, qhs, #28/prescription
    - Cumulative dosing 0.5 mg/year

  - **Estradiol Ring**: Place in upper vagina every 90 days
    - FDA Approved: Estring, 2 mg/ring, releases 0.0075 mg estradiol/day)
    - Cumulative dosing 2.7 mg/year

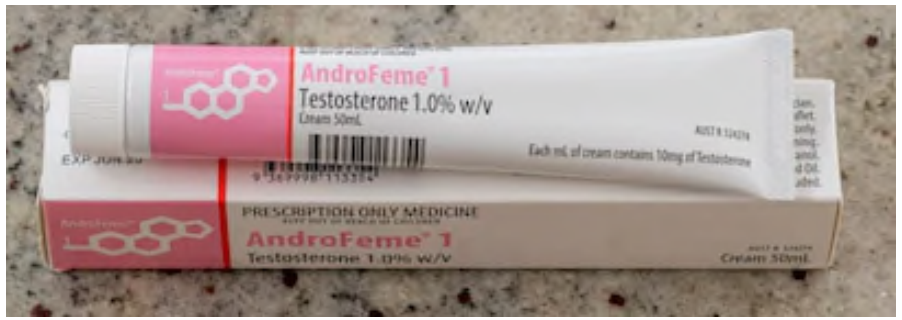


Vaginal DHEA for VVA, Dyspareunia, and HSDD

- Efficacy in women with breast cancer
  - Women with hormone-positive breast cancer on AIs with VVA:
    - 1 randomized, placebo-controlled study
    - Barton 2017, 353 women - 3.25 vs 6.5 DHEA vs placebo over 12 weeks
    - 6.5 mg rapidly improved VVA, dyspareunia, as well as arousal, libido, and orgasm.
  - Serum hormone levels remain in postmenopausal ranges
  - Use for HSDD alone is not recommended by 2019 consensus guidelines as it has not been tested for HSDD alone. HSDD is felt to improve from the healing of VVA symptoms.
- Use
  - One 6.5 mg suppository at bedtime, nightly for 2-4 weeks until healed, then 1-3 times per week as needed for symptom control.
- FDA approved for postmenopausal women with dyspareunia:
  - Not approved but Guideline Supported for women with breast cancer
  - Women with hormone-positive breast cancer on AIs have been studied
- Products
  - Prasterone (Intrarosa) 6.5 mg is 50% bioavailable DHEA
    - FDA approved but variable insurance coverage, often high co-pay if covered
  - Compounded options for similar dosing available online
    - Compounded cream to deliver 6.5mg/gm Versabase cream can be much less cost than the prescription Intrarosa

Using Vaginal Testosterone for VVA and HSDD of GSM

- No FDA-approved T products for women
- 2019 Multi-Society Consensus Guidelines for Use of T in Women
  - Including women with breast cancer after shared decision-making
  - Improves HSDD as primary sexual domain independent of VVA improvements
  - ISSWSH Dosing Recommendations:
    - **300 µg/day testosterone patch/ 2.5 mg testosterone cream vulva/vagina** Compound intravaginal T cream or gel needed or use 1/10 male products
    - 1% USP Testosterone in Versabase cream, use 1/4cc=1click =2.5mg nightly on vulva
  - Lab testing
    - Measure total T at the start, at 6-12 weeks, then q6mo
    - Adjust T dosing ONLY for symptoms or if levels supraphysiologic
  - Only testosterone lab goal is to avoid supraphysiologic levels (data on this minimal…)
    - Premenopausal T ranges 15-70 ng/dL
    - Women can get symptom relief at levels 15-25 ng/dL
- Testosterone in Women (references)
  - Helps bones, heart, brain, mood, VVA & Libido
  - Systemic use lowers breast cancer risks 40-50%



Vaginal Testosterone for VVA and HSDD of GSM

- Efficacy in women with breast cancer
  - Women with ER+ breast cancer on aromatase inhibitors: 4 studies of intravaginal T cream 150-300 µg/day for women on AIs improved VVA symptoms, HSDD, and other sexual health domains. No rise in serum E2 x at higher doses in 1 study.
    - Whiterby 2011 21 women over 8 wk (150 or 300 µg/day T intravaginal cream)
    - Dahir 2014 13 women over 8 wk (300 µg/day T intravaginal cream)
    - Melisko 2016 76 women over 12 wk (5000 µg 3x/wk vs E2 ring, 12% had rise in E2 serum)
    - Davis 2018 44 women over 26 wk (300 µg/day T intravaginal cream vs placebo)
  - Glazer studies of T + AI pellets in women with breast cancer- decreases menopausal symptoms
    - Glazer 2014 JCO
- 10-year, prospective cohort study of 1267 pre- and post-menopausal women given SQ pellets for symptoms of menopause/low libido
    - Every 13 (+/-4) weeks with dose adjustments based on symptoms
    - T or T (60 mg)+ AI (4 mg) between 3/08 and 3/13 had NO INCREASED breast cancer risk.
    - 40% LESS IDC, 50% less DCIS.
    - Concluded SQ pellets of T or T + AI are safe and further studies are warranted (Glaser, 2019) (Glazer, BMJ 2018)
  - Testosterone and Women +/-Breast Cancer Review:
    - Glazer 2021 Androgens: Clinical Research and Therapeutics Review
  - Women with ER- breast cancer: Felt safe to use, but no studies of use in ER-women.

"Unless health care providers address sexual issues first – cancer patients rarely reveal their sexual concerns"

Kang BMC Health Services Research 2018

Questions and feedback are welcome

- This talk is part of a series of talks and cased based educational talks to:
  - Help oncology clinicians learn more about sexual health issues
  - Learn how to assess and address sexual health issues in women with breast cancer
  - Build an evidence-based knowledge set of resources to combat myths and update studies on therapy options for women with breast cancer
  - Improve comfort asking and addressing patient questions about the risks and benefits of therapy options
  - REDUCE SUFFERING and POOR QUALITY OF LIFE for the MILLIONS of women with BREAST CANCER and SEXUAL TOXICITIES

- PLEASE: Send me any challenging cases and I will work to send evidence-based options
- Please send any feedback on this talk and other materials you need to be most effective

Thank you! Please reach out to me at: lbosserman@coh.org

Sexual Activity has Health Benefits

- Many Benefits have been noted in various studies of various quality, few are large, highly powered trials. Studies show:
  - Women and Men
    - Improved mood, relationship, physiologic and physiological relaxation, and mental well-being via oxytocin release by hypothalamus
    - Immune system effectiveness improved: increased IgA in one 2004 study
    - Intimacy with a partner improved both sexual and non-sexual aspects of relationships, decreases cortisol levels in men and women, reduces stress.
    - Sex releases oxytocin, endorphins, and other hormones that can lessen stress and improve wellbeing
    - Sex improves sleep by reducing stress and anxiety as well as feelings of well-being
    - Sexual activities are effective in burning calories
    - Increases brain networks and blood flow to areas related to pain and emotions (insula and secondary somatosensory cortex)

    (Luke Curtis, Sex saves lives, European Journal of Preventive Cardiology, Volume 29, Issue 1, January 2022, Page e38, https://doi.org/10.1093/eurjpc/zwaa102)

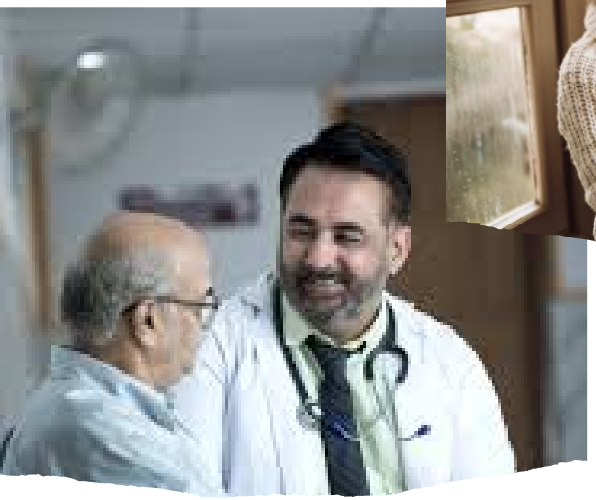
  - Women
    - Less Cardiovascular events in women with regular partnered sexual activity
    - Lower Blood Pressure in women with satisfactory sex lives
    - Brain activity increased with sex to areas that process emotions, sensations of pain, regulation of metabolic processes and decision-making (like music and dance)
    - Oxytocin thought a cause of reduced breast cancer risk from pregnancy and lactation in women, theoretical benefit from frequent sexual activities
  - Men
    - Men who resumed frequent sexual activity after MI improved survival in two long-term studies vs those who did not, 50% less MI after 2x/week sex in men
    - 33% less prostate cancer risk in men who ejaculate 21 times/month (~5 times per week) compared to those who ejaculate only 4-7 times/month (~1/week) with 10 year follow up. US study had HR 0.81 (0.72-0.92) age 20-29 and HR 0.78 (95% CI 0.69-0.89) ages 40-49: Rider, Eur Urol 2016.

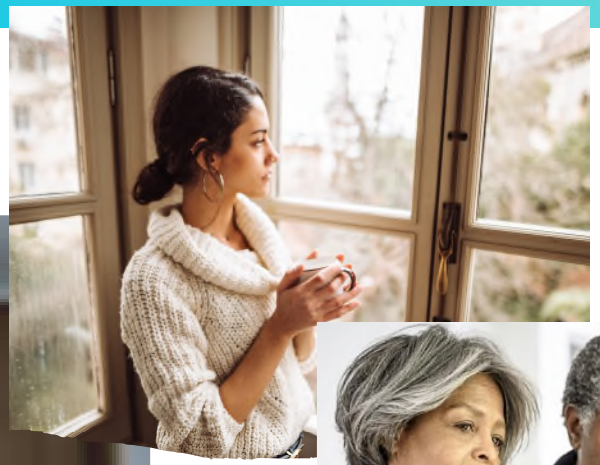
References and Science for Further Study

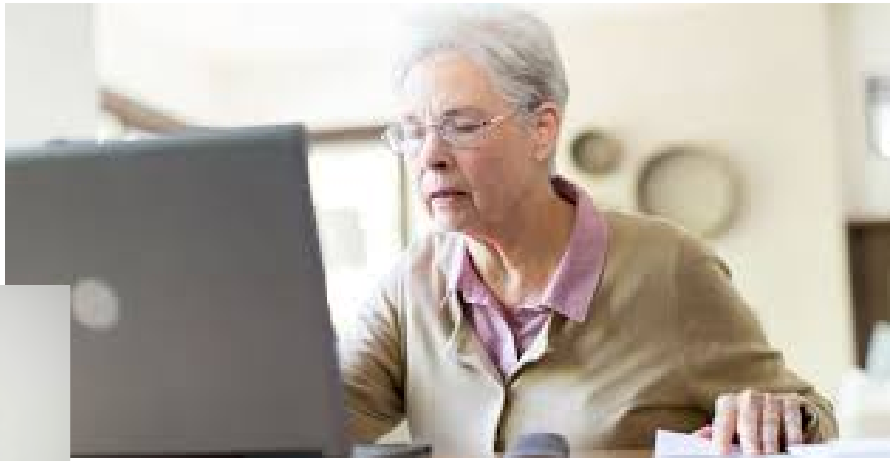
Many Other Issues can Impact Sexual Health Knowing Local Resources Can Help for Referrals

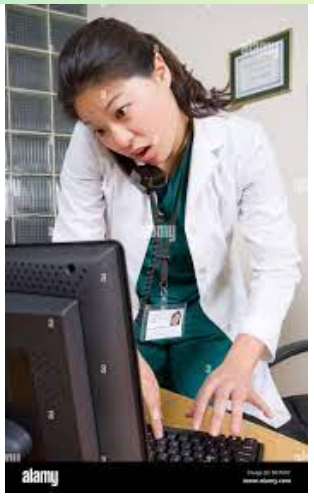
- Issues to explore
  - Identity, independence and intimacy
  - Relationships
  - Body image issues
  - Existential issues
  - Religious and cultural issues
  - Past trauma – sexual and other
  - Family issues
  - Non-heterotypical issues
  - Non-neurotypical issues

- Resources to support care
  - Marriage and family therapists and psychologists
  - Sex therapists: many certified by AASECT, many differing specialty areas
  - Pelvic floor physical and occupational therapy specialists
  - Gynecologists specializing in sexual health issues and therapies
  - Medical specialists for alternative medical therapies and mediations addressing sexual health side effects
  - Religious experts open to discussing specific patient issues









Ask about sexual health before, during, and after a Cancer Diagnosis, Treatment and Follow Up

- Sexual dysfunction is one of the most common and distressing side effects of cancer treatments for cancer survivors.
- All treatments have the potential to negatively affect physical sexual function both acutely and long term, including sexual desire, arousal, pleasure and body functions.
- Sexual health , impacted by altered body image, low self-esteem, sexual satisfaction, psychosocial distress, lack of knowledge, and communication challenges between clinicians and a patient's partner(s) can lead to lower quality of life.
- The type and incidence of sexual dysfunction may differ based on the underlying malignancy, the treatment(s) a patient gets, their baseline sexual health issues and relationship changes during treatment and survivorship.

3 Ways to Improve Provider-Patient Communication

- "As part of clinical practice, **screening and assessment of sexual functioning** should be included early in treatment for all patients and continue during all stages of care" (Bober, 2012).
- "Patients may be reluctant to raise the topic of sexual functioning during appointments. Initiating conversations about sexual functioning as part of standard clinical care can help to facilitate discussions about these issues". Patients consistently state that they feel more comfortable if **providers bring up the topic** of sexual functioning (Flynn, 2012).
- "Maintain **referral resources and information** regarding treatment options for sexual dysfunction for patients and their partners". Health care providers report that lack of knowledge about treatment options and concerns about treating sexual dysfunction within their scope of practice may limit their ability to discuss these issues with patients (Averyt, 2014).

Sex Improves Mortality and Morbidity

- Luke Curtis, Sex saves lives, European Journal of Preventive Cardiology, Volume 29, Issue 1, January 2022, Page e38, https://doi.org/10.1093/eurjpc/zwaa102

Male Validated Sexual Toxicity Questionnaires

- PROMIS: Patient-Reported Outcomes Measurement Information System-Sexual Function Profile for Men
    - 8 questions for men with cancer covering erectile function, orgasm, sexual satisfaction, and enjoyment
    - Practical and available in Epic and other EHRs and through other options
- International Index of Erectile Function (IIEF): 15 questions covering erectile function, orgasm, desire, penetrative intercourse satisfaction, and overall sexual satisfaction (only for heterosexual men)
- Sexual History Inventory for Men (SHIM or IIEF-5): 5 questions on erectile function
- Prostate Cancer Index Sexual Function and Sexual Bother (PCI): 20 questions for men with prostate cancer covering bowel, urinary and sexual toxicities.

Developing Reference List for Sexual Health

- Sex Therapists: knowledgeable about the range of impacts on sexual health, trauma, past experiences, cultural, religious, neurodivergent, and other aspects of sexuality as well as preferences and options
- Psychologists and Couple's Therapists: can discuss relationship issues, expectations, options, beliefs and education on sexual issues
- Occupational Therapists:
  - COH OTs are experienced in discussing, educating, and demonstrating ways men can improve their sexual health alone or with a partner.
  - COH OTs can demonstrate and educate men on the use of toys to enhance personal and partner sexual pleasure as well as options for erectile support: medications, vacuum devices, and penile implants.
- Urologists
  - Evaluate for hormone levels and erectile function. Can prescribe medications, educate, and provide erectile devices and Implants.
  - Can implant urinary continence devices
- Bio-identical or iso-molecular hormone replacement experts
  - Know the data on testosterone, DHEA, and other natural hormones in improved health
    - Can discuss data on risks and benefits
  - Although Baseline levels have been associated with risks of cancer (likely due to insulin resistance, inflammation, lipid alterations, and visceral fat impacts on cancer development with higher T levels only a side effect- association not causation)
  - Replacement of T has not been associated with increasing cancer risks in men or women
- Medical Oncologists: Expanded education so they can discuss treatment options, assess the risks/benefits of therapy options, and support sexual health care during and after cancer therapies.

Tools for Men Patients on Cancer and Sexuality

Web Sites with Patient Information:

Sex and the Adult Male with Cancer: ACS: https://www.cancer.org/cancer/managing-cancer/side-effects/fertility-and-sexual-side-effects/sexuality-for-men-with-cancer.html

Sexual Health and Cancer Treatment: Men: https://www.cancer.net/navigating-cancer-care/dating-sex-and-reproduction/sexual-health-and-cancer-treatment-men

Sexual Health Issues in Men with Cancer: NCI: https://www.cancer.gov/about-cancer/treatment/side-effects/sexuality-men

Books for Men and their Partners:

- Prostate Cancer and the Man You Love: Anne Katz, 2012
- Man Cancer Sex by Anne Katz, 2009
- Saving your Sex Life: A Guide for Men with Prostate Cancer: JP Mulhall, 2010
- Sexuality and Fertility After Cancer: LR Schover, 2007

Testosterone Replacement References

- T replacement does not increase CV Toxicities: Lincoff AM, Bhasin S, Flevaris P, Mitchell LM, Basaria S, Boden WE, Cunningham GR, Granger CB, Khera M, Thompson IM Jr, Wang Q, Wolski K, Davey D, Kalahasti V, Khan N, Miller MG, Snabes MC, Chan A, Dubcenco E, Li X, Yi T, Huang B, Pencina KM, Travison TG, Nissen SE; TRAVERSE Study Investigators. Cardiovascular Safety of Testosterone-Replacement Therapy. N Engl J Med. 2023 Jul 13;389(2):107-117. doi: 10.1056/NEJMoa2215025
- T replacement does not lead to aggressive prostate ca: Walsh, T. J., Shores, M. M., Krakauer, C. A., Forsberg, C. W., Fox, A. E., Moore, K. P., Korpak, A., Heckbert, S. R., Zeliadt, S. B., Kinsey, C. E., Thompson, M. L., Smith, N. L., & Matsumoto, A. M. (2018). Testosterone treatment and the risk of aggressive prostate cancer in men with low testosterone levels. *PLOS ONE*, *13*(6), e0199194. https://doi.org/10.1371/journal.pone.0199194

Testosterone Replacement in Hypogonadal Men Does not Increase Risk of CV Events

Lincoff, TRAVERSE STUDY. NEJM 2023

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Cardiovascular Safety of Testosterone-Replacement Therapy

Lincoff AM et al. DOI: 10.1056/NEJMoa2215025

CLINICAL PROBLEM

The cardiovascular effects of testosterone-replacement therapy in middle-aged and older men with hypogonadism have not been determined. Studies have yielded conflicting results or have been of inadequate size or duration.

CLINICAL TRIAL

Design: A phase 4, multicenter, double-blind, randomized, placebo-controlled, noninferiority trial assessed the effects of testosterone-replacement therapy on the incidence of cardiovascular events among men with hypogonadism and established cardiovascular disease or an elevated cardiovascular risk.

Intervention: 5246 men who were 45 to 80 years of age with preexisting cardiovascular disease or an increased cardiovascular risk, at least one symptom of hypogonadism, and two fasting serum testosterone levels <300 ng per deciliter were assigned to receive either daily transdermal 1.62% testosterone gel (dose adjusted to maintain testosterone levels between 350 and 750 ng per deciliter) or placebo gel. The primary cardiovascular safety end point was the first occurrence of any component of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, assessed in a time-to-event analysis.

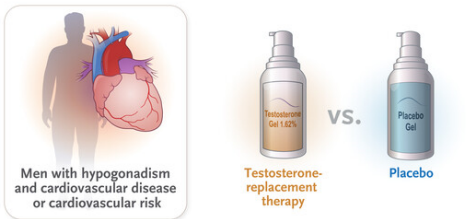
RESULTS

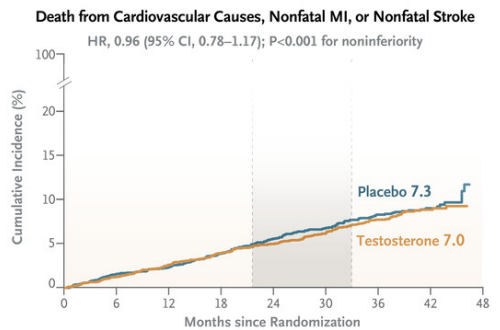
The mean duration of treatment was 22 months; the mean duration of follow-up was 33 months. Testosterone-replacement therapy was noninferior to placebo with respect to the incidence of major adverse cardiac events. The incidence of prostate cancer was similar in the two groups. The increase in prostate-specific antigen levels from baseline was greater in patients in the testosterone group than in those in the placebo group.

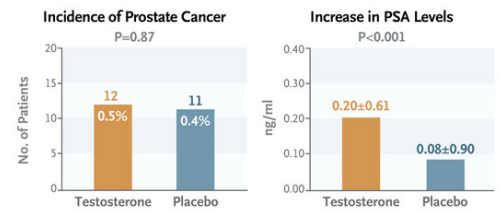
LIMITATIONS

- Levels of adherence and retention were lower in this trial than in most cardiovascular outcome studies; the effect of nonretention in particular is difficult to quantify, and bias due to informative censoring is possible.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

In middle-aged and older men with hypogonadism and preexisting cardiovascular disease or an increased cardiovascular risk, daily treatment with transdermal testosterone for approximately 2 years was noninferior to placebo with respect to the incidence of major adverse cardiac events.

Books for Clinicians on Breast Cancer and Sexuality

- *Woman Cancer Sex* by Anne Katz
- *Breaking the Silence on Cancer and Sexuality: A Handbook for Healthcare Providers* (Second Edition) by Anne Katz
- *Sex and Cancer: Intimacy, Romance, and Love after Diagnosis and Treatment* by Saketh R. Guntupalli and Maryann Karinch

Books and Articles Updating HRT/MRT Studies: Estrogen (E2) and Estrogen + micronized Progesterone Do not cause Breast Cancer

- **Estrogen Matters** by Dr. Avrum Blooming MD and Carol Tavris PhD

- ACOG March 15, 2024 article reviewing scandal of WHI and estrogen (E2) and natural progesterone studies. by Dr. Barbara Levy and colleague
- Bluming AZ, Hodis HN, Langer RD. 'Tis but a scratch: a critical review of the Women's Health Initiative evidence associating menopausal hormone therapy with the risk of breast cancer. Menopause. 2023 Dec 1;30(12):1241-1245. doi: 10.1097/GME.0000000000002267.

National Organizations Addressing Women's Sexual Health

National Organizations Focused on Sexual Health
American Association of Sexuality Educators, Counselors and Therapists (AASECT) https://www.aasect.org/
International Board of Sexual Professionals (IBOSP) https://www.ibosp.org/
The International Society for the Study of Women's Sexual Health (ISSWSH) https://www.isswsh.org/
The Menopause Society (formerly North American Menopause Society) www.menopause.org
The Scientific Network on Female Sexual Health and Cancer (The Network) www.cancersexnetwork.org

Cancer Center Websites for Breast Sexual Health

City of Hope National Cancer Center and Network Sites in CA, GA, AZ, and IN. Dr. Linda Bosserman, Sherry Hite (CA), Dr. Ruchi Garg (GA), Cyndi Ingram, and others. Sexual Health after Cancer https://www.cityofhope.org/patients/survivorship/survivorship-programs/breast-cancer-survivorship-program
Cleveland Clinic https://my.clevelandclinic.org/departments/obgyn-womens-health/patient-education/resources#treatment-guides-tab
Dana-Farber Cancer Institute Dr. Sharon Bober and Dr. Sandy Falk, Sexual Health, Intimacy and Cancer https://www.dana-farber.org/health-library/articles/sexual-health,-intimacy,-and-cancer/
Lifespan Cancer Institute/Legorreta Cancer Center at Brown University: The Oncology Sexual Health First Responders Clinic (Dr. Don Dizon)
Massachusetts General Hospital Cancer Program: MA: https://www.massgeneral.org/medicine/infectious-diseases/treatments-and-programs/sexual-health-program
Mayo Clinic Menopause and Women's Sexual Health Clinic https://www.mayo.edu/research/centers-programs/womens-health-research-center/patient-care/clinical-services

Memorial Sloan Kettering Cancer Center (Dr. Jeanne Carter and Dr. Shari Goldfarb) https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/sexual-health-fertility/health
OHSU Knight Cancer Institute https://www.ohsu.edu/knight-cancer-institute/womens-sexual-health-after-cancer
Sylvester Comprehensive Cancer Center: Menopause Urogenital Sexual Health and Intimacy Clinic (MUSIC), lead Dr. Kristin E. Rojas https://umiamihealth.org/en/sylvester-comprehensive-cancer-center/cancer-support-services/sexual-health
UC San Francisco Cancer Center https://www.ucsfhealth.org/education/breast-cancer-self-care-and-recovery-sexuality
University of California Davis https://health.ucdavis.edu/cancer/support/support-services/sexual.html
University of Wisconsin, Women's Integrative Sexual Health (WISH) program https://www.uwhealth.org/treatments/womens-integrative-sexual-health-wish
Yale Cancer Center https://www.yalemedicine.org/departments/sexuality-intimacy-and-menopause-program

Patient Focused Educational Websites: Breast Cancer and Sexual Toxicities

American Cancer Society (ACS) https//cancer.org and https://reach.cancer.org/
ASCO's Cancer Net for Patient Education https://www.cancer.net
Breast Cancer Research Foundation (BCRF) https://www.bcrf.org/
Oncology Nursing Society (ONS) https://ons.org
Susan G. Komen Foundation https://www.komen.org/
UpToDate www.uptodate.com
Young Survival Coalition (YSC) https://youngsurvival.org/

Basic 'Ask Your Doctor' Patient Focused Cancer and Sexual Health Resources

"Sex and the Woman With Cancer" (American Cancer Society)
"Facing Cancer Together" (American Psychological Association)
"Female Sexual Health After Cancer" (LiveSTRONG)
"Male Sexual Health After Cancer" (LiveSTRONG)
"Sexuality and Reproductive Issues" (National Cancer Institute)
"Sexuality for the Man with Cancer" (American Cancer Society)

Books for Patients on Breast Cancer and Sexuality

- *Breaking the Silence: On Cancer and Sexuality*
  - *by Anne Katz PhD, RN, FAAN*
- *Woman Cancer Sex (second edition)*
  - *by Anne Katz, PhD,RN, FAAN*
- *Sex and Cancer: Intimacy, Romance, and Love after Diagnosis and Treatment*
  - *by Saketh Guntupalli, MD and Maryann Karinch*
- *Intimacy After Breast Cancer: Dealing With Your Body, Relationships and Sex*
  - *by Gina M. Maisano*
- *Sexuality and Fertility After Cancer*
  - by Leslie R. Schover, PhD
- *Living in the Postmastectomy Body: Learning to Live in and Love Your Body Again*
  - by Rebecca Zuckweiler
- *Seven Weeks to Better Sex*
  - by Domeena Renshaw, MD

20 Years of Study Results of Vaginal Estradiol or Estriol in Women with HR+ Breast Cancer on EDT with VVA

Observational Trials

6 trials with long-term follow-up

• Vassiloupoulou	1997	7.9 yr. median f/u	RR & OS
• Dew	2003	5.5 yr median f/u	RR & OS
• Le Ray	2012	3.5 yr mean f/u	RR
• Cold	2022	9.8 yr median f/u	RR
		15.2 yr median f/u	OS
• Sund	2023	5.1 yr median f/u	OS
• McVicker	2023		
Scottish		5.0 yr median f/u	OS
Welsh		8.0 yr median f/u	OS

- **6,309 women with BRCA on EDT using vaginal E2 or E3**
- **76,459 control women** with BRCA on EDT without E2 or E3 use
- **SYMPTOMS IMPROVED** significantly on vaginal E2 or E3
- **NO increased breast cancer recurrence risks in long-term follow-up** (one non-risk-controlled subgroup on AI had increased recurrence risk but no increased mortality in Cold, while larger McVicker studies showed no increased RR or mortality with AI use).
- **No increase in mortality in long-term follow-up**

Prospective Trials

8 trials with very short-term follow-up

• Kendall	2006	12-wk f/u	7 women on AI
• Biglia	2010	12-wk f/u	18 women on tam + GNRH
• Pfeiler	2011	4-wk f/u	6 women on AI
• Willis	2012	12-wk f/u	24 women on AI or SERM
• Donders	2014	12-wk f/u	16 women on AI
• Melisko	2016	12-wk f/u	40 women on AI
• Hirschberg	2020	12-wk f/u	50 women on AI or tam + OS
• Streff	2021	16-wk f/u	14 women (8 prospect/6 retro)

- **175 women with br ca on EDT got vaginal E2 or E3**
- **51 control women** with breast cancer on EDT without E2 or E3 use
- **SYMPTOMS IMPROVED** significantly on E2 or E3
- **SHORT TERM F/U:** 4-16 weeks
- Mixed results of E2 serum level rises, most returned to baseline on short-term follow-up, seems levels drop when VVA heals, but some women have baseline and persistent elevated E2 serum levels.
- No evidence of increased recurrence risks; only concerns raised about some E2 level rises or FSH/LH changes on short-term follow-up

References: Large, Long-term Low-Dose Vaginal Estrogens in Women with Breast Cancer Part 1

- **E2 & E3: 3.5-20 Years** With 6 Observational Trials **6,309 Women** Got E2 Or E3, **76,459 Control** Women
  - **Vassilopoulou-Sellin 1997**: Vassilopoulou-Sellin, R., Theriault, R., Klein, M. J. (1997). Estrogen Replacement Therapy In Women With Prior Diagnosis And Treatment For Breast Cancer. *Gynecologic Oncology, 65*(1), 89-93. Https://Doi.Org/10.1006/Gyno.1997.4621
  - **Dew 2003:** Dew, J. E., Wren, B. G., & Eden, J. A. (2003). A Cohort Study Of Topical Vaginal Estrogen Therapy In Women Previously Treated For Breast Cancer. Climacteric : The Journal Of The International Menopause Society, 6(1), 45–52.Le Ray 2012
  - **Le Ray 2012:** Le Ray, I., Dell'aniello, S., Bonnetain, F., Azoulay, L., & Suissa, S. (2012). Local Estrogen Therapy And Risk Of Breast Cancer Recurrence Among Hormone-treated Patients: A Nested Case-control Study. Breast Cancer Research And Treatment, 135(2), 603–609. Https://Doi.Org/10.1007/S10549-012-2198-y
  - **Cold 2022:** Cold S, Cold F, Jensen M-B, Cronin-fenton D, Christiansen P, Ejlertsen B. Systemic Or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study. J Natl Cancer Inst. 2022;114(10):1347-1354.
    - **Commentary: Cathcart-rake**, E. J., & Ruddy, K. J. (2022). Vaginal Estrogen Therapy For The Genitourinary Symptoms Of Menopause: Caution Or Reassurance?. Journal Of The National Cancer Institute, 114(10), 1315–1316. Https://Doi.Org/10.1093/Jnci/Djac113
  - **Sund 2023:** Sund, M., Garmo, H., Andersson, A., Margolin, S., Ahlgren, J., & Valachis, A. (2023). Estrogen Therapy After Breast Cancer Diagnosis And Breast Cancer Mortality Risk. Breast Cancer Research And Treatment, 198(2), 361–368. Https://Doi.Org/10.1007/S10549-023-06871-w
  - **McVicker 2023:** McVicker, L., Labeit, A. M., Coupland, C. A. C., Hicks, B., Hughes, C., Mcmenamin, Ú., Mcintosh, S. A., Murchie, P., & Cardwell, C. R. (2023). Vaginal Estrogen Therapy Use And Survival In Females With Breast Cancer. JAMA Oncology, E234508. Advance Online Publication. Https://Doi.Org/10.1001/Jamaoncol.2023.4508

Summary of 6 Large, Long-Term Studies of VET Use in Women with Breast Cancer

Trial	Follow-up Time	Study Population	No. Patients per Therapy	Conclusion
Vassilopoulou-Sellin 1997	Median: 95 mo (7.9 yr)	MD Anderson Cancer Center 49 women total 2 groups: Retrospective HRT or entered prospective HRT study Had ≥ 2 years HRT	HRT types for at least 2 yr 43 women, oral HRT 6 women, VET Premarin cream Started mean 49 mo from dx Median duration use 47 mo Median f/u 95 mo = 7.9 yr No recurrences, no deaths	**No recurrence or deaths in VET users** • RR: None Median f/u 95 mo No HR calculated • OS: All VET users alive Median f/u 95 mo No HR calculated
Dew 2003	Median: 5.5 yr RR	Sydney, Australia, 3-hospital database 1,472 br ca	342/1,472 used HRT for menopausal symptoms 273/1,472 used systemic HRT 69/1472 used VET, as only had VVA (4.7%) Median time on VET: 1 yr 48% of VET users also used tam 6/69 (9%) VET users recurred vs. 330/1472 (22.4%) recurred total Median DFS 4.5 yr (0.5-29 yr) Type of VET: 33 pts: E2, 25 µg tablet 36 pts: E3, 50 µg cream/sup 1,406 cohort no VET use	**No increased br ca recurrence risk** • RR: Less in VET users: HR 0.30 (95% CI, 0.11-0.8) vs. database, uncorrected • RR: Less in VET users: HR 0.57 (95% CI, 0.20-1.58) vs. database, corrected: adjusted for other br ca risk factors • OS: Better with VET 4/69 deaths (6%) VET users vs. 169/1,472 deaths (11.5%) total
Le Ray 2012	Mean: 3.5 yr RR AI: 2.6 yr Tam: 4.5 yr	UK database Nested case control study 13,479 newly diagnosed between 1998-2008, and used tam or AI Study group: 10,933 >1-yr f/u 1,724 on AI 9,209 on tam	917 of 10,933 women on tam/AI recurred: 21 had VET 896 had no VET Controls: 274 got tam/AI + VET vs. 8,611 got tam/AI + no VET Type of VET: E2 10 µg cream E2 tablets E2 ring (pessary)	**No increased br ca recurrence risk** • RR, no increase in VET users; HR 0.78 (95% CI, 0.48-1.25) • RR, no increase in VET users on tam; HR 0.83 (95% CI, 0.51-1.34) • RR, not calculable in VET users on AI, NO recurrences • RR, no increase in VET users post tam/AI; HR 0.83 (95% CI, 0.51-1.34)

Note. AI, aromatase inhibitor; CI, confidence interval; EBT, early breast cancer; ER+, estrogen receptor positive; EDT, estrogen deprivation therapy; FSH, follicle stimulating hormone; HR, hazard ratio; NED, no evidence of disease; OS, overall survival; VET, vaginal estrogen therapy; VVA, vulvovaginal atrophy. Information from Vassilopoulou-Sellin et al., 1997; Dew et al., 2003; Le Ray et al., 2012; Cold et al., 2022; Sund et al., 2023; McVicker et al., 2023.

Summary of 6 Large, Long-Term Studies of VET Use in Women with Breast Cancer (Continued)

Trial	Follow-up Time	Study Population	No. Patients per Therapy	Conclusion
Cold 2022	Median: 9.8 yr RR 15.2 yr OS	Danish database ER+ EBC diagnosed 1997-2004 Tam/AI/both	1,957 VET: E2: 25 µg tablets E2: 7.5 µg/d ring E3: 500 µg cream 6,371 never VET	**No increased br ca recurrence risk** **Same survival for VET vs. no VET** • RR, no increase in VET users • RR, increase in VET users on AI or tam → AI, HR 1.39 (number of recurrences not reported, of 822 at risk) • OS, same in VET vs. no VET use; HR 0.94 • OS, same in VET users on tam • OS, same in VET users on AI
Sund 2023	Median: 5.1 yr OS	Swedish database 15,198 women ER+ EBC diagnosed 1992-2012 Tam/AI/both/off 1,262 died of br ca	VET users: 159 E2/E3 died 1,170 E2/E3 alive VET non-users: 1,103 died 10,850 alive	**Same survival for VET vs. no VET** • OS, same +/- VET; OR 0.94 (0.81-1.1) • OS, same in VET users on tam; OR 1.3 (0.91-1.86) • OS, same in VET users on AI; OR 0.87 (0.62-1.22) • OS, same in VET users on tam → AI; OR 1.14 (0.74-1.74) • OS, same in VET users off EDT; OR 0.61 (0.43-0.87)
McVicker 2023	Median: 5-yr OS Scottish 8-yr OS Welsh	Scottish (S) and Welsh (W) databases ER+ EBC diagnosed 2010-2017 (S) diagnosed 2000-2016 (W) Tam/AI/both/off 49,237 with EBC 5,795 br ca deaths	2,557 VET users (5%): 1,155 E2 tablets/ring 45% 1,109 E3 creams 43% 293 E2/E3 1% 26,130 no VET use 120 deaths out of 11,437 person-years of VET use	**Same survival for VET vs. no VET (br ca specific and all cause)** • OS breast cancer, same VET/no VET; HR 0.77 (95% CI, 0.63-0.94) • OS breast cancer on AI, same VET/no VET; HR 0.72 (95% CI, 0.58-0.91) • OS all cause, same VET/no VET; HR 0.80 (95% CI, 0.71-0.90)

Note. AI, aromatase inhibitor; CI, confidence interval; EBT, early breast cancer; ER+, estrogen receptor positive; EDT, estrogen deprivation therapy; FSH, follicle stimulating hormone; HR, hazard ratio; NED, no evidence of disease; OS, overall survival; VET, vaginal estrogen therapy; VVA, vulvovaginal atrophy. Information from Vassilopoulou-Sellin et al., 1997; Dew et al., 2003; Le Ray et al., 2012; Cold et al., 2022; Sund et al., 2023; McVicker et al., 2023.

References: Low-Dose Vaginal Estrogens in Women with Breast Cancer – Part 2

- **E2 Or E3 4-16 Weeks In 8 Prospective Trials: 175 Women With BrCa On EDT Compared With 40 Controls**
  - **Kendall 2006**: Kendall, A., Dowsett, M, Folkerd, E., Smith, I. Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. Annals Of Oncology 17 (4) P584-587 2006. doi:https://doi.org/10.1093/annonc/mdj127
  - **Biglia 2010:** Biglia, N., Peano, E., Sgandurra, P., et al. (2010). Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: A preliminary study. Gynecological Endocrinology : The Official Journal Of The International Society Of Gynecological Endocrinology, 26(6), 404–412. https://doi.org/10.3109/09513591003632258
  - **Pfeiler 2011:** Pfeiler, G., Glatz, C., Königsberg, R., et al. (2011). Vaginal estriol to overcome side-effects of aromatase inhibitors in breast cancer patients. Climacteric : The Journal Of The International Menopause Society, 14(3), 339–344. Https://Doi.Org/10.3109/13697137.2010.529967
  - **Willis 2012**: Wills, S., Ravipati, A., Venuturumilli, P., et al. (2012). Effects of vaginal estrogens on serum estradiol levels in postmenopausal breast cancer survivors and women at risk of breast cancer taking an aromatase inhibitor or A selective estrogen receptor modulator. Journal Of Oncology Practice, 8(3), 144–148. https://doi.org/10.1200/jop.2011.000352
  - **Donders 2014:** Donders, G., Neven, P., Moegele, M., et al. (2014). Ultra-low-dose estriol and lactobacillus acidophilus vaginal tablets (Gynoflor(®)) for vaginal atrophy in postmenopausal breast cancer patients on aromatase inhibitors: pharmacokinetic, safety, and efficacy Phase I Clinical Study. Breast Cancer Research And Treatment, 145(2), 371–379. https://doi.org/10.1007/s10549-014-2930-x
  - **Melisko 2016:** Melisko, M. E., Goldman, M. E., Hwang, J., et al. (2016). Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: A randomized clinical trial. JAMA Oncology, 3(3), 313–319. https://doi.org/10.1001/jamaoncol.2016.3904
  - **Hirshberg 2020:** Hirschberg, A. L., Sánchez-rovira, P., Presa-lorite, J., et al. (2020). Efficacy and safety of ultra-low dose 0.005% estriol vaginal gel for the treatment of vulvovaginal atrophy in postmenopausal women with early breast cancer treated with nonsteroidal aromatase inhibitors: A phase II, randomized, double-blind, placebo-controlled trial. Menopause (New York, N.Y.), 27(5), 526–534. https://doi.org/10.1097/gme.0000000000001497
  - **Streff 2021:** Streff, A., Chu-pilli, M., Stopeck, A., & Chalasani, P. (2021). Changes in serum estradiol levels with estring in postmenopausal women with breast cancer treated with aromatase inhibitors. Supportive Care In Cancer, 29(1), 187–191. https://doi.org/10.1007/s00520-020-05466-1

Chart Summary of 8 Short-Term Studies VET + Breast Cancer

Trial Reference	Median f/u	No. of Women and EDT	No. of Women and Low-Dose Vaginal Therapy	Elevated Final E2 if Measured	Conclusions
Kendall 2006	12 wk	7 pts: AI	6 pts: E2 25 µg tablets 1 pts: CE cream	2/7 d 84 (137 pg/mL, 209 pg/mL)	• **Effective** • **Caution** from 2 final E2 levels • Testing accuracy issues (RIA)
Biglia 2010	12 wk	26 pts: tamoxifen + OS	8 pts: E2 12.5 µg 10 pts: E3 0.25 mg/250 µg 8 pts: Placebo	No	• **Effective and safe** • Minimal E2/E3 raises, all returned to normal • Testing method: RIA
Pfeiler 2011	4 wk	6 pts: AI	6: E3 0.5 mg/500 µg	No	• **Effective** • **Caution** from lower FSH/LH • Testing method: GC/MS
Willis 2012	12 wk	48 pts: tamoxifen or AI	14 pts: E2 25 µg tab 10 pts: E2 7.5 µg ring 24 pts: Placebo	No (2/20 d60 only, 38 pg/mL, 175 pg/mL)	• Efficacy not evaluated • **Caution** due to transient E2 raise, but all normal by end of study • Testing accuracy issues (RIA)
Donders 2014	12 wk	16 pts: AI	16 pts: E3 0.03 mg/30 µg + lactobacillus	No	• **Effective and safe** • Transient E3 elevations, but all normal by end of study • Testing method: GC/MS
Melisko 2016	12 wk	69 of 76 pts: AI or AI + OS	35/40 pts: E2 7.5 µg ring 34/36 pts: T cream 500 µg	None on E2 ring; 4 on T	• **Effective and safe** • Baseline E2: >20 pg/mL: 19/40 on ring and 9/36 T • Final E2: All ≤ 20 pg/mL, normal, on ring, and 4/34 20-40 pg/mL on T • Testing method: RIA + LC/MS
Hirschberg 2020	12 wk	61 pts: AI	50 pts: E3 0.05 mg/50 µg 11 pts: Placebo	No	• **Effective and safe** • Highly sensitive testing used • Testing method: GC/MS/LC
Streff 2021	16 wk	14 pts: AI	8 pts: E2 7.5 µg ring 6 pts: Placebo	No	• **Effective and safe** • Transient E2 rise wk 4 only, normal by end of study • Testing method: Mostly LC/MS

Note. AI, aromatase inhibitor; CE, conjugated estrogen; EDT, estrogen deprivation therapy; FSH, follicle stimulating hormone; GC, gas chromatography; LC, liquid chromatography; LH, luteinizing hormone; MS, mass spectrometry; OS, ovarian suppression; RIA, radioimmunoassay (less accurate, potential exemestane interference); T, vaginal testosterone cream. Information from Pfeiler et al., 2011; Willis et al., 2011; Donders et al., 2014; Melisko et al., 2016; Hirschberg et al., 2020; Streff et al., 2021.

References: Vaginal Estrogens, Progestins Not Needed

- Biehl C, Plotsker O, Mirkin S. A systematic review of the efficacy and safety of vaginal estrogen products for the treatment of genitourinary syndrome of menopause. Menopause. 2019;26(4):431–453. https://doi.org/10.1097/Gme.0000000000001221
- Consensus Statement By The American College Of Obstetricians And Gynecologists Committee On Clinical Consensus. Treatment Of Urogenital Symptoms In Individuals With A History Of Estrogen-dependent Breast Cancer. Obstetrics & Gynecology 138:6 December 2021.
- North American Menopause Society. The 2022 Hormone Therapy Position Statement Of The North American Menopause Society. Accessed July 7, 2022. https://www.menopause.org/publications/professional-publications/position-statements-other-reports
- The 2023 Nonhormone Therapy Position Statement Of The North American Menopause Society. Menopause 30(6):p 573-590, June 2023. https://doi.org/10.1097/Gme.0000000000002200
- Faubion SS, Larkin LC, Stuenkel CA, et al. Management Of Genitourinary Syndrome Of Menopause In Women With Or At High Risk For Breast Cancer: Consensus Recommendations From The North American Menopause Society And The International Society For The Study Of Women's Sexual Health. Menopause. 2018 Jun;25(6):596-608. https://doi.org/10.1097/Gme.0000000000001121.
- NCCN Guidelines: Sexual Function, Part Of Survivorship Gguideline 1.2023-march 24, 2023. Pssh-1-ssh-b. https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf
- Interventions To Address Sexual Problems In People With Cancer: American Society Of Clinical Oncology Clinical Practice Guideline Adaptation Of Cancer Care Ontario Guideline. Jeanne Carter, Christina Lacchetti, Barbara L. Andersen, et al. Journal Of Clinical Oncology 2018 36:5, 492-511
- Managing Genitourinary Syndrome Of Menopause In Breast Cancer Survivors Receiving Endocrine Therapy. Tamara A. Sussman, Megan L. Kruse, Holly L. Thacker, And Jame Abraham. Journal Of Oncology Practice 2019 15:7, 363-370
- Cold S et al. Systemic Or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study. J Natl Cancer Inst 2022 Jul 20; [E-pub]. https://doi.org/10.1093/jnci/djac112.
- Cathcart-rake EJ and Ruddy KJ. Vaginal Estrogen Therapy For The Genitourinary Symptoms Of Menopause: Caution Or Reassurance? J Natl Cancer Inst 2022 Jul 20; [E-pub]. https://doi.org/10.1093/jnci/djac113.
- Tamara A. Sussman, Megan L. Kruse, Holly L. Thacker, And Jame Abraham. Managing Genitourinary Syndrome Of Menopause In Breast Cancer Survivors Receiving Endocrine Therapy. Journal Of Oncology Practice 2019 15:7, 363-370

Do Not Need Progestins With Vulvovaginal Estrogen Use:

- Constantine GD, Graham S, Lapane K, et al. Endometrial Safety Of Low-dose Vaginal Estrogens In Menopausal Women: A Systematic Evidence Review. Menopause. 2019 Jul;26(7):800-807. https://doi.org/10.1097/Gme.0000000000001315.

References: DHEA Vaginally, Testosterone Vaginally and Systemically

DHEA - Prasterone for GSM and Low Libido in Breast Cancer Survivors:

- Labrie F, Archer D, Bouchard C, et al. Effect Of Intravaginal Dehydroepiandrosterone (Prasterone) On Libido And Sexual Dysfunction In Postmenopausal Women. Menopause. 2009 Sep-oct;16(5):923-31. Doi: 10.1097/Gme.0b013e31819e85c6.
- Archer Df. Dehydroepiandrosterone Intra Vaginal Administration For The Management Of Postmenopausal Vulvovaginal Atrophy. J Steroid Biochem Mol Biol. 2015 Jan;145:139-43. Doi: 10.1016/J.Jsbmb.2014.09.003. Epub 2014 Sep 6.
- Mension E, Alonso I, Cebrecos I, et al. Safety Of Prasterone In Breast Cancer Survivors Treated With Aromatase Inhibitors: The VIBRA Pilot Study. Climacteric. 2022 Oct;25(5):476-482. Doi: 10.1080/13697137.2022.2050208. Epub 2022 Mar 28.
- Basson, Rosemary. When VVA Involves Loss Of Genital Sensation: Vaginal DHEA Shows Promise. December 3, 2013. https://thischangedmypractice.com/local-dhea/

Testosterone for GSM Symptoms and Low Libido in Women and Women With Breast Cancer:

- Davis Sr, Baber R, Panay N, et al. Global Consensus Position Statement On The Use Of Testosterone Therapy For Women. J Sex Med. 2019 Sep;16(9):1331-1337. Doi: 10.1016/J.Jsxm.2019.07.012.
- Pitsouni E, Grigoriadis T, Douskos A, et al. Efficacy Of Vaginal Therapies Alternative To Vaginal Estrogens On Sexual Function And Orgasm Of Menopausal Women: A Systematic Review And Meta-analysis Of Randomized Controlled Trials. Eur J Obstet Gynecol Reprod Biol. 2018 Oct;229:45-56. Doi: 10.1016/J.Ejogrb.2018.08.008.
- Islam, R. M., Bell, R. J., Green, S., Page, M. J., & Davis, S. R. (2019). Safety And Efficacy Of Testosterone For Women: A Systematic Review And Meta-analysis Of Randomized Controlled Trial Data. The Lancet. Diabetes & Endocrinology, 7(10), 754–766. Https://Doi.Org/10.1016/S2213-8587(19)30189-5
- Melisko, M. E., Goldman, M., & Rugo, H. S. (2010). Amelioration Of Sexual Adverse Effects In The Early Breast Cancer Patient. Journal Of Cancer Survivorship: Research And Practice, 4(3), 247–255. Https://Doi.Org/10.1007/S11764-010-0130-1
- Glaser, R., York, A.E. & Dimitrakakis, C. Incidence Of Invasive Breast Cancer In Women Treated With Testosterone Implants: A Prospective 10-year Cohort Study. BMC Cancer 19, 1271 (2019). Https://Doi.Org/10.1186/S12885-019-6457-8
- Scott, A., & Newson, L. (2020). Should We Be Prescribing Testosterone To Perimenopausal And Menopausal Women? A Guide To Prescribing Testosterone For Women In Primary Care. The British Journal Of General Practice, 70(693), 203-204. https://doi.org/10.3399/bjgp20x709265
- Donovitz G, Cotten M. Breast Cancer Incidence Reduction in Women Treated with Subcutaneous Testosterone: Testosterone Therapy and Breast Cancer Incidence Study. Eur J Breast Health. 2021 Mar 31;17(2):150-156. doi: 10.4274/ejbh.galenos.2021.6213. PMID: 33870115; PMCID: PMC8025725.
- Donovitz, G. S. (2022). A Personal Prospective On Testosterone Therapy In Women—what We Know In 2022. Journal Of Personalized Medicine, 12(8). Https://Doi.Org/10.3390/Jpm12081194
- Basson R. Testosterone Therapy For Reduced Libido In Women. Ther Adv Endocrinol Metab. 2010 Aug;1(4):155-64. Doi: 10.1177/2042018810379588.
- Uloko M, Rahman F, Puri Li, Rubin Rs. The Clinical Management Of Testosterone Replacement Therapy In Postmenopausal Women With Hypoactive Sexual Desire Disorder: A Review. Int J Impot Res. 2022 Nov;34(7):635-641 https://doi.org/10.1038/S41443-022-00613-0. Epub 2022 Oct 5.
- Snabes MC, Milling WM, Simes SM. Without FDA-approved Testosterone To Treat Women With Hypoactive Sexual Desire Disorder Providers Rely On Off-label Prescribing. J Sex Med. 2011;8:185. Abstract 18A. (Survey data on the prescribing of testosterone by U.S. physicians in 2009 found that approximately 4 million prescriptions for estrogen/androgen oral medications, compounded testosterone, or brand testosterone approved for use in men were written off-label for women.)
- K Dumas, S Singh, J Kohn, et al. Vaginal Estrogen Therapy For Vulvovaginal Atrophy In Women With A Personal History Of Breast Cancer – A Claims Database Analysis, The Journal Of Sexual Medicine, Volume 19, Issue Supplement_3, August 2022, Pages S4–s5, Https://Doi.Org/10.1016/J.Jsxm.2022.05.014 (Inadequate # Prescriptions Given Need)

Compounding References

- Compounding
  - ACOG: Compounded Bioidentical Menopausal Hormone Therapy Committee Opinion Number 532 August 2012 Https://Www.Acog.Org/Clinical/Clinical-guidance/Committee-opinion/Articles/2012/08/Compounded-bioidentical-menopausal-hormone-therapy 8-31-23 Pub Simultaneously: Fertility And Sterility August 2012
  - Stuenkel CA. Compounded bioidentical menopausal hormone therapy - A physician perspective. Climacteric. 2021 Feb;24(1):11-18. Doi: 10.1080/13697137.2020.1825668
  - Thompson JJ, Ritenbaugh C, Nichter M. Why women choose compounded bioidentical hormone therapy: lessons from A qualitative study of menopausal decision-making. BMC Women's Health. 2017 Oct 2;17(1):97. Doi: 10.1186/S12905-017-0449-0. Pmid: 28969624.
  - Sellers, S., & Utian, W. H. (2012). Pharmacy compounding primer for physicians: prescriber beware. Drugs, 72(16), 2043–2050. https://doi.org/10.2165/11640850-000000000-00000