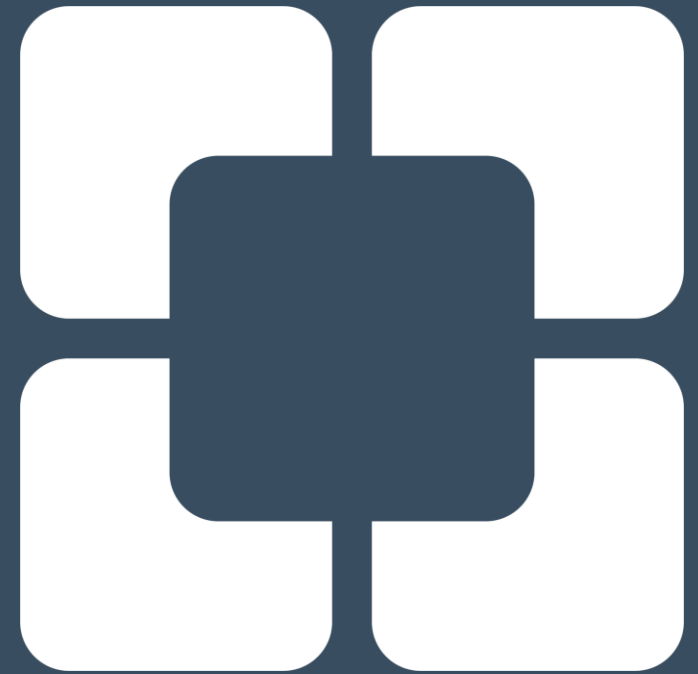
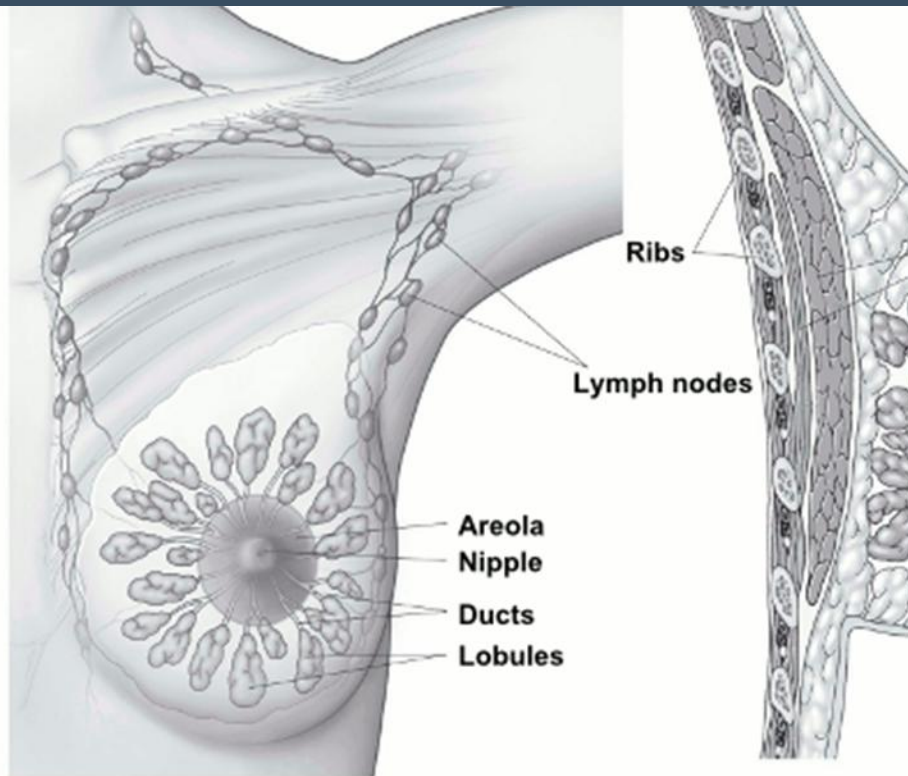


Hormones and Breast Cancer Risk

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Objectives



Interpret

Interpret the evidence linking hormonal contraception and menopausal hormone therapy with breast cancer risk, including relative and absolute risk.

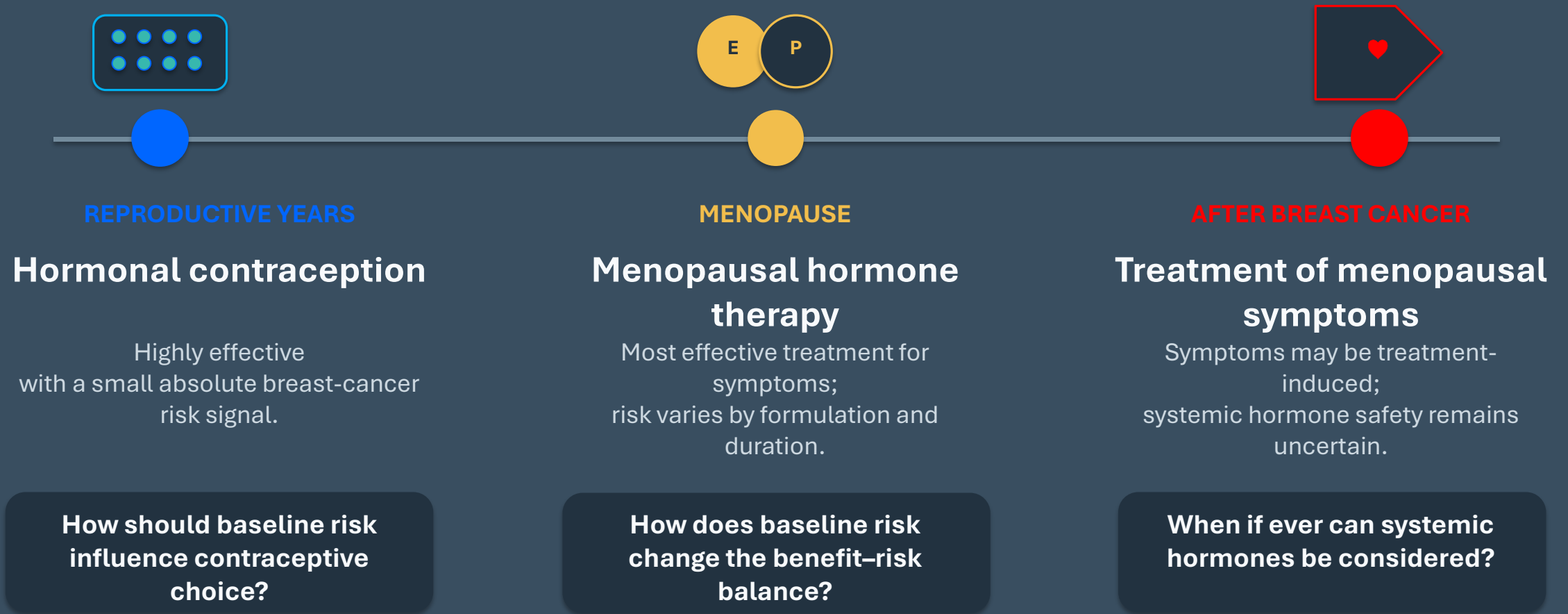
Explain

Explain how clinical context modifies counseling, including hormone formulation, duration of use, baseline breast cancer risk, hereditary susceptibility, and high-risk breast lesions.

Apply

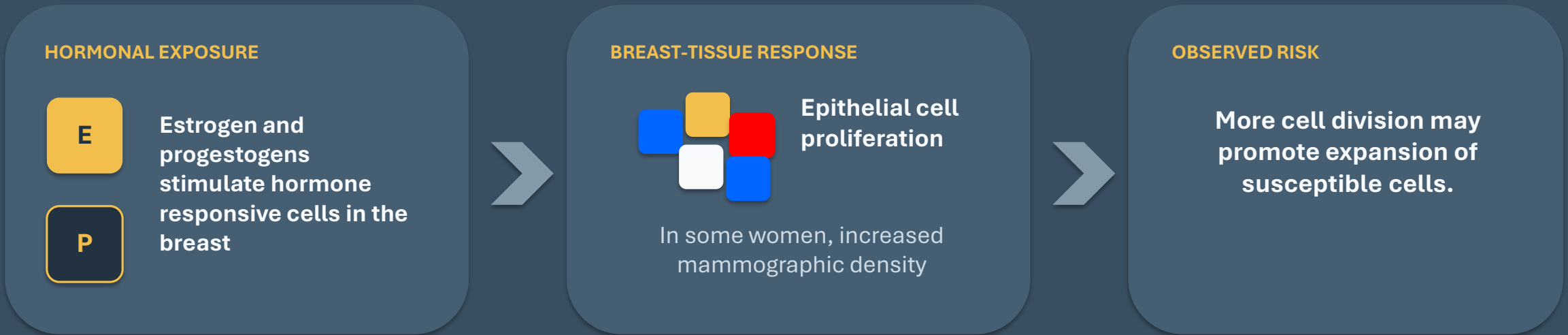
Apply an evidence-based approach to contraception and menopausal symptom management in breast cancer survivors, distinguishing systemic hormone therapy from local treatment for genitourinary symptoms.

Hormones across the lifespan: the clinical question changes



Not simply, “Are hormones safe?” → Which hormone? Which patient? Which stage of life?

Hormones influence breast risk by changing tissue growth



WHAT MODIFIES THE EFFECT?

Regimen estrogen alone vs combined; progestogen type and schedule

Exposure dose, duration, and whether use is current or remote

Host age, involution/density, inherited risk, atypia, or prior cancer

Absolute impact = Relative treatment effect × baseline breast cancer risk

Hormonal Contraception and Breast Cancer Risk

Study	Population	Relative Association	Absolute Increase
Mørch et al., 2017	1.8 million Danish women	RR 1.20	13 per 100,000 person-years
Johansson et al., 2025	2 million Swedish women	HR 1.24	~1 additional case per 7,752 users per year

Hormonal Contraception and Breast Cancer Risk

Observational differences between formulations can inform counseling but do not establish that any hormonal method is breast-neutral

Contraceptive Type	Breast Cancer HR
Any hormonal contraception	1.24
Combined oral	1.12
Progestin-only pill	1.21
Oral desogestrel only	1.18
Oral desogestrel combined	1.19
Etonogestrel implant	1.22
Levonorgestrel-only pill	1.09
Levonorgestrel IUD	1.13
Medroxyprogesterone injection	NS
Etonogestrel ring	NS
Combined oral drospirenone	NS

Combined hormonal contraceptives decrease both ovarian and endometrial cancer risk

- Average risk women and *BRCA1* and *BRCA2* pathogenic variant carriers
- Consistent reductions of 30-50% have been noted
- Risk reduction increases with duration of use
 - Schrijver et al – showed greater than 10 years of use reduced ovarian cancer risk in *BRCA* carriers by 63%, with benefits lasting about 15 years.

With Courtesy of Dr. Holly Pederson

1. Chen L, Blank SV, Burton E, Glass K, Penick E, Woodard T. Reproductive and hormonal considerations in women at increased risk for hereditary gynecologic cancers: Society of Gynecologic Oncology and American Society for Reproductive Medicine evidence-based review. *Gynecol Oncol* 2019;155:508–514. doi: 10.1016/j.ygyno.2019.06.01
2. Collaborative Group on Epidemiological Studies on Endometrial Cancer. Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. *Lancet Oncol*. 2015;16(9):1061-1070. doi:10.1016/S1470-2045(15)00212-0
3. Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. *Am J Obstet Gynecol*. 2017;216(6):580.e1-580.e9. doi:10.1016/j.ajog.2017.02.002
4. Schrijver LH, Antoniou AC, Olsson H, et al. Oral contraceptive use and ovarian cancer risk for *BRCA1/2* mutation carriers: an international cohort study. *Am J Obstet Gynecol* 2021;225:51.e1–51.e17. doi: 10.1016/j.ajog. 2021.01.014

Contraception in elevated-risk women and survivors

Clinical Context	Copper IUD	LNG-IUD	Progestin-only pill, implant, DMPA	Combined hormonal contraception
Family history	No restriction	No restriction	No restriction	No restriction
Benign breast disease	No restriction	No restriction	No restriction	No restriction
Pathogenic variant carrier without breast cancer*	Eligible	Eligible	Eligible	Eligible
Current DCIS or Invasive breast cancer	No restriction	Unacceptable risk	Unacceptable risk	Unacceptable risk
Previous breast cancer, disease-free >5 years	No restriction	Risks usually outweigh benefits	Risks usually outweigh benefits	Risks usually outweigh benefits

* The US MEC does not provide a separate category for pathogenic variant carriers

Menopausal symptoms are common. Evidence after breast cancer is not.

**Up to
80%**

of women experience
vasomotor symptoms

**7.4
years**

median duration of
frequent vasomotor symptoms

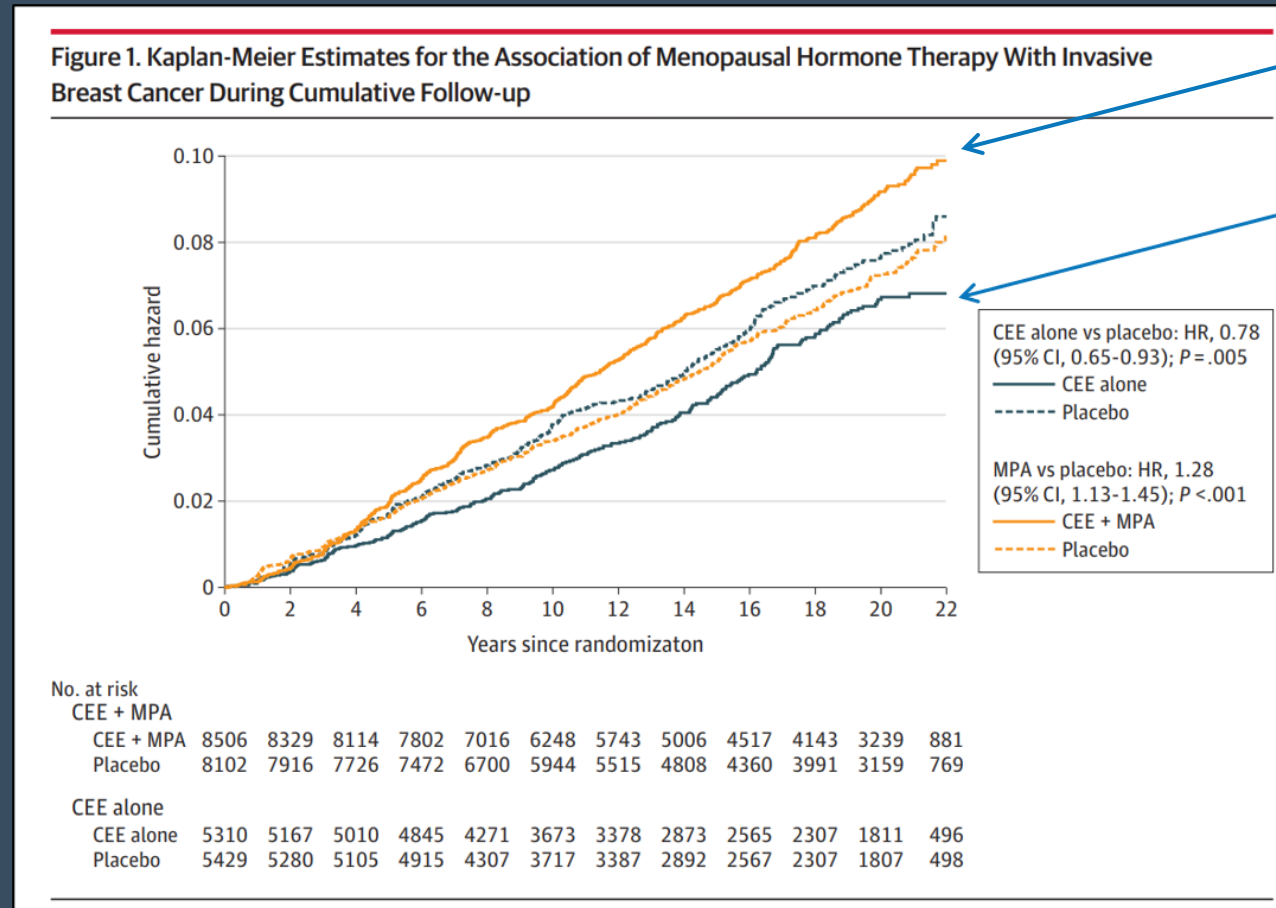
Symptoms can disrupt sleep, mood, cognition, sexual health, work, and quality of life.

AFTER BREAST CANCER

Systemic MHT is often avoided; recurrence-safety evidence remains limited and difficult to individualize.

TODAY: average risk → inherited or otherwise high risk → breast cancer survivors

WHI: 20 years median cumulative follow up



Estrogen + Progestin

Estrogen alone

Breast cancer risk may differ by progestogen

Progestogen	Example	Key Findings
Medroxyprogesterone acetate	CEE + MPA (synthetic)	↑ Invasive BC incidence (HR 1.28 , WHI)
Progesterone (bioidentical)	Micronized progesterone	No significant ↑ (RR 1.00 , E3N)
Dydrogesterone	Duphaston® Not available in the US	Slight, non-significant ↑ (RR 1.16, E3N)
Other synthetic progestins	Norethindrone, Levonorgestrel, Desogestrel	Substantial ↑ (RR ≈ 1.6–1.7 , E3N)
Newer agents	Drospirenone / Nomegestrol	Mixed / limited data

Observational studies suggest a more favorable risk profile with micronized progesterone, but randomized comparative breast cancer data are lacking.

MHT regimen matters and density shows breast response

Randomized WHI ancillary studies: adjusted treatment difference in mammographic percent density at 1 year

REGIMEN MATTERS

Combined therapy produces a larger density response



Separate WHI ancillary trials. Values are adjusted differences versus placebo.

Formulation changes the average biologic effect on the breast.

INDIVIDUAL RESPONSE MATTERS

Within the WHI estrogen + progestin arm



Highest quintile of density increase (>19.3 %):

3.6-fold higher odds



Density change is a marker of breast response, not a validated monitoring rule for MHT

MHT in women at elevated risk

Clinical Context	Practical Approach
Family history alone	MHT may be considered when clinically indicated
Genetic predisposition without cancer	MHT is recommended in most cases or early surgical menopause. Consider gene, breast and uterine status, formulation, and duration (ie estrogen alone*)
Atypical hyperplasia or Lobular neoplasia	MHT may still be considered after individualized counseling; recognize that it prevents concurrent use of risk reducing medications (SERMS or Ais)
Personal history of breast cancer	Systemic MHT is generally avoided, with exceptional individualized consideration

Elevated risk alone does not automatically preclude MHT. Consider health benefit and symptom relief versus an incremental absolute breast cancer risk. In atypia/LCIS, loss of the opportunity to use endocrine risk-reducing medication.

MHT was not associated with increased breast cancer risk in BRCA1/2 carriers

- Matched prospective analysis of BRCA 1/2 carriers who underwent risk reducing salpingo-oophorectomy
 - 676 MHT users matched to 676 nonusers
 - Breast cancer: 87 cases among users v 128 among nonusers
 - HR 0.37 in estrogen only
 - HR 0.94 estrogen + progesterone

Bazedoxifene/CE: reassuring breast signals, no outcome data

Tissue-selective estrogen complex: estrogen paired with a SERM rather than a progestogen.

SMART-1 / SMART-5

No increase in mammographic density

SMART-1 507 women • 24 months • comparable with placebo

SMART-5 940-woman density substudy • 12 months

-0.38%

BZA/CE 0.45

-0.44%

BZA/CE 0.625

-0.32%

Placebo

CE/MPA comparator: +1.60% density (P<.001)

Breast tenderness was also similar to placebo and lower than with CE/MPA.

PROMISE

Early antiproliferative signal in DCIS

141

postmenopausal women with DCIS
CE/BZA vs placebo for ~4 weeks

↓ epithelial proliferation

in ER-positive DCIS

No adverse quality-of-life signal. **Presurgical biomarker endpoint only.**

Not a recurrence, progression, or breast-cancer prevention trial.

**CLINICAL
INTERPRETATION**

Reassuring surrogate breast endpoints; cancer-outcome safety remains unknown.

Randomized Trials of Systemic MHT after Breast Cancer

TRIAL	POPULATION	MHT REGIMEN	KEY FINDING
STOCKHOLM	N=378 • 57% ER+	Cyclic estradiol ± MPA	↑ Contralateral BC • HR 3.6
HABITS	N=442 • 59% ER+	Estradiol and noresthisterone; regimens varied	↑ New breast cancer events • HR 2.4 • stopped early
LIBERATE*	N=3098 • 71% ER+	Tibolone	↑ Recurrence • HR 1.4 • study terminated early
Vassilopoulou-Sellin	N=77 • HR negative	CEE	No difference in DFS

*LIBERATE: no increased risk was demonstrated in the HR-negative subgroup, but analysis was not powered to establish safety

Systemic MHT after breast cancer

**For all patients with a history of breast cancer: begin with evidence-based nonhormonal treatment.
Routine systemic MHT is not recommended**

Breast Cancer History	Considerations	Individualization
DCIS	ER status; remaining breast tissue (ie mastectomy); endocrine treatment	May be more reasonable when symptoms remain severe, particularly after bilateral mastectomy or if ER negative
Invasive ER positive	Stage and recurrence risk; time since diagnosis; endocrine treatment adherence/completion	Generally avoided given randomized recurrence data and biologic plausibility
Invasive ER negative	Stage; disease-free interval; genetics and new primary risk	No evidence establishes safety and a longer disease-free interval may support consideration



Shared decision-making should address symptom burden, quality of life, recurrence and new-primary risk, nonhormonal treatment response, uterine status, and patient preferences.

Non hormonal management

Cognitive behavioral
therapy

Yoga and
mindfulness

Oxybutynin

SSRIs/SNRIs

Gabapentin

NK3 receptor
antagonist

Vaginal Estrogen: What does the evidence show?

Minimal systemic exposure

10 µg estradiol insert: serum estradiol generally remains within postmenopausal range

7.5 µg estradiol ring: low systemic exposure

Low-dose creams can have limited absorption, varies by amount of product used

Observational outcomes

2025 systemic review and meta-analysis

118,659 breast cancer survivors

6,358 used vaginal estrogen

No increased breast cancer recurrence
RR 0.87 (95% CI, 0.67-1.11)

Danish cohort found no overall recurrence but AI subgroup had an increased recurrence estimate, RR 1.39 with no increase in mortality

Low dose vaginal estrogen has not been associated with increased recurrence or mortality, but the evidence is observational.

Vaginal Estrogen after breast cancer



- **Tamoxifen: less concern about breast stimulation**
- **Aromatase inhibitor: involve oncology as systemic estradiol suppression is the therapeutic goal**
- **Use the lowest effective dose**

Key Takeaways

- Hormonal contraception is associated with a small absolute increase in breast cancer diagnoses; formulation and duration may influence the association.
- **For women without breast cancer, MHT risk depends substantially on whether a progestogen is required and which regimen is used.**
- Elevated baseline risk does not automatically preclude MHT, but hereditary risk, atypia, and previous breast cancer require different counseling.
- **After breast cancer, routine systemic MHT remains discouraged; low-dose vaginal estrogen has a separate and generally more reassuring evidence base.**



Every life deserves world class care.

Type of Progestogen Matters

Menopausal hormone therapy formulation and breast cancer risk

Objective: To evaluate whether the increased risk of breast cancer is dependent on the formulation of menopausal hormone therapy (HT) used.

Results:

- Case-Control Study, UK women aged 50+, 43,183 cases of breast cancer were identified and matched to 431,830 control
- Compared with never users, estrogens were not associated with breast cancer
- Progestogens associated with breast cancer, OR 1.28 compared with micronized progesterone, OR 0.99

MHT and breast density

- Prospective sub study WHI Population looked at 413 postmenopausal women and mammogram density (CEE+ MPA v placebo)
 - After 1 year, CEE+MPA group had a mean density increase difference of 4.9 percent
- Byrne et al. in a subsequent nested case-control study of 174 women from WHI showed that density change was associated with higher BC risk
 - Each 1% density increase → 3% higher breast cancer risk
 - Highest quintile of increase (>19.3%) → ~3.6× risk in breast cancer
 - Density change mediates breast cancer risk

Product Type	Composition	Dosing
Vaginal Cream (Premarin)	Conjugated estrogens(0.625mg/1g cream)	0.5-2g/day of cream 2x/week
Vaginal Cream (Estrace)	Estradiol (100mcg/1g cream)	2-4g of cream for 1-2 weeks then 1g 1-3x/week
Vaginal Tablet (Vagifem)	Estradiol (10mcg per tablet)	1 tablet/day for 2 weeks then 1 tablet 2x/week
Vaginal Insert (Imvexxy)	Estradiol (4 or 10mcg per insert)	1 insert/day for 2 weeks then 1 insert 2x/week
Vaginal Ring (<u>Estring</u>)	Estradiol	7.5mcg/day for 90 days

Adapted from Dr Lutsberg, Kling, and Larkin's presentation at SABCS 2025