Reproductive Health Work Group

September 13, 2024

Federal Advisory Committee for
Breast Cancer and Young Women

Reproductive Health Work Group

Purpose:

- Provide the ACBCYW committee with an overview of current issues in sexual health, including resource gaps, and evidence-based interventions for young women facing breast cancer.

Goals

1. Improve collaboration and documentation towards an acknowledgment, assessment, and interventions offered for reproductive and sexual health concerns in young women with breast cancer
2. Offering recommendations to improve value and service for the ACBCYW

Current Members: Dr. Maryam Lustberg, Dr. Brooke Vuong, Arin Ahlum Hanson

Complex Unmet Needs and Gaps in Care

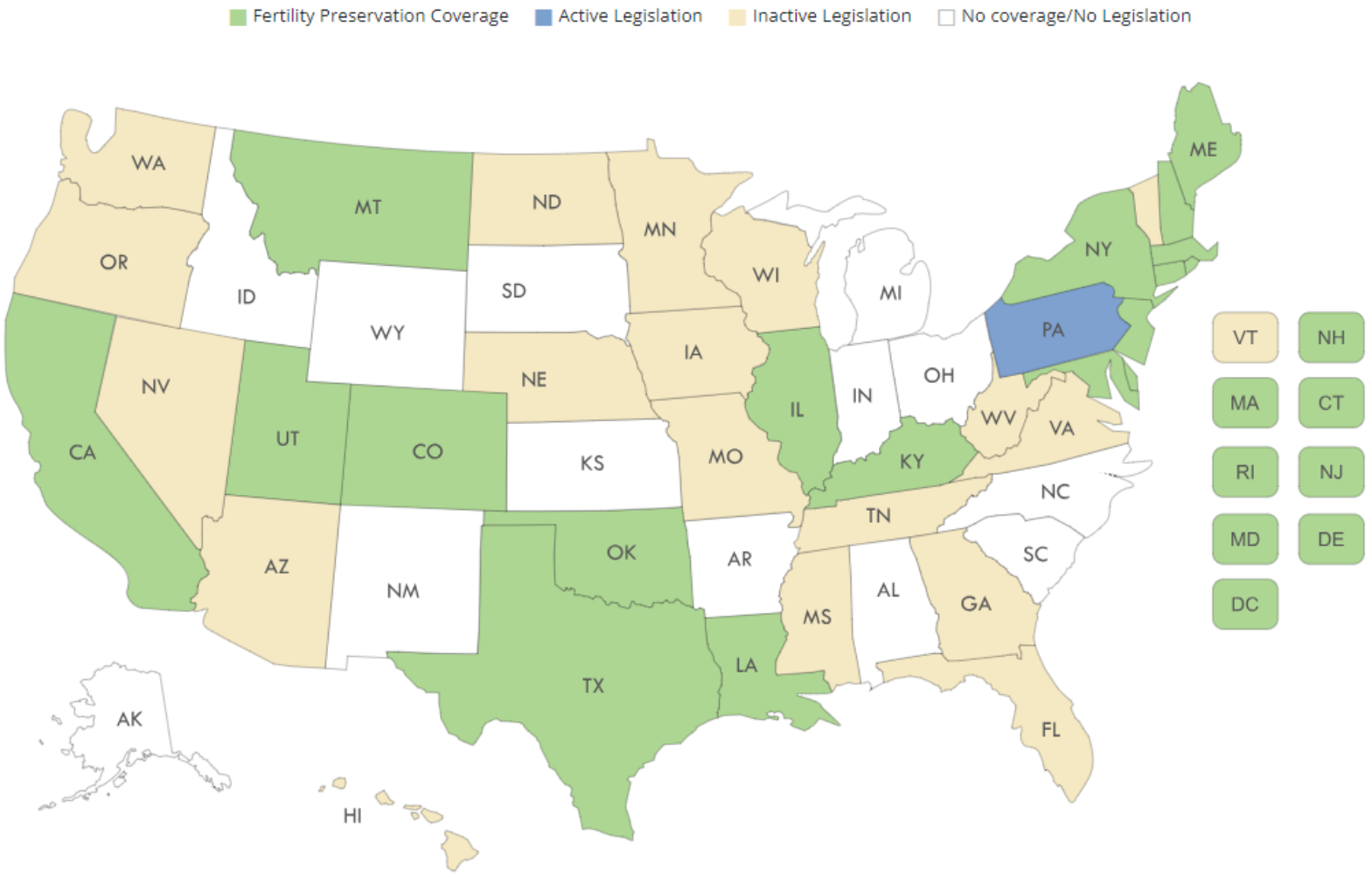
- Oncofertility and Fertility Preservation
- Pregnancy after Breast Cancer
- Sexual Health Concerns
- Body Image
- Decisional Regret
- Libido
- Relationship Image
- Diversity and inclusion of resources for LGBTQ
- Fear of recurrence
- Provider education and comfort with topic
- Financial toxicity of treatment options
- Metastatic community needs
- Endocrine medication adherence
- Culture and taboos around sexuality
- Misinformation

Fertility Preservation

Access to fertility preservation and iatrogenic infertility treatments

- Fertility preservation, storage, and transfer procedures are very expensive and majority of YBCS do not have insurance coverage.
- Insurance coverage is improving for fertility services (Kaiser Family Foundation)
- Needs assessments have some that fertility impacts is top concern for YWBCS
- Recent personhood bills and abortion bans are impacting the reproductive care of YWBCS in some states.

19 States with Fertility Preservation Coverage



Updated 8/1/2024

Potential Fertility Preservation Recommendations

- Committee to advocate for fertility preservation to be considered as a medically necessary part of treatment for YWBCS and a standard of care.
- Request that CDC research the economic and quality of life impacts of fertility preservation on YWBCS
- Request that CDC develop interventions to support YWBCS in making fertility decisions.

Fertility Preservation Citations

- Gabriela Weigel, U. R., & 2020, S. (2020, September 15). *Coverage and use of fertility services in the U.S.* Kaiser Family Foundation. https://www.kff.org/womens-health-policy/issue-brief/coverage-and-use-of-fertility-services-in-the-u-s/
- *Opposing personhood: Resolve: The National Infertility Association*. RESOLVE. (2022, February 16). https://resolve.org/take-action/our-issues/opposing-personhood/
- Reinecke, J., & Smith, K. (n.d.). *Legislation of mandated insurance for fertility preservation* . YouTube. https://www.youtube.com/watch?v=VEco2T4PO_s
- *State Laws & Legislation*. Alliance for Fertility Preservation. (n.d.). https://www.allianceforfertilitypreservation.org/state-legislation/

Pregnancy After Breast Cancer

Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer (POSITIVE Trial)

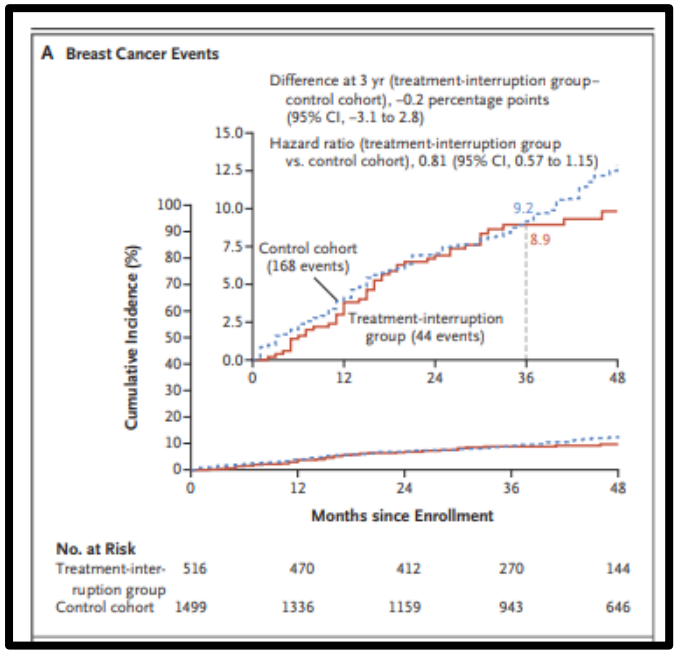
- Dec 2014 – 2019
- Median time from diagnosis to enrollment: 29 months
- Median age: 37 years
- 497 patients with Hormone Receptor positive (HR+) breast cancer
  - Stage I-III breast cancer
    - 93.4% Stage I or II
    - 29.3% had 1-3 positive lymph nodes
    - 62% received chemotherapy
  - On endocrine therapy for 18-30 months
- Intervention: Stop treatment for up to 2 years, then complete total 5-10 years
- External control: 1499 patients from SOFT and TEXT

Partridge AH, *et al* for the POSITIVE Trial Collaborators, NEJM, May 2023

POSITIVE Trial Results

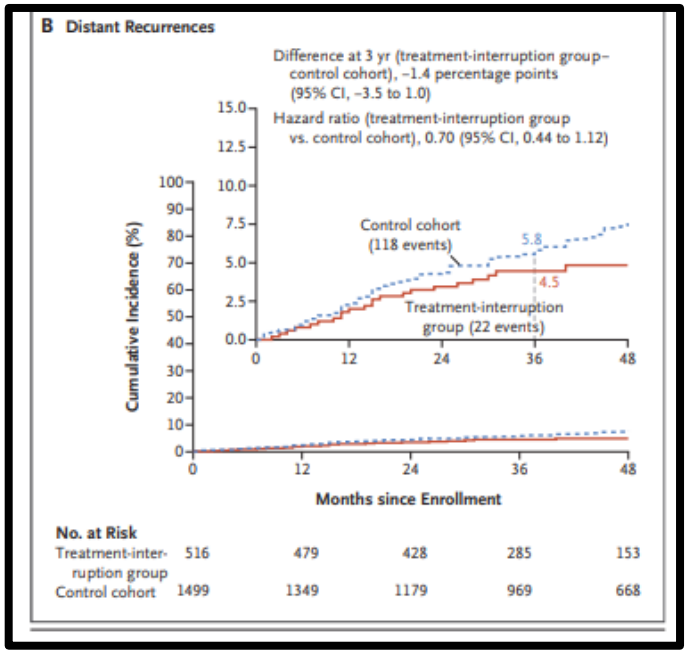
44 patients had a breast cancer event

- Defined as ipsilateral or locoregional invasive disease, distant recurrence, or contralateral invasive breast cancer
- **3Y incidence was 8.9% (vs 9.2% in external control)**



22 distant recurrences

- 3Y distant recurrence 4.5% (vs. 5.8% in external control)



Partridge AH, *et al* for the POSITIVE Trial Collaborators, NEJM, May 2023

POSITIVE Trial Results

- 368 patients had at least one pregnancy
  - 317 had at least one live birth
  - 365 babies were born
- Younger age related to successful pregnancy
  - **85.7%** <35y/o vs **76%** 35-39 y/o vs **52.7%** 40-42 y/o
- 15.4% did not restart endocrine therapy by 48 months
- HR for breast cancer event 0.53 (95% CI, 0.27 to 1.04)
  - No increased risk of breast cancer event associated with pregnancy
- **Temporary interruption of endocrine therapy did not appear to have a short-term effect on oncologic outcomes**

Table 2. Pregnancy Outcomes in Patients with at Least One Pregnancy during the Trial.*

Outcome That Occurred at Least Once	Patients with ≥1 Pregnancy (N=368)
	no. (%)
Live birth, full-term or preterm	317 (86.1)†
Full-term live birth	292 (79.3)
Preterm live birth	27 (7.3)
Miscarriage	93 (25.3)
Elective abortion	16 (4.3)
Stillbirth	1 (0.3)
Neonatal death	1 (0.3)

* Among the 368 women in whom pregnancy occurred during the trial, a total of 507 pregnancies were reported. A total of 110 women had more than one pregnancy; therefore, some women may be included in more than one outcome category. Overall, 258 women had one pregnancy, 88 had two pregnancies, 16 had three pregnancies, 5 had four pregnancies, and 1 had five pregnancies. Among the 507 pregnancies, 323 (63.7%) resulted in full-term live births, 27 (5.3%) in preterm live births, 114 (22.5%) in miscarriages or spontaneous abortions, 17 (3.4%) in elective abortions, 1 (0.2%) in stillbirth, and 1 (0.2%) in neonatal death; 20 (3.9%) were active (ongoing) pregnancies, and 4 (0.8%) had unknown outcomes.

† These 317 women accounted for 63.8% of the 497 women in the secondary end-point population.

Partridge AH, *et al* for the POSITIVE Trial Collaborators, NEJM, May 2023

Discussion

- Percentage of women who became pregnant higher than general rates of pregnancy in similar age group, irrespective of breast cancer diagnosis
- Women were enrolled at least 18 months after chemo
  - Women who conceived within 1 year of chemotherapy had a higher risk of preterm birth
- “Healthy mother effect”
- Relatively short-term follow-up considering recurrences can occur 20 years later

Secondary Analysis of POSITIVE Trial

Abstract GS02-11: Fertility preservation and assisted reproductive technologies (ART) in breast cancer patients interrupting endocrine therapy to attempt pregnancy

- 179 patients used embryo or oocyte cryopreservation prior to enrollment
- 215 used assisted reproductive technology (ART) to attempt pregnancy
  - Ovarian stimulation for IVF and embryo transfer
  - **9.7%** 3Y recurrence rate with ovarian stimulation vs. **8.7%** without ovarian stimulation
- Younger age and cryopreserved embryo transfer associated with higher chances of pregnancy
  - 82.4% became pregnant with embryo transfer
  - 80% of women age <35 pregnant vs. 50% if age >40
- Menstrual cycles returned within 6 months of pausing endocrine therapy
- Type of endocrine therapy had no impact

- Demonstrates **short-term** safety of fertility preservation and ART options

Azim, et al, presented at 2023 San Antonio Breast Symposium

Pregnancy After Breast Cancer in Young BRCA Carriers: An International Hospital-Based Cohort Study

- Jan 2000 – Dec 2020
- 78 centers
- Breast cancer diagnosis ≤ age 40, all subtypes with BRCA1 and/or BRCA2
- N= 4732
  - 659 had at least 1 pregnancy
  - Median age at diagnosis: 35
- Medium f/u 7.8 years
- 1 in 5 conceived within 10 years of diagnosis
- Majority (79.2%) of the pregnancies occurred spontaneously
- No difference in disease free survival was observed between patients with or without a pregnancy (aHR 0.99, 95% CI 0.81-1.2)
- Patients who had a pregnancy had significantly better breast-cancer specific survival and overall survival

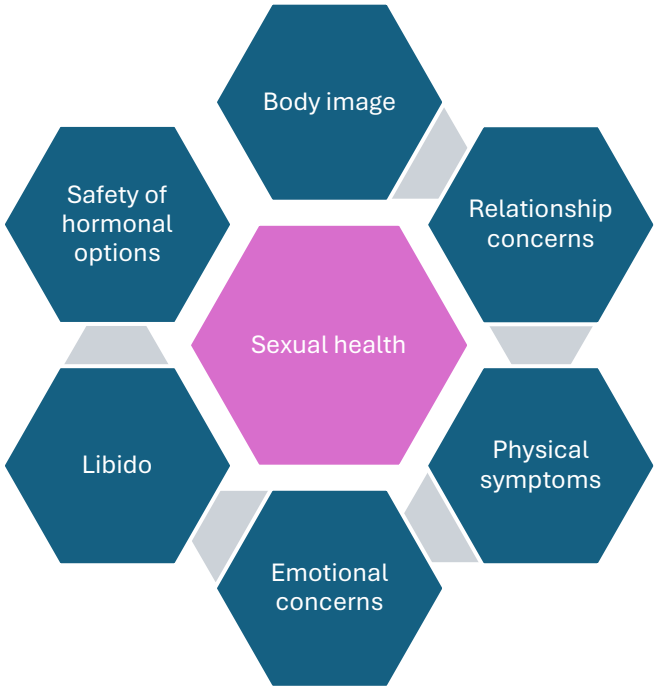
Lambertini, *et al* for the BRCA BCY Collaboration, JAMA, Dec 2023

Pregnancy After Breast Cancer Summary

- Recent data provides optimistic short-term results about the ability to conceive after pregnancy
  - Temporary interruption in endocrine therapy (up to two years) does not affect oncologic outcomes.
  - Ovarian stimulation did not appear to affect 3Y recurrence rates.
  - Pregnancy does not appear to affect disease-free survival among BRCA carriers.

Sexual concerns

Sexual health impacts multiple domains.



Sexuality is a human right

- It is **as important** as ensuring fertility is discussed (with those of child-bearing potential)
- Oncology clinicians must **open the door** for people with cancer to discuss sexuality after cancer
- If QOL is important, we cannot ignore this.

Sexual Concerns and Interventions in Young Women with Breast Cancer

Symptom	Intervention
Vaginal dryness	Vaginal moisturizers Hyaluronic acid-containing moisturizers Vaginal lubricants Local hormone therapy
Pelvic floor dysfunction	Referral to pelvic floor physical therapist Vaginal dilators
Insertional dyspareunia	Topical lidocaine
Sexual response	Assessment of medication lists Psychosocial/psychosexual counseling Sensate focus Mindfulness Exercise Flibanserin* Bremelanotide*
Body image concerns	Psychosocial counseling

Hormonal therapies

Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-021-06436-9

REVIEW

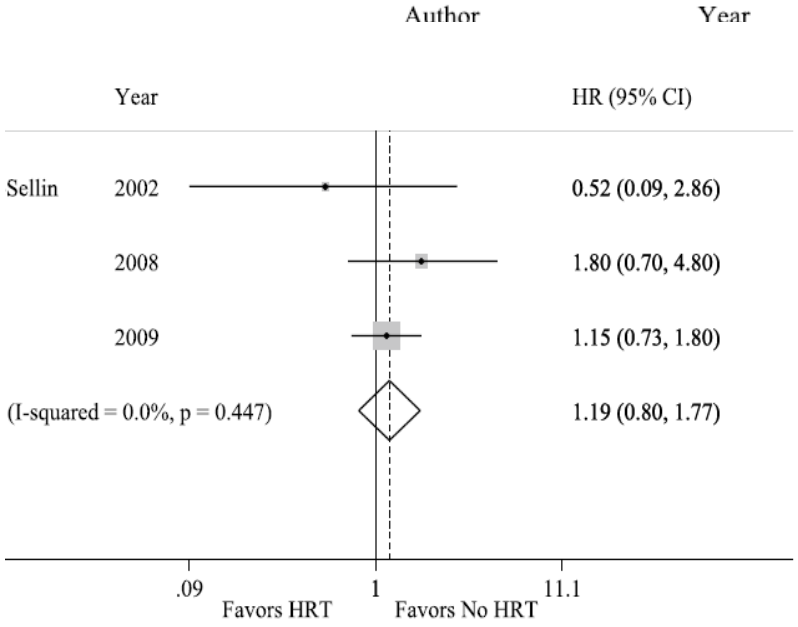
Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis

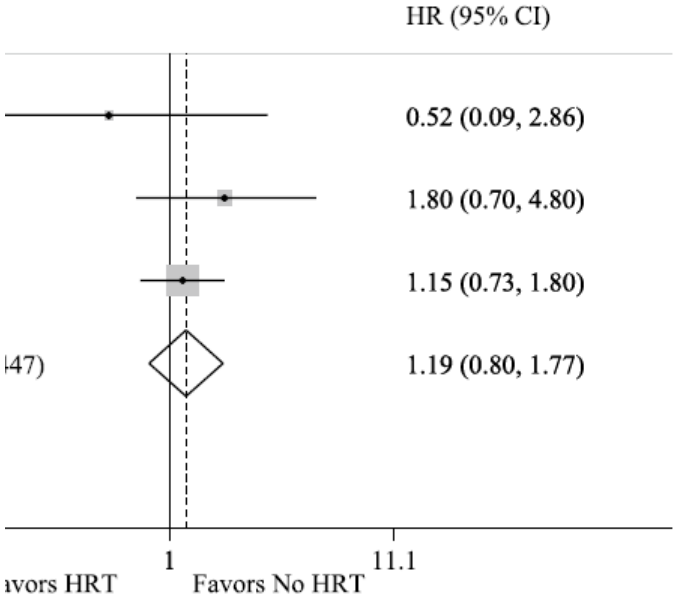
Francesca Poggio[1] · Lucia Del Mastro[2,3] · Marco Bruzzone[4] · Marcello Ceppi[4] · Maria Grazia Razeti[5] · Piero Fregatti[6,7] · Tommaso Ruelle[1] · Paolo Pronzato[1] · Claudia Massarotti[8] · Maria Alice Franzoi[9] · Matteo Lambertini[3,5] · Marco Tagliamento[1,3]

Received: 6 August 2021 / Accepted: 25 October 2021

First author (trial)	Patients, *n* *	HR+, *n* (%)	HR-, *n* (%)	Type of HRT	Type of endocrine therapy in HR+ pts	Median follow-up, *months*
Vassilopoulou-Sellin	77	0	54 (70.1)	Conjugated estrogen treatment	NA	71
Holmberg (HABITS)	442	261 (59.0)	42 (9.5)	Continuous combined or sequential estradiol hemihydrate and norethisterone	34%: Tamoxifen	48
Kenemans (LIBERATE)	3098	2185 (71)	623 (20.1)	Tibolone	67%: Tamoxifen; 6.5%: Aromatase inhibitors	36
Fahlen (STOCKHOLM)	378	216 (57.1)	51 (13.5)	Cyclic estradiol/MPA or estradiol alone	52%: Tamoxifen	120
Total	3995	2662 (66.6)	770 (19.3)			

Impact of HRT in Breast Cancer Survivors





Vaginal estrogen

Vaginal Estrogen: ACOG Opinion

1

Nonhormonal approaches are the first-line choices during or after treatment for breast cancer.

2

Reserve vaginal ERT for women who do not benefit from #1.

- Collaboration important
- Shared decision making critical

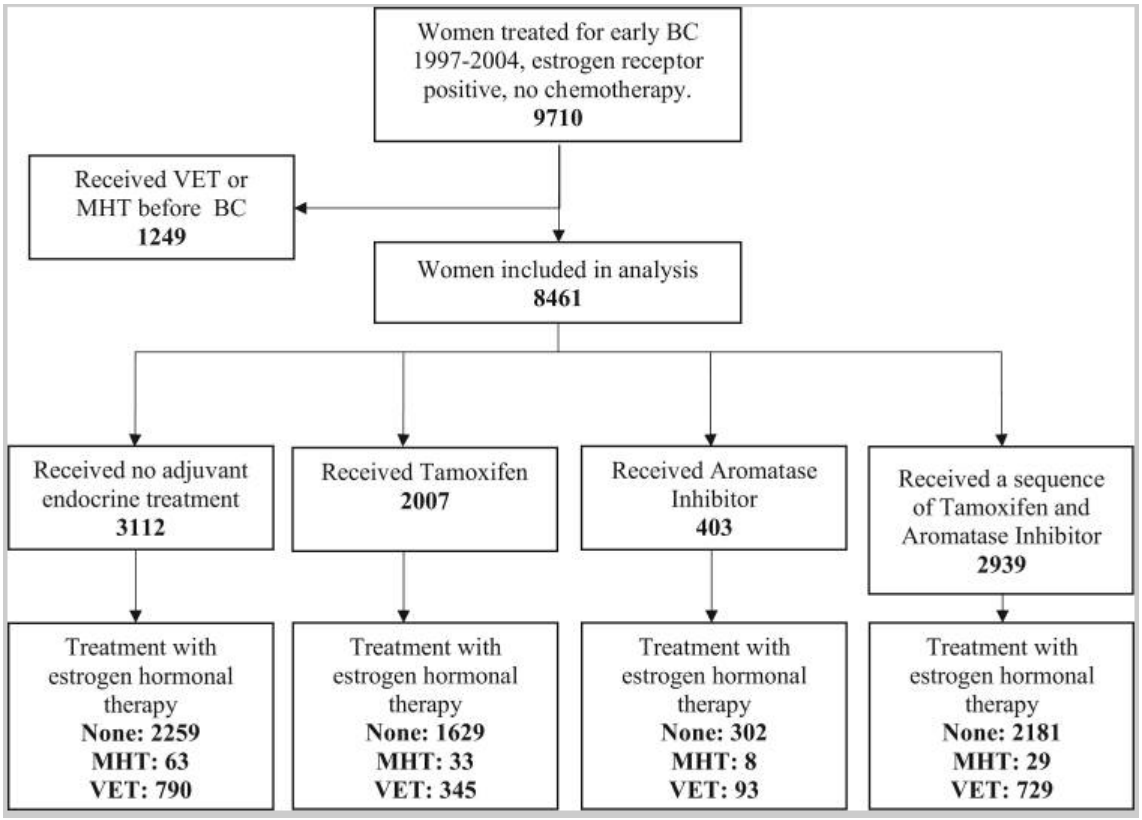
3

Data do not show an increased risk of recurrence after breast cancer with use of vaginal estrogen

Is it safe for patients with breast cancer?

Danish Observational Cohort Study:

- Risk of BC recurrence with oral hormone (OHT) vs vaginal estrogen therapy (VET)
- Population:
  Postmenopausal women, ER+ breast cancer, 1997-2004; not related with chemotherapy (n=8461)



Findings (15y follow-up)

Breast Cancer Event	Neither	OHT	VET
Recurrence (n=1333, 16%)	1206	16 Adj HR 1.05 (0.62-1.78)	111 Adj HR 1.08 (0.89-1.32)
Mortality (n-3370, 40%)	2526	Adj HR 0.94 (0.70-1.26)	Adj HR 0.78 (0.71-0.87)
Absolute OS at 10y(%)	73.8	80.5	79.5
Recurrence Risk by adjuvant Endocrine therapy: -Tamoxifen -Aromatase Inhibitor or AI+Tamoxifen in sequence			Adj HR 0.64 (0.39 -1.06) 1.39 (1.04-1.85)
Mortality Risk with VET by: -Tamoxifen -Aromatase Inhibitor or AI+Tamoxifen in sequence			Adj HR: 0.76 (0.58-0.99) 0.94 (0.70-1.26)

Cautious Interpretation is warranted

- Population-based studies are prone to bias:
  - Cannot comment of adherence to ET
  - Cannot comment of frequency of use for VET
  - Study uses older formulations for VET
  - What about lifestyle?

- Findings of association based on a subset analysis
- Results with MHT are contrary to reports from RCT:
  - HABITS trial show increased recurrence rick with MHT

JAMA Oncology | Brief Report

Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer

Lauren McVicker, PhD; Alexander M. Labeit, PhD; Carol A. C. Coupland, PhD; Blánaid Hicks, PhD; Carmel Hughes, PhD; Úna McMenamin, PhD; Stuart A. McIntosh, PhD; Peter Murchie, MD; Chris R. Cardwell, PhD

Table 1. Patient Characteristics by Hormone Replacement Therapy (HRT) Use After Diagnosis

Characteristic	Patients in Scotland, No. (%)			Patients in Wales, No. (%)		
	No HRT	Systemic HRT	Only vaginal estrogen therapy	No HRT	Systemic HRT	Only vaginal estrogen therapy
Age, y						
40-49	4207 (17)	32 (15)	184 (14)	3491 (17)	49 (14)	184 (15)
50-59	7444 (29)	86 (39)	455 (34)	6143 (30)	153 (45)	411 (34)
60-69	8231 (32)	71 (33)	436 (32)	6685 (32)	104 (31)	394 (33)
70-79	5506 (22)	29 (13)	281 (21)	4423 (21)	32 (9)	206 (17)

RESULTS The 2 cohorts comprised 49 237 females with breast cancer (between 40 and 79 years of age) and 5795 breast cancer–specific deaths. Five percent of patients with breast cancer used vaginal estrogen therapy after breast cancer diagnosis. In vaginal estrogen therapy users compared with HRT nonusers, there was no evidence of a higher risk of breast cancer–specific mortality in the pooled fully adjusted model (HR, 0.77; 95% CI, 0.63-0.94).

CONCLUSIONS AND RELEVANCE Results of this study showed no evidence of increased early breast cancer–specific mortality in patients who used vaginal estrogen therapy compared with patients who did not use HRT. This finding may provide some reassurance to prescribing clinicians and support the guidelines suggesting that vaginal estrogen therapy can be considered in patients with breast cancer and genitourinary symptoms.

Approaching sexual health: PLISSIT

Permission

- Invites patient to enter into a discussion about sexual health
- “I’d like to review how you are doing as it related to both sexuality and intimacy. Would that be okay?”
- “Are you (and your partner) having problems being intimate?”

Limited Information

- Normalizes that issues related to sexual health are common
- “ some women complain that sex and intimacy are different now.. In fact, it is pretty common. How has your experience been?”
- “ A common complaint is pain during intercourse. Is this that is happening with you?”

Specific Suggestions

- Offer advice that can be actionable and easy to incorporate if possible
- “If you have some trouble with vaginal dryness, it may help to use a lubricant before and during sex.”

Intensive Therapy

- If one is not comfortable with issues brought up or does not know what to advise, offer expert consultation locally (if possible) or refer to educational resources (Table 4)
- “ It sounds like you might benefit from seeing an expert in sexual health. Can I suggest a referral?”

Dizon, Suzon, and McBrenna The Oncologist 2014, 19 202 -10

Sexual Concerns Summary

- There are many opportunities to better sexual health concerns in younger women.
- Educational interventions for patients
- Education for clinicians
- Peer support
- Others

Next steps for our group?

We welcome your suggestions and input.

Our working group would like to add 1-2 additional members. Please consider joining us!

Complex Unmet Needs and Gaps in Care

- Oncofertility and Fertility Preservation
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- Fear of recurrence
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Discussion and Questions