Hormone Therapy

Clinical Benefits + Breast Cancer Link

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Disclosure

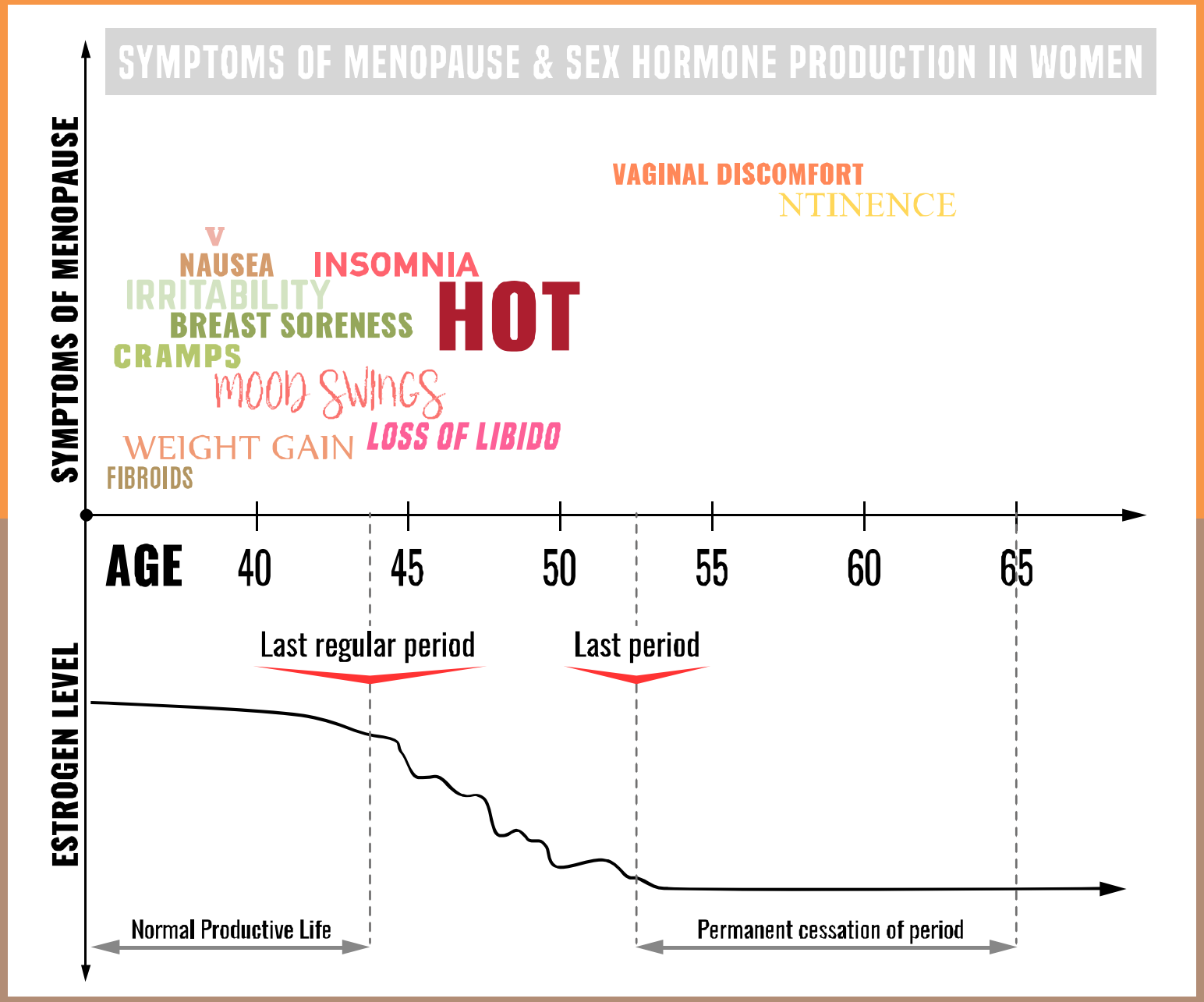
The individual listed below have declared that they have no financial arrangements or affiliations with any corporate organization offering financial support or grant monies for this CME program or with any corporate organization whose product will be discussed in their presentation:

Sara Gottfried, MD, FACOG

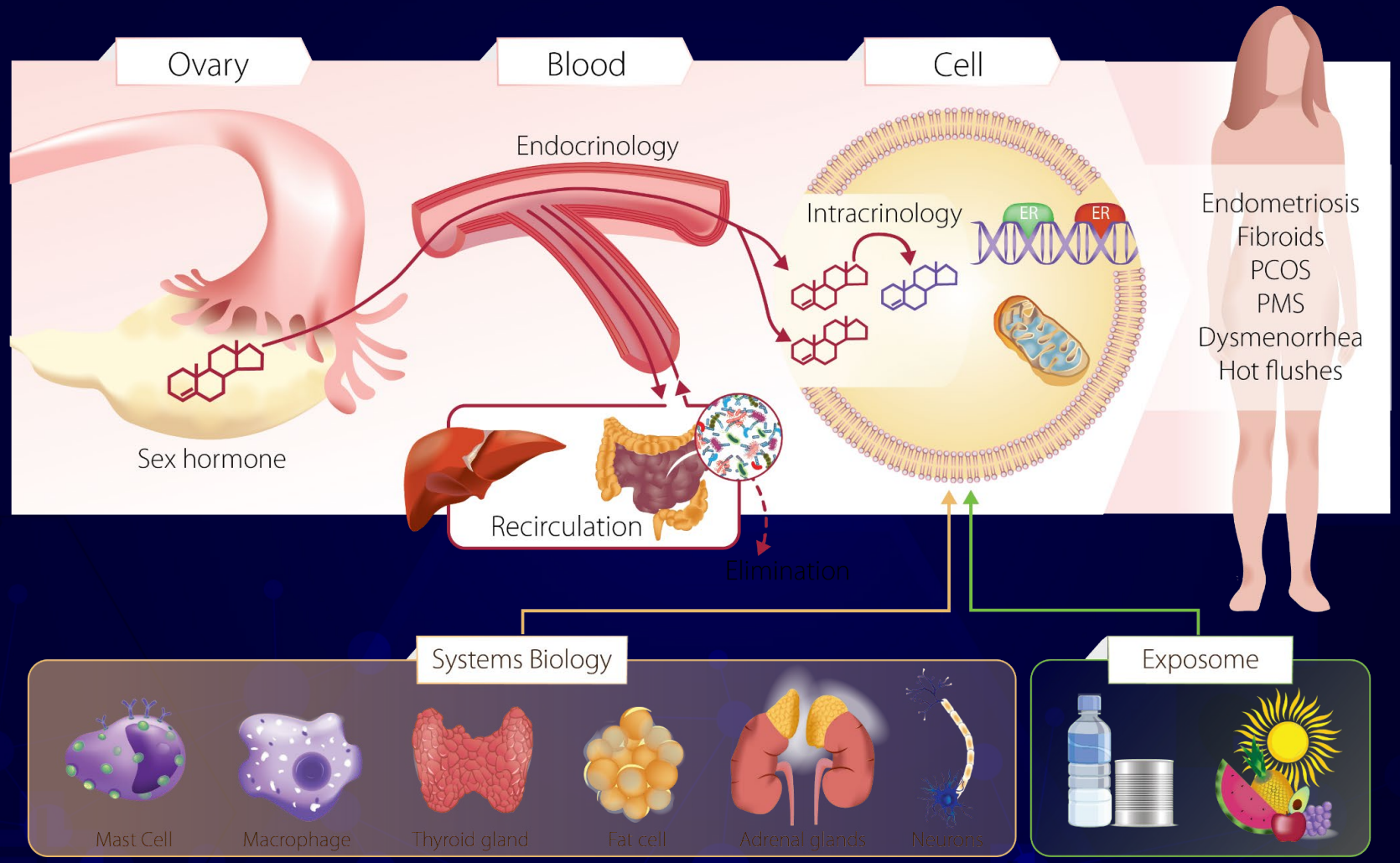
Reference

Learning Objectives

- Identify the evidence-based benefits that women experience with hormone therapy beginning in perimenopause or menopause and how it impacts broader risk profile
- Review the **risks and benefits of hormone therapy** with estrogen, progesterone, and testosterone based on the latest evidence and guidelines with regard to breast cancer risk
- Apply an **evidence-based approach** to monitoring exogenous bioidentical hormone therapy, and understand that one test does not fit all.
- Synthesize the latest guidelines for high-risk populations including women with a family history of breast cancer, personal history of breast cancer, or high-penetrance gene mutations such as BRCA


SYMPTOMS OF MENOPAUSE & SEX HORMONE PRODUCTION IN WOMEN
SYMPTOMS OF MENOPAUSE
VAGINAL DISCOMFORT
NTINENCE
V
NAUSEA
INSOMNIA
IRRITABILITY
HOT
BREAST SORENESS
CRAMPS
MOOD SWINGS
WEIGHT GAIN
LOSS OF LIBIDO
FIBROIDS
AGE
40
45
50
55
60
65
ESTROGEN LEVEL
Last regular period
Last period
Normal Productive Life
Permanent cessation of period

Hormone PTSD in Precision Framework



Labrie F. *Mol Cell Endocrinol.* 1991 Jul;78(3):C113-8; Labrie F, et al. *Menopause.* 2017 Jun;24(6):702-712; Gibson DA, et al. *Int J Mol Sci.* 2018 Oct 22;19(10):3276; Penning TM, et al. *J Steroid Biochem Mol Biol.* 2020 Feb;196:105499.

Perimenopause and Menopause

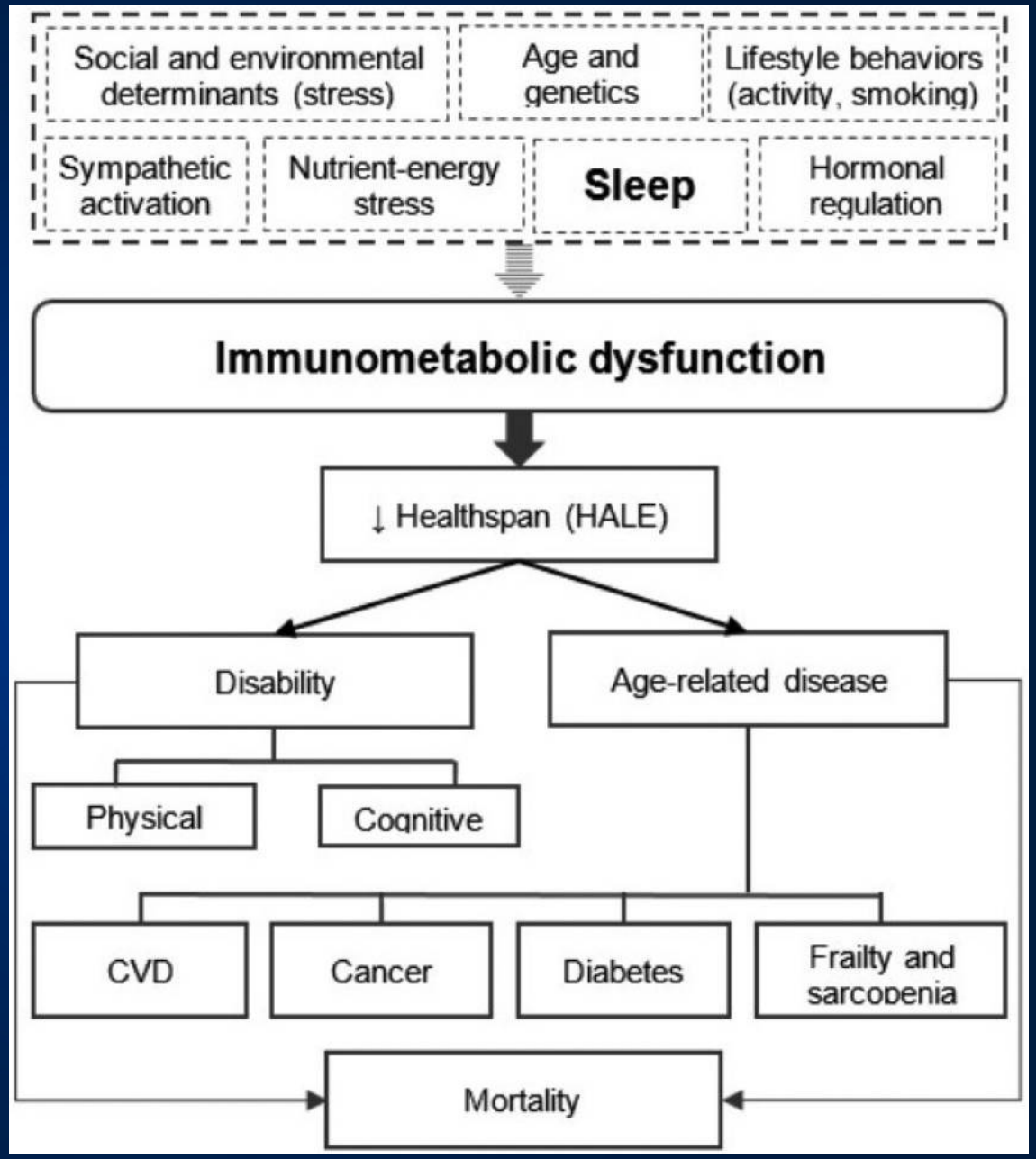
- **80% of women experience psychological or physical symptoms[1]**
- **Mood: Women > 2X to be afflicted[2,3] observed in U.S. and globally[4]**
- **Sleep disorders[5]**
  - 2X reflecting bidirectional relationship between sleep/wake cycle and sex hormones/gonadotropins
  - Menopause-related sleep disturbance may influence eating behaviors/timing, directly affect immunometabolism, particularly abdominal adiposity
  - Menopause is associated with increased risk of sleep apnea.[6] Each year in the MT associated with 4% greater apneahypopnea index.[7]
- **VMS associated with indicators of cardiovascular disease (CVD) risk, e.g., adverse CVD risk factor profile, greater subclinical CVD and, in emerging work, CVD events[8]**
  - Untreated vasomotor instability impairs endothelial function-–increased risk of HTN, osteoporotic fracture, CVD, depression, and cognitive impairment[9]

See next slide

Perimenopause and Menopause

1. Gracia CR, et al. *Obstet Gynecol Clin North Am* 45, no. 4 (2018):585-597.
2. Kessler RC, et al., *Archives of General Psychiatry* 62, no. 6 (2005): 593-602.
3. Bekker MHJ, et al., *Gender Medicine* 4, Suppl B (2007): S178-93.
4. Seedat S, et al., *Archives of General Psychiatry* 66, no. 7 (2009): 785-95
5. Kravitz HM, et al. *Obstet Gynecol Clin North America* 2018 Dec;45(4):679-694.
6. Tufik S, et al. *Sleep Med* 2010 May; 11(5):441-6.
7. Mirer AG, et al. *Menopause* 2017 Feb; 24(2):157-162.
8. Thurston RC. *Climacteric* 2018 Apr;21(2):96-100.
9. Biglia N, et al. *Climacteric* 2017 Aug;20(4):306-312.

Sleep

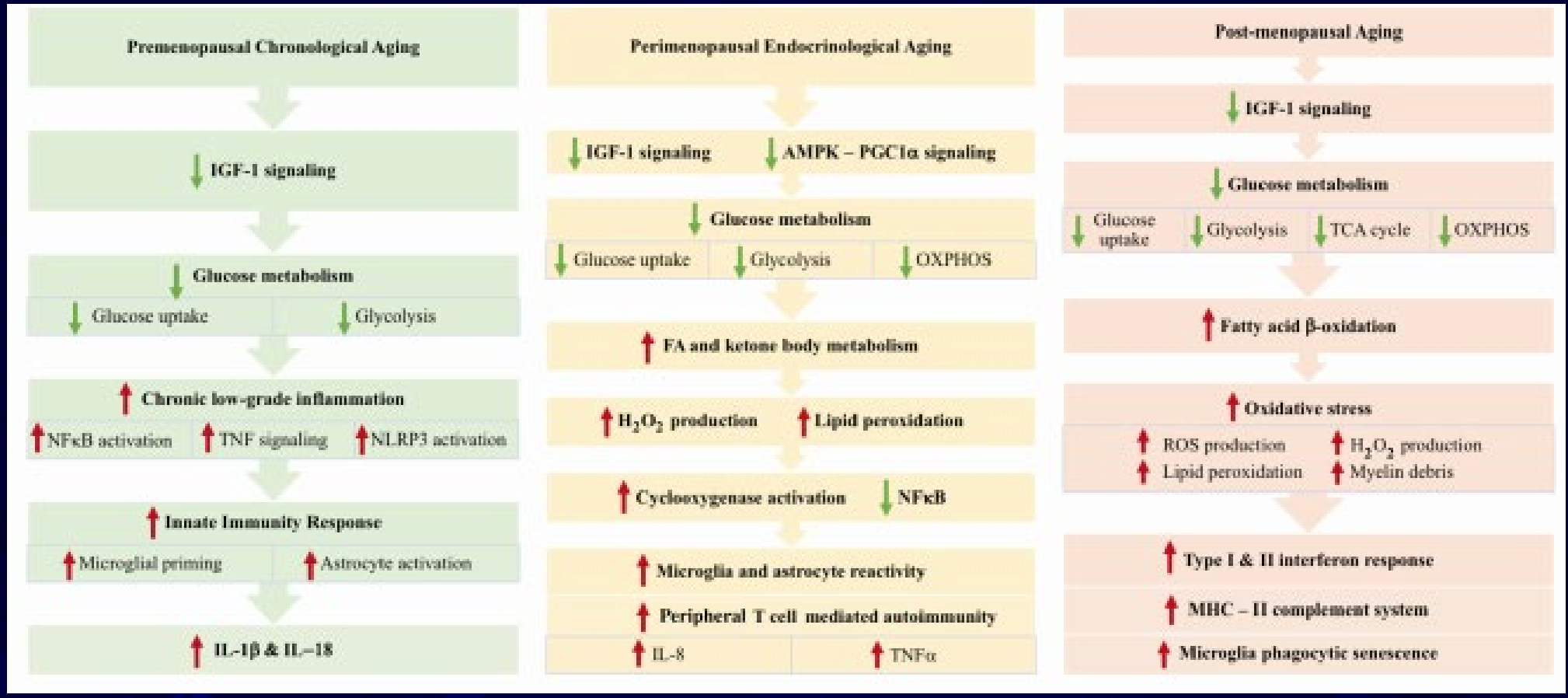


Kravitz HM, et al. *Obstet Gynecol Clin North America* 2018 Dec;45(4):679-694.

Hormonal Assessment

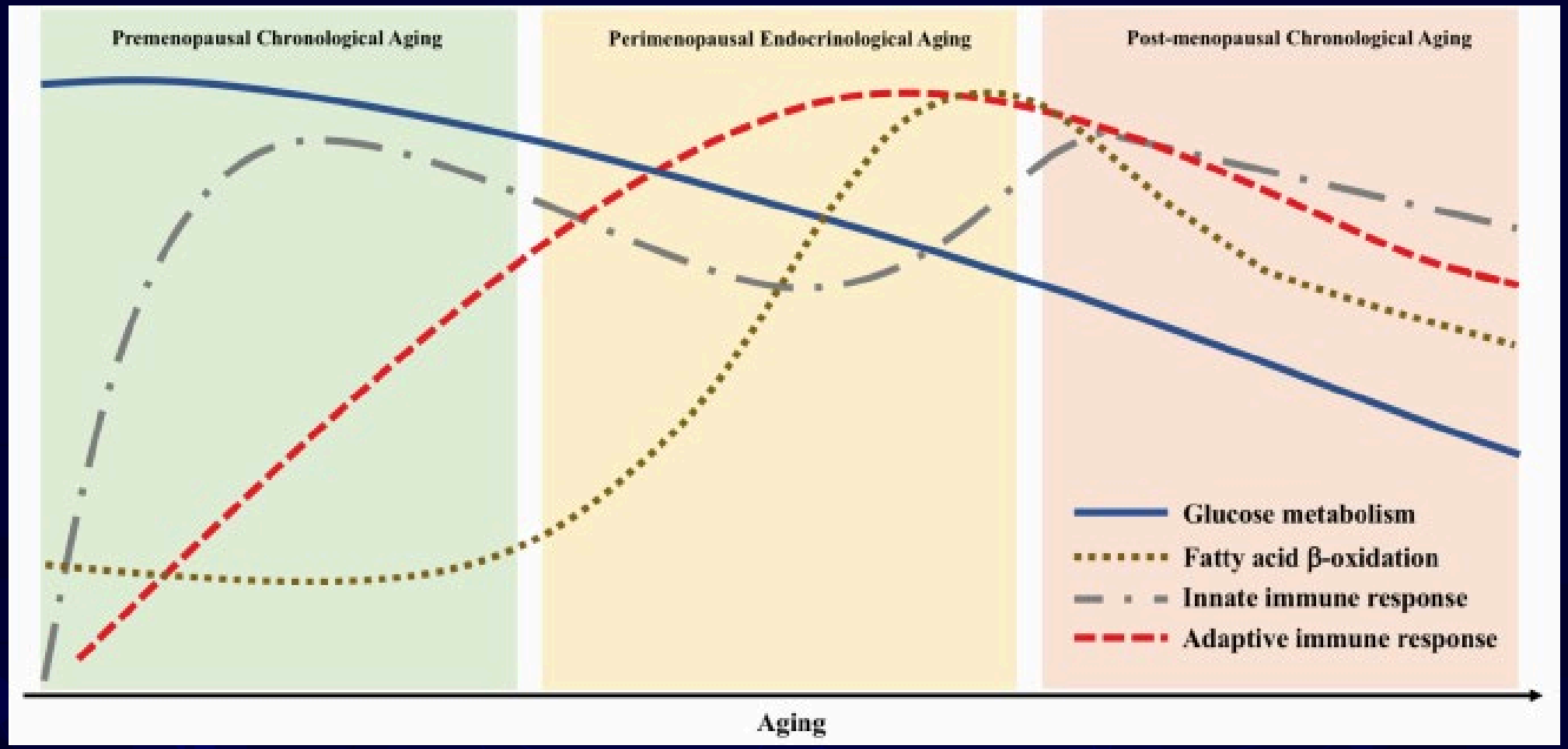
- HCM (full exam, Pap/HPV, mammo, colonoscopy)
- Genomics
- Serum: Cardiometabolic assessment + hormone panel
- Coronary Artery Calcium Score +/- CIMT
- Micronutrients, heavy metals
- Wearables: sleep, activity, HRV, continuous glucose monitoring
- As needed: Stool testing, intestinal permeability, OAT
- Dried urine testing for HPA (saliva for CAR), metabolism
- Topical estrogen: consider saliva, may reflect aromatization better
- Topical progesterone: use blood spot, serum underrepresents, saliva overrepresents

Metabolic and Immune Signaling



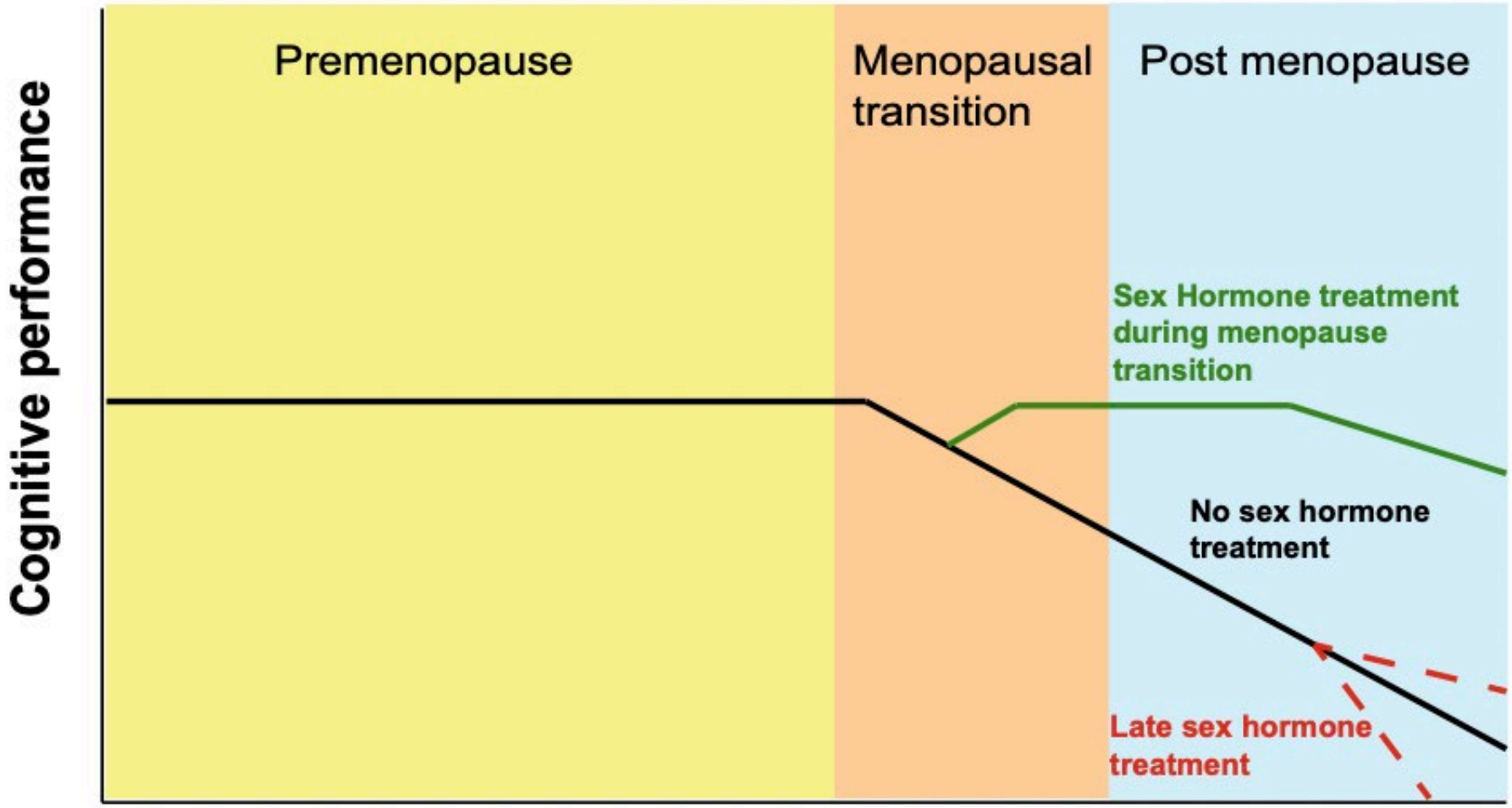
Wang V, et al. F1000 Faculty Rev-68. 2020 Jan 30. doi: 10.12688/f1000research.21599

Metabolic and Immune Signaling



Wang V, et al. F1000 Faculty Rev-68. 2020 Jan 30. doi: 10.12688/f1000research.21599

Cognitive Function in Women



Russell JK, et al. Neurotherapeutics. 2019 Jul;16(3):649-665.

Indications for Hormone Therapy

- Vasomotor symptoms
- Mood
- Anxiety
- Sexual dysfunction
- Cognitive decline
- Healthspan

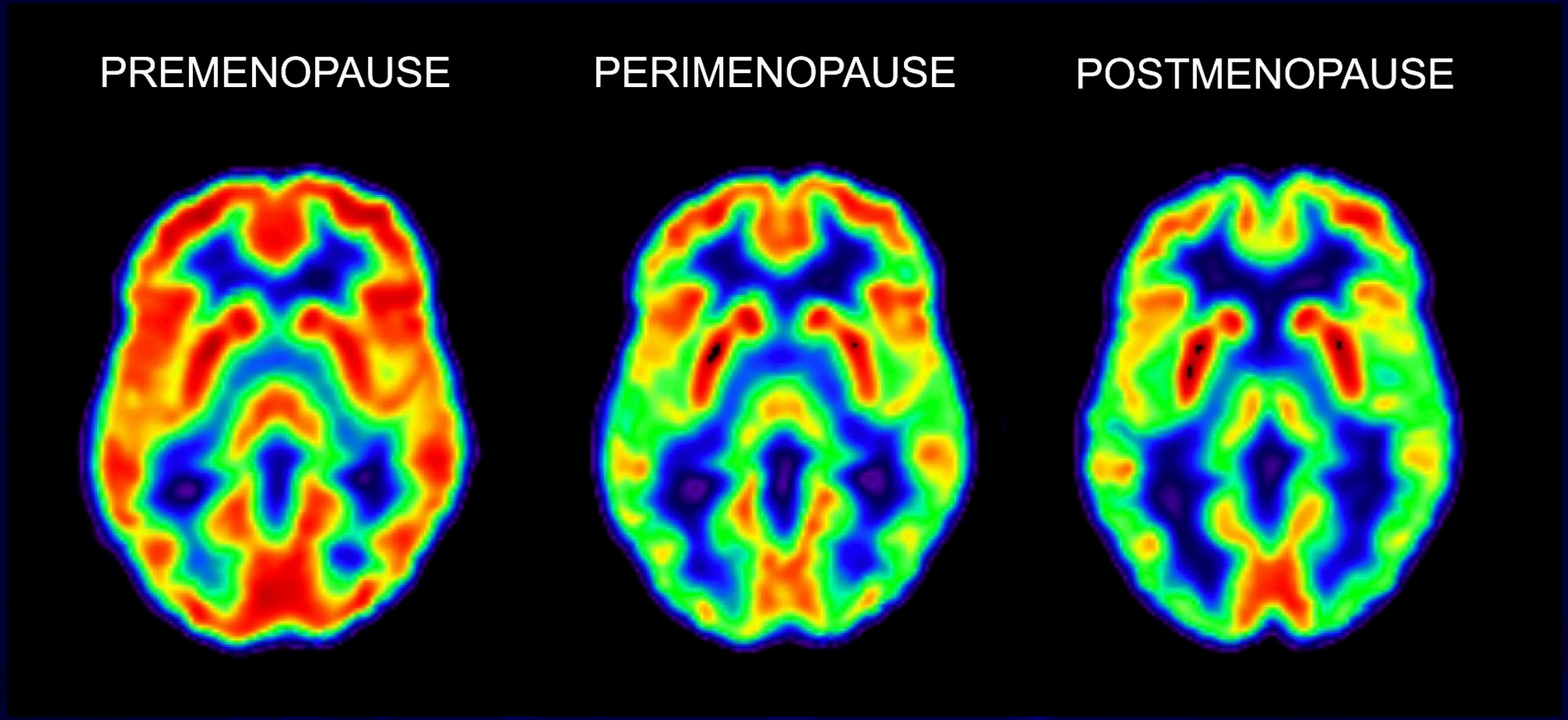
Brain Aging Starts at 40

- Stress ***reduces total brain volume*** in 40s in women only
- Symptoms of perimenopause and menopause associated with cerebral hypometabolism or "low brain energy" at this time
- Brain's use of glucose as fuel begins to falter, leading to a decline in mitochondrial function and difficulty using glucose
- Role of "thyropause"
- Critical window may be shorter (5 years)

*"We found **memory loss** and **brain shrinkage** in relatively young people long before any symptoms could be seen."*
– Dr. Sudha Seshadri, Professor of Neurology, UT, San Antonio

Echouffo-Tcheugui JB, et al. *Neurology* (2018) 91(21):e1961-e1970
Brinton RD et al. Nat Rev Endocrinol. 2015;1(7):393-405; Mosconi L et al. PLoS One. 2017 Oct 10;12(10)

PET Imaging



Mosconi L et al. *PLoS One*. 2017 Oct 10;12(10)

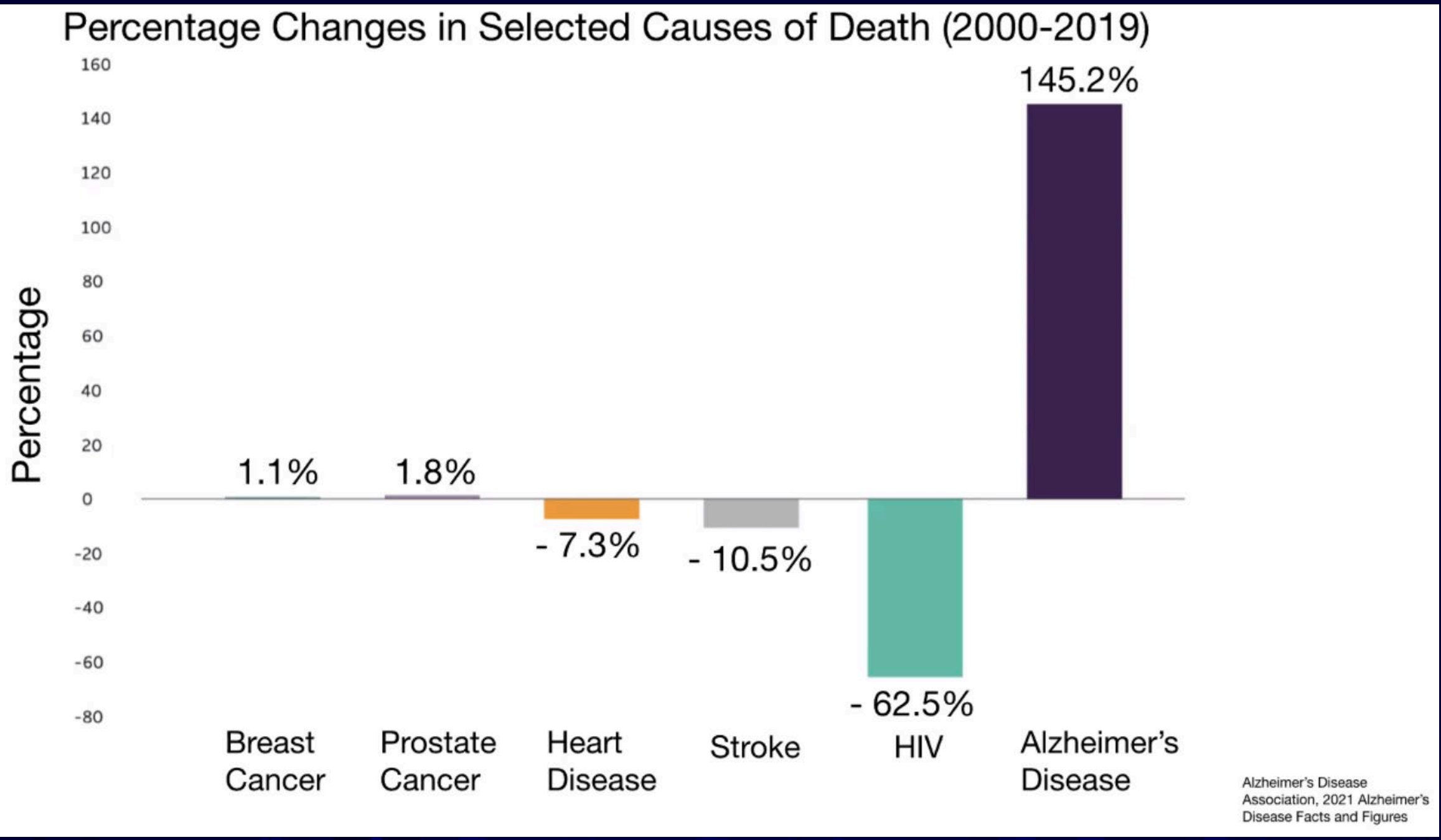
WOMEN AND BRAIN SCIENCE

"If you look at the brain scans of men and women in midlife – say their 40s through their 60s – the women show more plaque, more brain atrophy, reduced connectivity and reduced glucose metabolism. We should not think of dementia as a disease that starts in old age."

DR. LISA MOSCONI

DIRECTOR OF WOMEN'S BRAIN INITIATIVE, WEILL CORNELL MEDICAL COLLEGE

https://www.aarp.org/health/brain-health/global-council-on-brain-health/womens-report/, accessed 5/21/20


Percentage Changes in Selected Causes of Death (2000-2019)
Percentage
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
1.1%
1.8%
- 7.3%
- 10.5%
- 62.5%
145.2%
Breast Cancer
Prostate Cancer
Heart Disease
Stroke
HIV
Alzheimer's Disease
Alzheimer's Disease Association, 2021 Alzheimer's Disease Facts and Figures

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Hormone Therapy for Postmenopausal Women

JoAnn V. Pinkerton, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A healthy 53-year-old nonobese, menopausal woman presents with an 8-month history of menopausal symptoms, noting worsening hot flashes, soaking night sweats, and sleep disruption with fatigue that is affecting her work. Her mother had breast cancer at 75 years of age. Results of a recent mammogram were negative. The patient has heard that hormone therapy may be harmful but worries about functioning at work. How would you advise this patient?

Pinkerton JV. Hormone Therapy for Postmenopausal Women. *N Engl J Med*. 2020 Jan 30;382(5):446-455.

KEY CLINICAL POINTS

HORMONE THERAPY FOR POSTMENOPAUSAL WOMEN

- Women younger than 60 years of age or within 10 years after the onset of menopause who have symptomatic menopausal hot flashes or night sweats are most likely to benefit from hormone therapy.
- For women with early menopause without contraindications, hormone therapy is recommended until at least the average age of natural menopause.
- Observational studies suggest that the risk of thromboembolism and stroke is lower with transdermal therapy than with oral hormone therapy.
- Compounded bioidentical hormone therapies that have not been approved by the Food and Drug Administration are not recommended owing to safety concerns.
- Hormone therapy is not recommended for primary or secondary prevention of coronary heart disease or dementia.
- Nonhormone therapies that have been shown to reduce hot flashes include low-dose selective serotonin-reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, gabapentinoids, weight loss, hypnosis, and cognitive behavioral therapy.
- For women with only genitourinary symptoms, local vaginal hormone therapies are recommended.

Pinkerton JV. Hormone Therapy for Postmenopausal Women. *N Engl J Med.* 2020 Jan 30;382(5):446-455.

RISK/BENEFIT FROM WHI

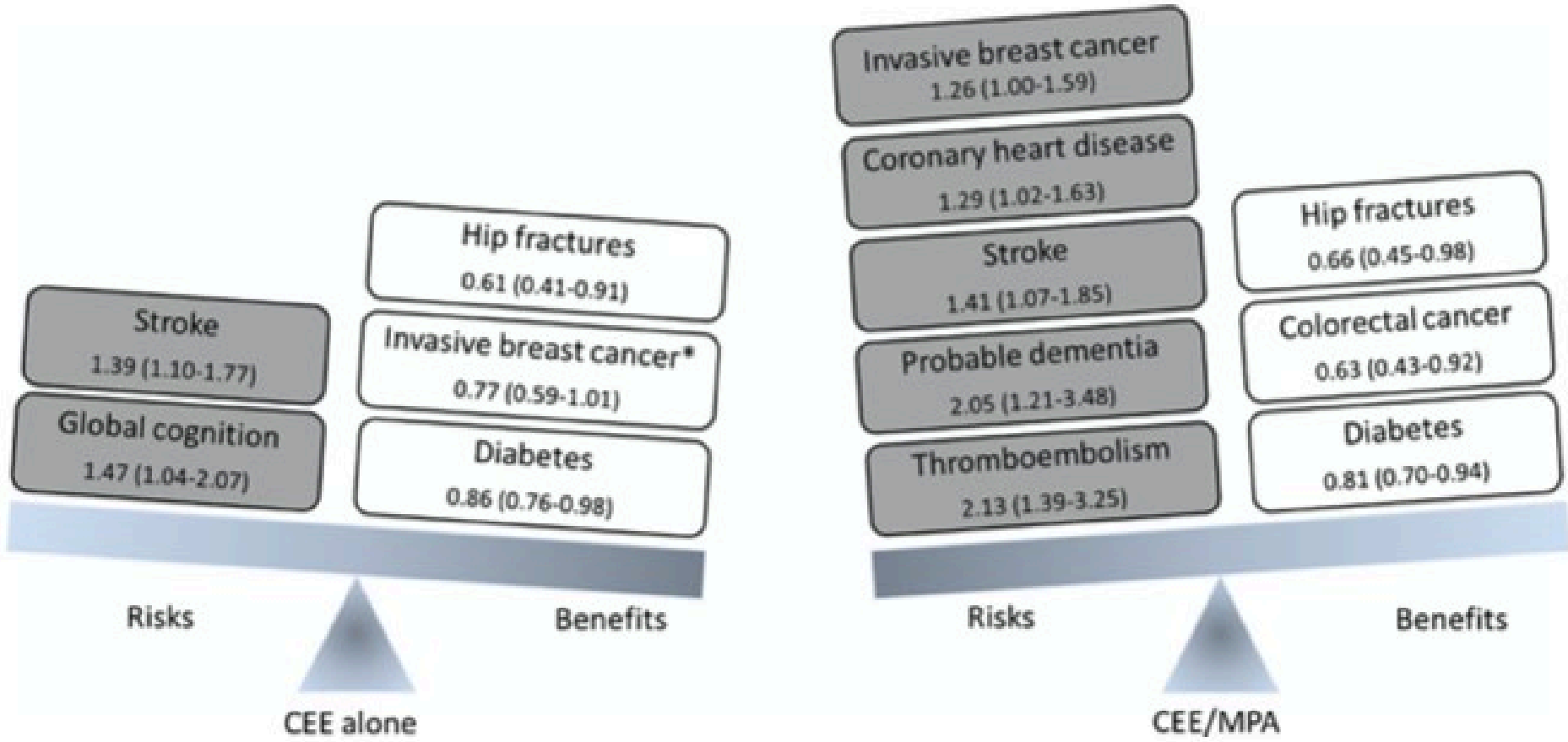
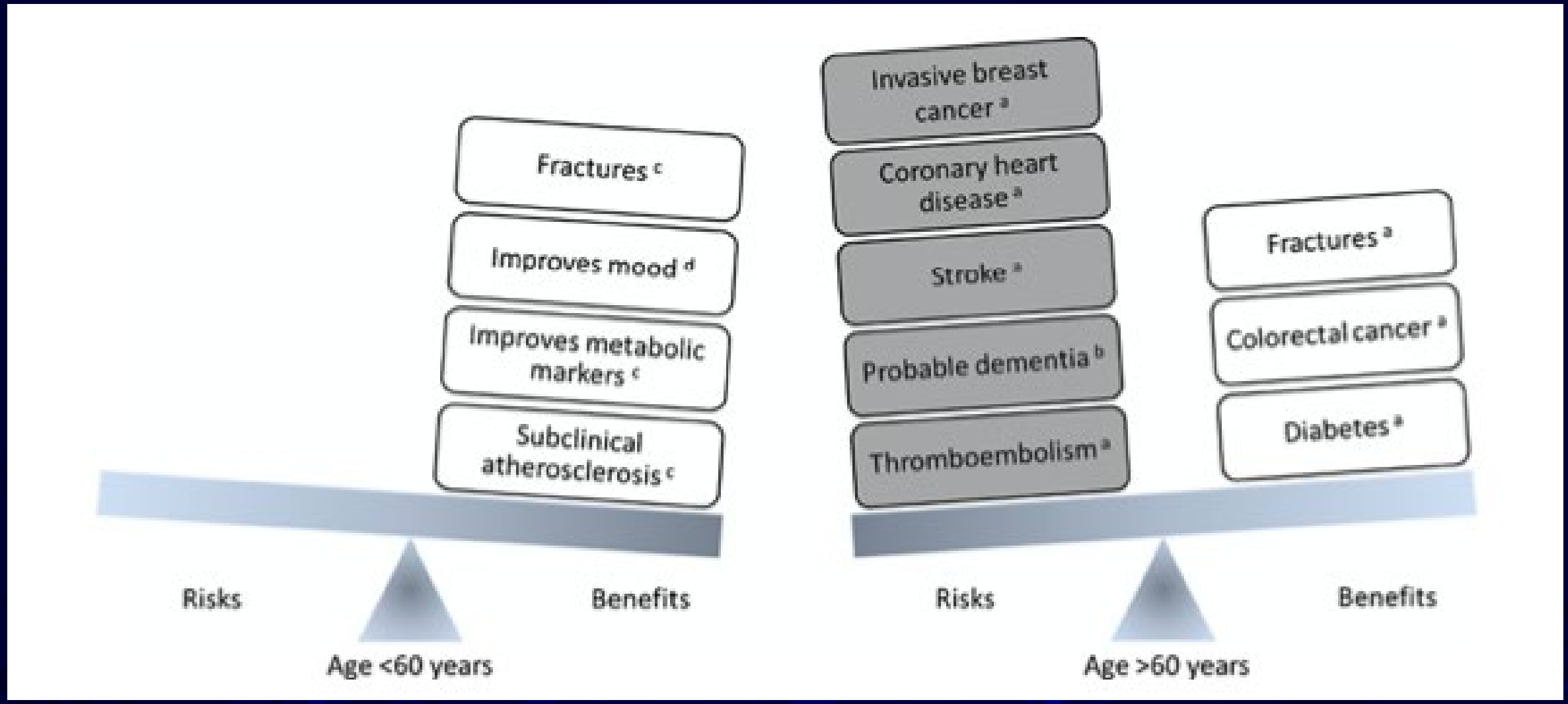


Fig. 1. Risk and benefit balance of CEE alone and CEE/MPA therapy based on early Women's Health Initiative publications (Rossouv et al., 2002; Rapp et al., 2003; Shumaker et al., 2003; Anderson et al., 2004; Espeland et al., 2004); Hazard ratios are shown with 95% confidence intervals; *, near significant trend; CEE, conjugated equine estrogen; CEE/MPA, conjugated equine estrogen plus medroxyprogesterone acetate.

Jay Jay Thaung Zawa, et al. Postmenopausal health interventions: Time to move on from the Women's Health Initiative? *Ageing Research Reviews 48 (2018) 79–86*

Risk/Benefit from WHI



Zawa JJT, et al. Postmenopausal health interventions: Time to move on from the Women's Health Initiative? *Ageing Research Reviews 48 (2018) 79–86*

MENOPAUSAL HORMONE THERAPY + BREAST CANCER

Overview

- **RCTs**
- **Observational studies**
- **Guidelines**
- **How to counsel patients**

Bottom line:

- ***Both estrogen-alone and estradiol-alone decrease breast cancer incidence and mortality*** [1,2,3]
- ***Progesterone is NOT associated with an increased risk of breast cancer based on observational study,[4] but synthetic progestins (medroxyprogesterone, norethisterone and levonorgestrel) do increase risk[5]***

1. Mikkola TS, et al. *Menopause.* 2016; 23(11): 1199-1203.
2. Hodis HN, et al. *Climacteric.* 2018; 21(6): 521-528.
3. Chlebowski RT, et al. *JAMA.* 2020; 324(4): 369-380.
4. Fournier A, et al. E3N-EPIC cohort. Int J Cancer. 2005 114(3):448-54.
5. Vinogradova Y, et al. *BMJ.* 2020 371:m3873

Slide adapted from Doreen Saltiel MD

Hormone Therapy + Breast Cancer

Observational studies discordant with randomized trials[1]

Mainstream colleagues: "The influence of menopausal hormone therapy on breast cancer incidence and breast cancer mortality remains controversial, with discordant findings reported from prospective observational studies[2,3,4] compared with randomized clinical trials." [5,6,7,8]

1. Chlebowski RT, et al. *JAMA.* 2020 324(4):369-380.
2. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 2019;394(10204):1159-1168.
3. Kim S, Ko Y, et al. *Breast Cancer Res Treat*. 2018;170(3):667-675.
4. Beral V, et al. *Lancet*. 2019;394(10204):1139.
5. Chlebowski RT, et al; WHI Investigators. *JAMA*. 2003;289(24):3243-3253.
6. Chlebowski RT, et al. WHI Investigators. *JAMA*. 2010;304(15):1684-1692.
7. Anderson GL, et al. *Lancet Oncol*. 2012;13(5):476-486.
8. Chlebowski RT, et al. *JAMA Oncol*. 2015;1(3):296-305.

Breast Cancer (BC) Studies Summarized

WHI: CEE alone Stefanick, 2006	• CEE 0.625mg/d alone vs placebo • Treatment for 7.2 years • 18 follow-up years	• Typical PMP woman, no previous MHT • Decreased BC incidence, 45% BC mortality reduction
WHI: CEE + MPA Chlebowski, 2003	• CEE 0.625mg/d + MPA 2.5mg/d vs placebo • Treatment for 5.6 years • 18 follow-up years	• Typical PMP woman, no previous MHT ○ Neutral effect on BC incidence and BC mortality • Older PMP woman, who had previously used MHT prior to randomization, those randomized to the placebo arm had a lower BC incidence that all other WHI RCT placebo groups and the WHI-OS comparator group

**WHI 2020 update
Chlebowski, 2020**
	• CEE-alone vs placebo, 7.2 treatment years
	• CEE + MPA vs placebo, 5.6 treatment years
	• 20 follow-up years
		• CEE-alone vs placebo: decreased BC incidence and mortality
		• CEE + MPA: null effect on BC mortality (similar to placebo), but because of faulty analysis that was never corrected, still reporting increased BC incidence (See Hodis and Sarrel WHI 2018 reanalysis)
		  ○ Placebo arm had a lower BC incidence than all other placebo groups in WHI studies
		  ○ CEE + MPA: no SS difference when compared to placebo

WHI: WHI-OS Shufelt, 2018	• CEE 0.625mg/d (18.5 years treated) • CEE < 0.625mg/d (17.4 years treated) • TD E2 dose and delivery unknown (14 years treated) • 8.2-year follow-up study	• PMP women s/p hysterectomy • CEE 0.625mg/d vs CEE < 0.625mg/d: no difference in invasive BC risk • CEE 0.625mg/d vs TD E2: TD E2 with a non-significant decreased BC risk • Time since menopause had no effect on invasive BC risk
FINNISH-OS Mikkola, 2016	• O-E2 1 or 2mg/d • TD E2 0.025-0.1mg/d patches • TD E2 0.5-1.5mg/d gels • Progestins used in PMP women with a uterus • Placebo	• All MHT users (even when combined with a progestogen) had an up to 54% BC mortality reduction • E2-alone had the greatest mortality reduction, regardless of age • Women 50-59 years old had the greatest mortality reduction • With E2 BC mortality 1 in 20 women, whereas without E2 BC mortality 1 in 10 women
Million Women Beral, 2003	• CEE, o-E2, TD E2, pellets: doses unknown • Never users (comparator)	• All increased BC "relative risk" and "relative" mortality risk • Increased BC and BC mortality occurred in women who likely had undiagnosed BC • Comparator group had a lower BC incidence than the general population, skewing the data
E3N-EPIC Fournier, 2005	• Primarily TD E2 • Some used o-E2 • Never users (comparator)	• Increased BC "relative risk" • Data not clean: large percentage in the TD E2-only group used combined therapy and large percentage in the TD E2 + OMP group used a progestin

Slide adapted from Doreen Saltiel MD

HT + BC: WHI in JAMA, 2020

In the trial that evaluated conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA), the increased breast cancer risk observed during a median of 5.6 years of the intervention was followed by a modest attenuation of this elevated risk,[8,9] but a sustained adverse effect on breast cancer risk was observed through 13 years of cumulative follow-up.[8,11]

In the CEE-alone trial, breast cancer risk reduction seen with a median of 7.2 years of the intervention was sustained through 13 years of cumulative follow-up.[11]

Chlebowski RT, et al. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA. 2020 Jul 28;324(4):369-380.

HT + BC: WHI in JAMA, 2020

- 10,739 women with prior hysterectomy
- 238 new cases breast cancer in women randomized to CEE (0.3%)
- 296 new cases placebo (0.37%)
- HR 0.78 (p=0.005)
- CEE associated with lower mortality from breast cancer: 30 vs 46 deaths (0.031% vs 0.046%, HR 0.60)—this has NOT been shown with other hormonal treatments for breast cancer such as tamoxifen or aromatase inhibitors

Chlebowski RT, et al. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA. 2020 Jul 28;324(4):369-380.

HT + BC: WHI in JAMA, 2020

- 16,608 women with intact uterus
- 584 new cases breast cancer randomized to CEE/MPA (0.45%)
- 447 new cases placebo (0.36%)
- HR 1.28 ($p<0.001$)
- Mortality from breast cancer not different 0.045% vs 0.035%

Chlebowski RT, et al. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA. 2020 Jul 28;324(4):369-380.

WHI Misinterpretation Continues…

"…any association that may exist between HT and BC appears to be rare and no greater than any other medications commonly used in clinical medicine."[1]

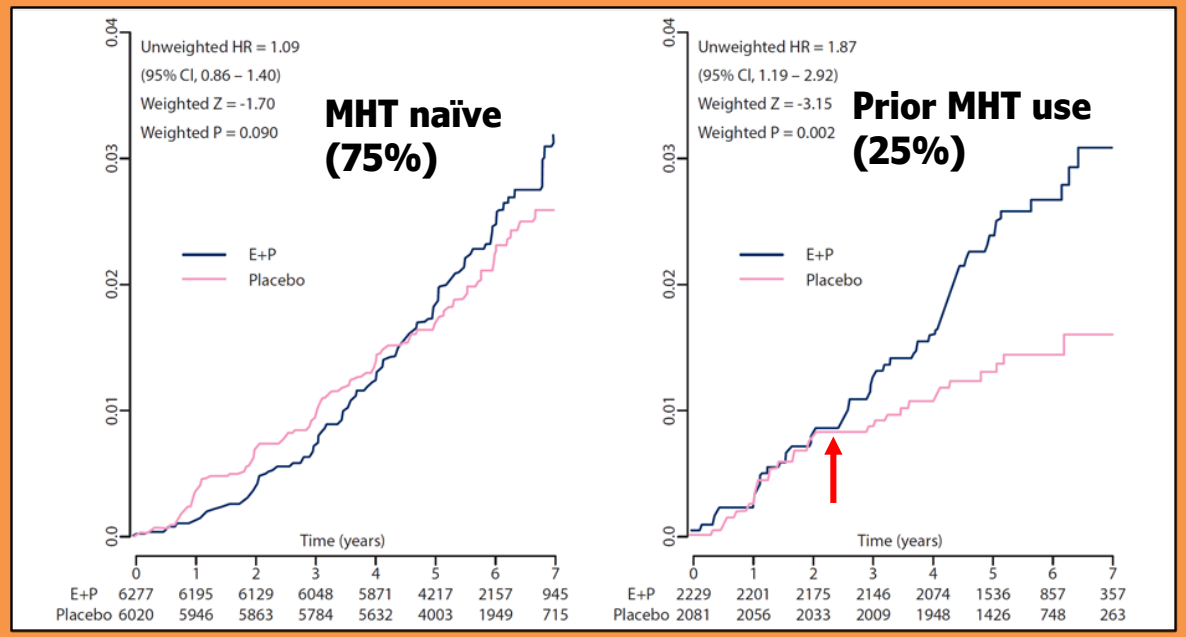
E/E2 therapy decreases BC incidence and BC mortality[2]

- WHI study: only 10% women were 50-54 years old, was NOT a BC trial
- CEE-alone vs placebo (WHI):
  - After 20 follow-up years, CEE-alone decreased both BC incidence and BC mortality (45% BC mortality reduction); median treatment 7.2 years
- CEE + MPA vs placebo (WHI):
  - In the hormone naïve group vs placebo (75%): no difference in BC incidence
  - In the prior treatment arm vs placebo (25%): falsely reported higher BC incidence, when actually the divergent curves were due to an unusually low placebo group BC incidence (not an increased BC incidence in the treatment arm); null effect on BC incidence; median treatment 5.6 years

Slide adapted from Doreen Saltiel MD

WHI: CEE + MPA

1



2

Subgroups	CEE + MPA Clinical Trial Placebo Group Annualized % Events	WHI-OS Hormone Therapy Non-Users Annualized % Events
No prior MHT use	0.36	0.35
Prior MHT use	0.25	0.38

3

Subgroup	CEE + MPA Clinical Trail CEE + MPA Group Annualized % Events	Dietary Modification Trial Low Fat Diet Group Annualized % Events	Dietary Modification Trial Usual Diet Group Annualized % Events
CEE + MPA overall	0.43	0.42	0.45

Adapted from Hodis HN, et al. Climacteric. 2018; 21(6): 521-528.

1. WHI + CEE vs Placebo Trial

- Mean age 63.3, 12-years since menopause
- Stratified by prior hormone use
- Similar trends for all subgroups except prior MHT placebo arm
  - MHT prior use placebo arm: sharp divergence without explanation
- This divergent trend line leads to false impression that treatment arm has higher BC incidence
- Elevated HR due to DECREASED BC incidence in PLACEBO treated women

2. Comparison of BC incidence rates between WHI-RCT and WHI-OS CEE + MPA vs Placebo

- Marked difference in prior MHT placebo arm when compared to RCT no prior use placebo arm + WHI-OS equivalent

3. CEE + MPA RCT Treatment Arm Overall vs Dietary Modification (DM) – BC was a primary outcome

- BC incidences = across all 3 groups

Hodis HN, et al. Climacteric. 2018; 21(6): 521-528.

Slide adapted from Doreen Saltiel MD

PEPI Trial: Mammographic Density

N=571 women, aged 45-64, baseline and 12-month mammo

Mammographic density

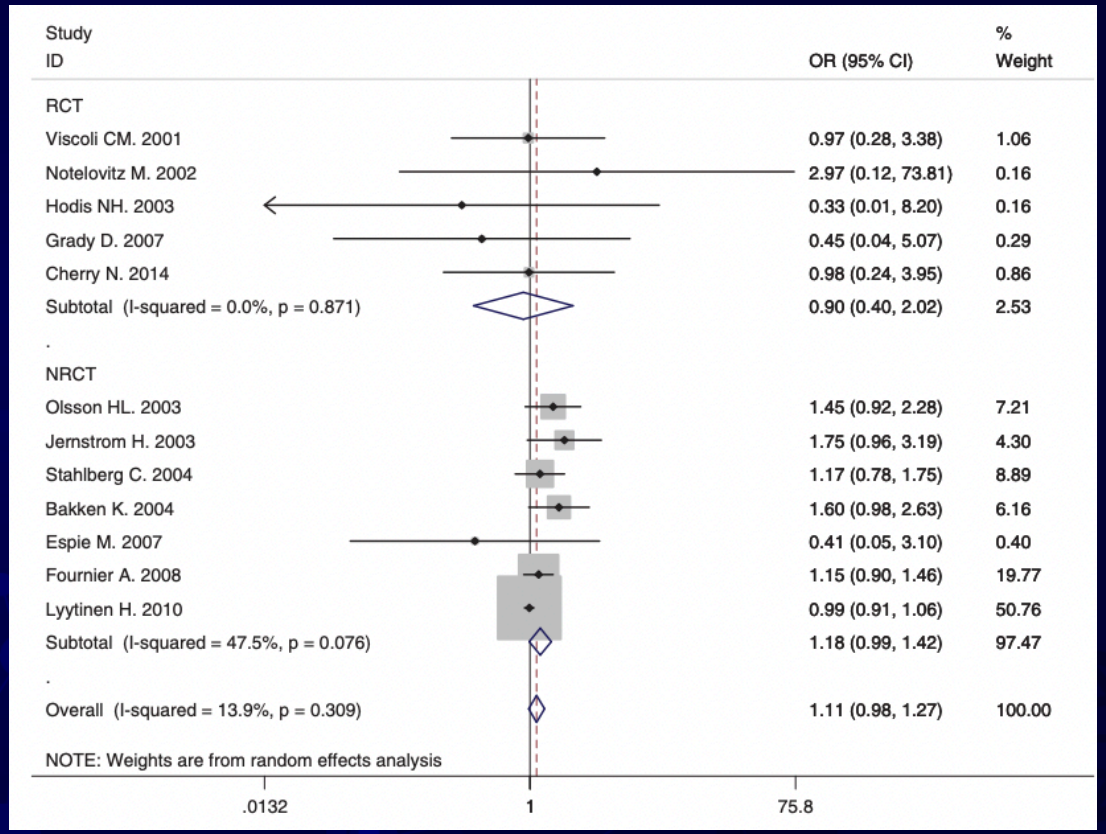
- CEE/MPA only 1.34%
- CEE/MPA cyclic -4.76%
- CEE/MPA continuous -4.58%
- Placebo -0.07%

Conclusion: CEE/MPA but not CEE alone was associated with increased mammographic density. The change in breast cancer risk remains unknown.

Greendale GA, et al.. Postmenopausal Hormone Therapy and Change in Mammographic Density, *JNCI: Journal of the National Cancer Institute*, Volume 95, Issue 1, 2003, Pages 30–37.

Estradiol-only Therapy and BC Risk

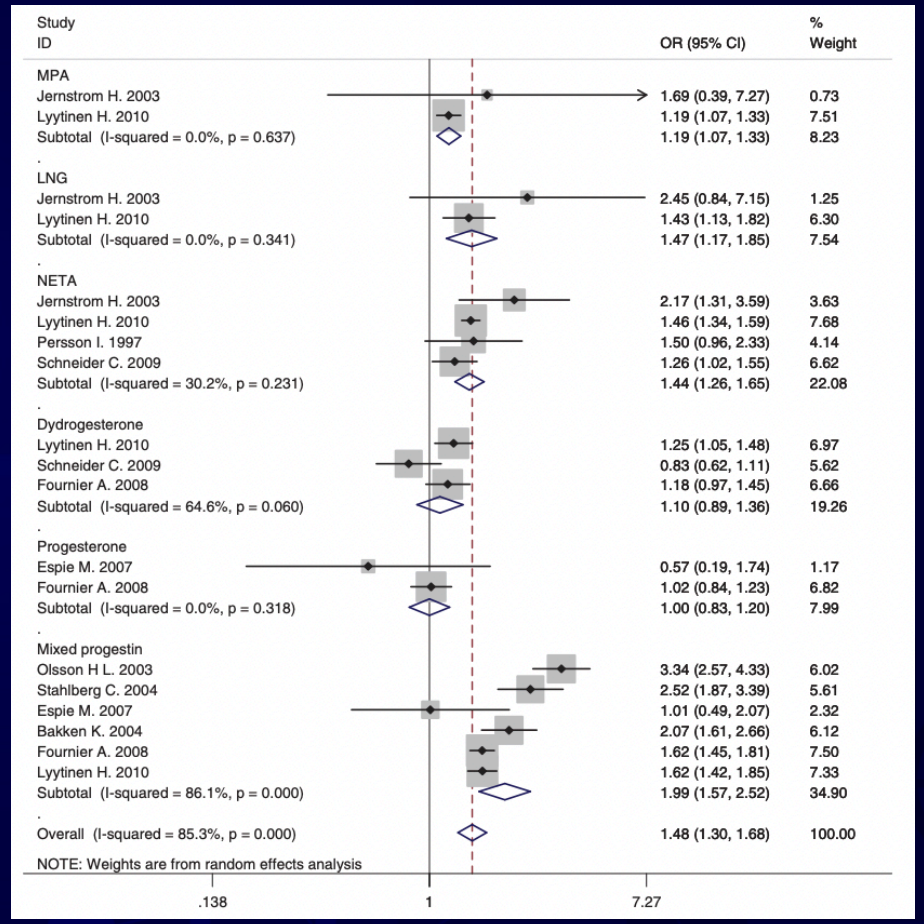
- 5 RCTs
- 7 Observational studies
- Meta-analysis of these 12 studies results in nonsignificant OR 1.11 (0.98-1.27) suggesting heterogeneity among studies



Yang Z, et al. Gynecological Endocrinology Volume 33, 2017 - Issue 2

Estradiol-Progestogen Therapy and BC Risk

- 9 Observational studies
- Grouped by types of progestogen: MPA, norethisterone acetate (NETA), levonorgestrel (LNG), dydrogesterone, progesterone, and mixed
- Overall OR 1.48 (1.30-1.68) with heterogeneity among studies
- No significant increased risk in dydrogesterone or progesterone group



Yang Z, et al. Gynecological Endocrinology Volume 33, 2017 - Issue 2

Duration and type of Regimen of Estradiol-Progestogen Therapy and BC Risk

- 5 cohort studies and 2 case control studies provided estimates on duration
- We divided the therapeutic duration into ‘‘<5 years’’ and ‘‘>=5 years’’ groups.
- Because of insufficient data, failed to estimate the exposure duration of different progestogen.
- Using estradiol-progestogen therapy less than 5 years results an overall pooled ORn1.39, 95% CI (1.09, 1.78)
- Estradiol progestogen therapy for more than 5 years results a higher pooled OR 2.25, 95% CI (1.82, 2.80)
- All analyses are heterogeneous

- Type of regimen: 4 cohort studies and 1 case-control study provided data by sequential or continuous therapy groups.
- Meta-analysis shows statistically increase of breast cancer risk in both treatment groups.
- Sequential estradiol-progestogen overall OR 1.76, 95% CI (1.28, 2.42).
- Continuous estradiol-progestogen therapy OR 2.90, 95% CI (1.82, 4.61), which presents an increase of breast cancer risk compared with sequential therapy

Yang Z, et al. Gynecological Endocrinology Volume 33, 2017 - Issue 2

What About Bioidentical MHT?

Observational studies with BC as outcome

- Fournier, 2005
- Fournier, 2008
- Mikkola, 2016
- Stute, 2018 (Meta-Analysis)
- Brusselaers, 2018

One RCT of breast effects of E2 + P4

Fournier A, et al. E3N-EPIC cohort. Int J Cancer. 2005 Apr
Mikkola TS, et al. Menopause. 2016; 23(11): 1199-1203.
Stute P, et al. *Climacteric.* 2018 Apr;21(2):111-122

Breast Effects of Oral E2 + P4

N=300, placebo=100 women age 40-65 with moderate to severe VMS were randomized 1:1:1:1:1 to five groups

- Oral TX-001HR doses of 1 mg E2/100 mg P4
- 0.5 mg E2/100 mg P4
- 0.5 mg E2/50 mg P4
- 0.25 mg E2/50 mg P4
- Placebo for 12 months

Liu JH, et al. *Menopause* 2020 Dec;27(12):1388-1395.

Breast Effects of Oral E2 + P4

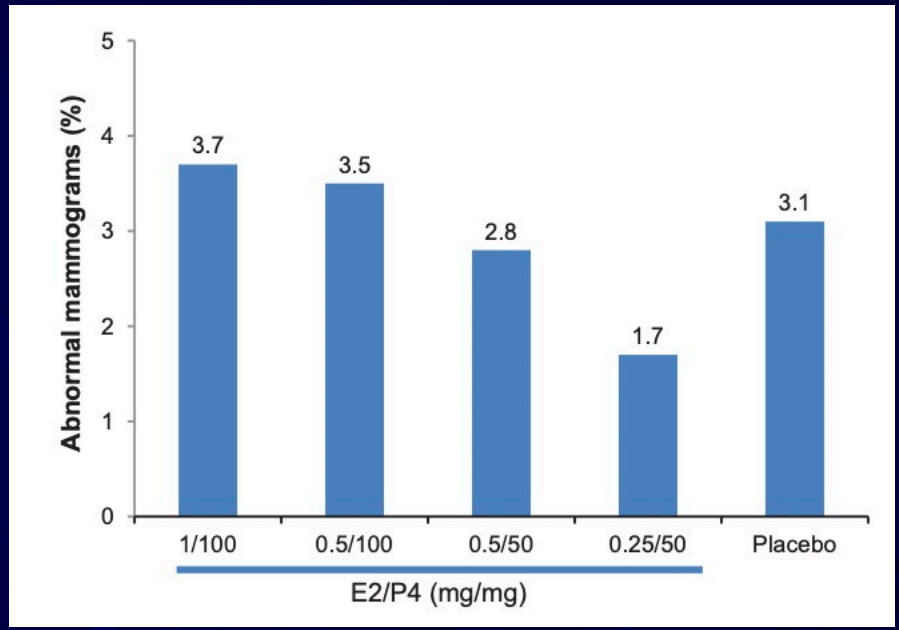
Baseline 8 (0.4%) of mammograms abnormal (BIRADS 3 or 4)

1 year: 39 (2.9%) abnormal

Breast cancer incidence 0.36% with active doses and 0% with placebo

Breast tenderness 2.4-10.8% with BHRT, 0.7% with placebo

- "E2/P4 may not be associated with increased risk of abnormal mammograms versus placebo, and the incidence of breast tenderness was low relative to most of the rates reported in other studies using hormone therapy."



Liu JH, et al. *Menopause* 2020 Dec;27(12):1388-1395.

Estradiol Lowers BC Mortality

Reduced risk of breast cancer mortality in women using postmenopausal hormone therapy: a Finnish nationwide comparative study

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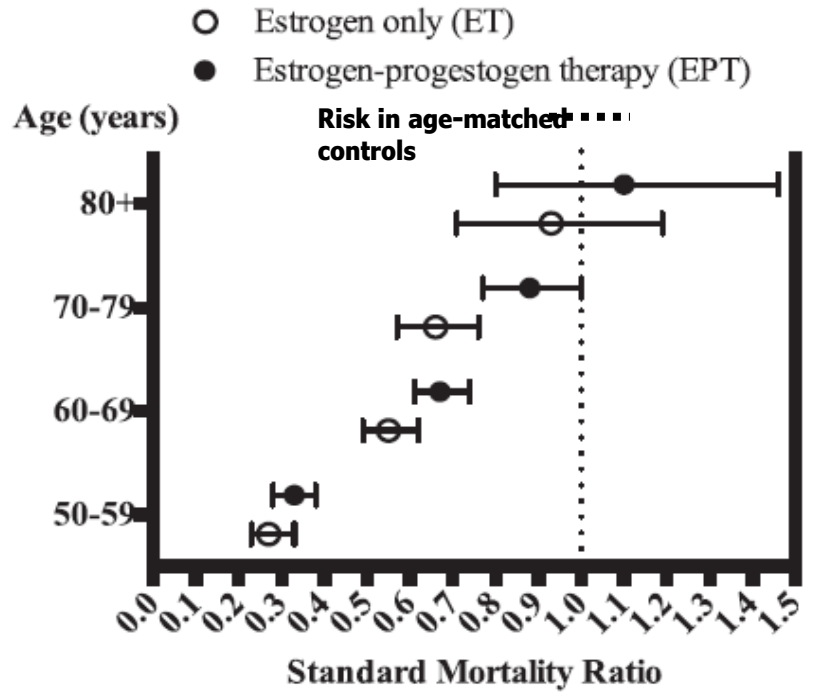

- Objective: To determine whether E2-alone or E2 combined with a progestin preceding a BC diagnosis would affect BC mortality
- Study: 15-year observational study using the Finnish Database
  - 489,105 PMP women mean age 52 years, mean MHT exposure: 6.8 ± 6.0 years, from 1994-2009, followed from HT initiation to BC death (n=1578)
  - E2 formulations: o-E2 1-2mg/d, TD E2 patch 0.025mg-0.1mg/d or TD E2 gel 0.5mg-1.5mg/d
  - Progestins: norethisterone acetate (43%), MPA (30%), dydrogesterone (13%)
- Results: when compared to age-matched controls
  - E2-based HT was associated with an up to 54% BC mortality reduction
    - Women 50-59 had the greatest BC mortality reduction: 67%
    - Overall E2-alone: 44-51% SS mortality reduction, regardless of duration, and a greater mortality reduction than EPT use
    - Overall EPT: 32-50% SS mortality reduction, regardless of duration
  - Risk not related to MHT duration or age at onset
- Conclusion: O-E2, TD E2 patches, and TD E2 gels SS decreased BC mortality up to 54%
  - Even when MHT use was > 10 years
  - Largest mortality reduction was at 5-10 years, in women 50-59, and in those using E2-alone
  - Age at initiation not related to BC mortality
  - **Whereas 1:10 women die from BC in the general population, 1: 20 MHT users die from BC, a 50% mortality reduction**

Mikkola TS, et al. Menopause. 2016; 23(11): 1199-1203.

Slide adapted from Doreen Saltiel MD

HT + BC: Observational Studies E3N-EPIC

- Assessed risk of breast cancer associated with HRT in 54,548 women who had never taken any HRT 1 year before entering the E3N-EPIC cohort study (mean age at inclusion: 52.8 years)
- 948 invasive breast cancers during follow-up (mean duration: 5.8 y)
- In this cohort where the mean duration of HRT use was 2.8 years, an increased risk in HRT users compared to nonusers was found (relative risk (RR) 1.2 (95% Confidence Interval 1.1-1.4)
- RR was nonsignificant 1.1 [0.8-1.6] for estrogens used alone and 1.3 [1.1-1.5] when used in combination with oral progestogens.

Fournier A, et al. E3N-EPIC cohort. Int J Cancer. 2005 114(3):448-54.

HT + BC: Observational Studies E3N-EPIC

- Risk significantly greater ($p < 0.001$) with HRT containing synthetic progestins vs. micronized progesterone RR 1.4 [1.2-1.7] and 0.9 [0.7-1.2], respectively.
- When combined with synthetic progestins, both oral and transdermal/ percutaneous estrogens associated with a significantly increased risk; for transdermal/percutaneous estrogens, even when exposure < 2 years.
- Our results suggest that, when combined with synthetic progestins, even short-term use of estrogens may increase breast cancer risk
- Micronized progesterone may be preferred to synthetic progestins in short-term HRT. This finding needs further investigation.

Fournier A, et al. E3N-EPIC cohort. Int J Cancer. 2005 114(3):448-54.

HT + BC: E3N-EPIC Follow up

- N=80,377, 40-65, followed 8.1 years, 2354 breast cancers
- 99% used transdermal estrogen
- Breast cancer risk highest in group that took synthetic progestins RR 1.69 (1.50–1.91)
- Estrogen only group had increased RR 1.29 (1.02-1.65)
- Group that took transdermal estrogen and micronized progesterone had NO INCREASED RISK of breast cancer compared to controls who never took hormones RR 1.00 (0.83-1.22)

Fournier, Breast Cancer Res Treat. 2008 Jan; 107(1): 103–111.

Micronized Progesterone (MP) and BC Risk: A Systematic Review

- Estrogens combined with oral (approved) or vaginal (off-label use) micronized progesterone do not increase breast cancer risk for up to 5 years of treatment duration;
- There is limited evidence that estrogens combined with oral micronized progesterone applied for more than 5 years are associated with an increased breast cancer risk;
- Counseling on combined MHT should cover breast cancer risk - regardless of the progestogen chosen.

Yet, women should also be counseled on other modifiable and non-modifiable breast cancer risk factors in order to balance the impact of combined MHT on the breast.

Stute P, et al. *Climacteric.* 2018 Apr;21(2):111-122.

RCTs: MHT with MP and Breast Density

Author (year)	Study design	Sample size, mean age (years) and BMI (kg/m^2) of the participants	Study duration	Treatment arms: Dosage and application regimen	Breast density assessment	Change in mammographic density
Greendale (1999)[9]	PC-RCT (PEPI substudy)	307 postmenopausal women, age 59.2 ± 4.2, BMI 27.1 ± 4.9	3 years	I. o-CEE 0.625 mg/day; II. o-CEE 0.625 mg/day + o-MPA 10 mg/day for 12 days/month; III. o-CEE 0.625 mg/day + o-MPA 2.5 mg/day; IV: o-CEE 0.625 mg/day + o-MP 200 mg/day for 12 days/month; V. Placebo	BI-RADS grades	% of women whose MD increased by at least one BI-RADS grade from baseline to 12 months: I. CEE 3.5 (95% CI 1.0–12.0); II. CEE + seqMPA 23.5 (95% CI 11.9–35.1); III. CEE + conMPA 19.4 (95% CI 9.9–28.9); IV. CEE + seqMP 16.4 (95% CI 6.6–26.2); V. Placebo 0.0 (95% CI 0.0–4.6); all MD increases were increases of one grade. Adjusted ORa for MD increase from baseline to 12 months: CEE vs. CEE + seqMPA OR 13.1 (95% CI 2.4–73.3; $p = 0.003$); CEE vs. CEE + conMPA OR 9.0 (95% CI 1.6–50.1; $p = 0.012$); CEE vs. CEE + seqMP OR 7.2 (95% CI 1.3–40.0; $p = 0.024$); no significant differences between EPT groups
Greendale (2003)[10]	PC-RCT (PEPI substudy)	571 postmenopausal women, age 56.0 ± 4.3, BMI 26.2 ± 4.5	12 months	I. o-CEE 0.625 mg/day; II. o-CEE 0.625 mg/day + o-MPA 10 mg/day for 12 days/month; III. o-CEE 0.625 mg/day + o-MPA 2.5 mg/day; IV: o-CEE 0.625 mg/day + o-MP 200 mg/day for 12 days/month; V. Placebo	Computer-assisted method	Mean change in mammographic percent density from baseline to 12 months[b]: V. Placebo −0.07% (95% CI −1.50–1.38%; p = n.s.); I. CEE 1.17% (95% CI -0.28–2.62%; $p = 0.241$); II. CEE + seqMPA 4.76% (95% CI 3.29–6.23%; $p \leq 0.001$); III. CEE + conMPA 4.58% (95% CI 3.19–5.97%; $p < 0.001$); IV. CEE + seqMP 3.08% (95% CI 1.65–4.51%; $p = 0.002$); no significant differences between EPT regimens
Crandall (2006)[11]	PC-RCT (PEPI substudy)	533 out of 875 postmenopausal women, age 56.1 ± 4.3, BMI 26.0 ± 4.5	12 months	I. o-CEE 0.625 mg/day; II. o-CEE 0.625 mg/day + o-MPA 10 mg/day for 12 days/month; III. o-CEE 0.625 mg/day + o-MPA 2.5 mg/day; IV: o-CEE 0.625 mg/day + o-MP 200 mg/day for 12 days/month; V. Placebo	Computer-assisted method	Mean 12-month change in percent breast density from baseline[c]: V. Placebo -0.4%; I. CEE 0.9% ($p = 0.25$); II. CEE + seqMPA 4.6% ($p = 0.003$); III. CEE + conMPA: 4.4% ($p < 0.001$); IV. CEE + seqMP 3.1% ($p < 0.001$); no significant differences between EPT regimens ($p = 0.68$); the demonstrated association between incident breast discomfort and increased percent breast density was similar in all active treatment arrns
Pettersen (2008)[13]	*Post-hoc* analysis of two PC-RCTs	Nasal MHT trial: 267 postmenopausal women; oral MHT trial: 89 postmenopausal women	2 years	Nasal MHT trial: group 1, nasal E2 150 µg/day + MP 200 mg/day on 14 days/month (route of application not reported); group 2, nasal E2 300 µg/day + MP 200 mg/day on 14 days/month; group 3, placebo. Oral MHT trial: group 1, trimegestone 0.125 mg/day (+ calcium 500 mg/day + vitamin D 400 IU/day); group 2, placebo	BI-RADS grades; computer assisted methods	Nasal MHT trial: no significant difference between baseline and after 2 years, no difference between placebo and MHT Oral MHT trial: significant increase in EPT vs. baseline and placebo ($p < 0.05$)
Lee (2012)[12]	PC-RCT (PEPI substudy)	210 postmenopausal women randomized to EPT with baseline and at least one follow-up mammogram, serum samples at baseline and 12 months, age 56.1 ± 4.3, BMI 26.2 ± 4.5	12 months	I. o-CEE 0.625 mg/day; II. o-CEE 0.625 mg/day + o-MPA 10 mg/day for 12 days/month; III. o-CEE 0.625 mg/day + o-MPA 2.5 mg/day; IV. o-CEE 0.625 mg/day + o-MP 200 mg/day for 12 days/month; V. Placebo	Computer assisted method	In all EPT arms combined (II–IV), increases of serum progestogen in the highest quartile were associated with 3.5% higher MD ($p = 0.046$) compared to increases in lowest quartiled; no strong indication that genetic variations in PGR had an impact on MD or modified impact of serum progestogen levels
Murkes (2012)[14]	RCT	77 postmenopausal women, age 44–66 years, BMI 18–30	2 months	Group 1: o-CEE 0.625 mg/day + o-MPA 5 mg/day for 14 days per 28 days per cycle; Group 2: t-E2 gel 1.5 mg/day + o-MP 200 mg/day for 14 days per 28 days per cycle	BI-RADS grades	BI-RADS grades increase of at least one BI-RADS grade: group 1, CEE + seqMPA 18.9% ($p = 0.01$); group 2, t-E2 + seqMP 6.3% (p = ns)

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RCTs: MHT with MP and Breast Biopsies

Author (year)	Study design	Sample size (recruited/analyzed), age (years), BMI (kg/m^2)	Study duration	Treatment arms: dosage and application regimen	Breast biopsy	Results
Chang (1995)[16]	PC-RCT	34/33 premenopausal women, age 18–45	11–13 days (start at CD 1)	I. Topical MP 25 mg/day; II. Topical E2 gel 1.5 mg/day; III. Topical E2 gel 1.5 mg/day + topical MP 25 mg/day; IV. Placebo	Surgery for removal of lump at CD 11–13 (macroscopically normal sample taken 1 cm away from the lump)	*Proliferation* Mitotic index = mitosis per 1000 cells: I. MP 0.17 ± 0.19; II. E2 0.83 ± 0.42 ($p < 0.05$ vs. I.); III. MP + E2 0.52 ± 0.42; IV. Placebo 0.51 ± 0.24 PCNA labeling index: I. MP 1.9 ± 0.5%; II. E2 17.4 ± 6.4% ($p < 0.05$ vs. IV); III. MP + E2 6.5 ± 4.4% ($p < 0.05$ vs. I.); IV. Placebo 7.8 ± 4.8%
Foidart (1998)[17]	PC-RCT	44/40 postmenopausal women, age 47–80, mean BMI 23.6–26.5	14 days	I. Topical MP 25 mg/day; II. Topical E2 gel 1.5 mg/day; III. Topical E2 gel 1.5 mg/day + topical MP 25 mg/day; IV. Placebo	Surgery for removal of lump on study day 15 (macroscopically normal sample taken 5 cm away from lump)	*Proliferation* Mitotic index = mitosis per 1000 cells: I. MP 0.19 ± 0.25; II. E2 0.6 ± 0.2 ($p < 0.05$ vs. group I, III and IV); III. 0.2 ± 0.15; IV. 0.15 ± 0.2 PCNA labeling index: I. MP 1.5 ± 0.6% ($p < 0.001$ vs. IV.); II. E2 11.5 ± 2.3% ($p < 0.001$ vs. I, III, IV); III. MP + E2 1.3 ± 1.1% ($p < 0.05$ vs. IV); IV. Placebo 0.1 ± 0.1%
Murkes (2011)[15], (2012)[14]	RCT	77/71 postmenopausal women, age 44–66, BMI 18–30	2 months	I. o-CEE 0.625 mg/day + o-MPA 5 mg/day for 14 days per cycle; II. t-E2 gel 1.5 mg/day + o-MP 200 mg/day for 14 days per cycle	Core needle biopsy (upper outer quadrant of left breast) at baseline and at end of second treatment cycle	*Proliferation* Mean Ki67/MIB positive cells (range in %): I. oCEE + o-seqMPA at baseline 1% (0–4), after 2 months 10% (0–56) ($p = 0.003$); II. t-E2 + o-seqMP at baseline 3.1% (0–21.5), after 2 months 5.8% (0–39) (n.s.) *Apoptosis* Mean Bcl-2-positive cells (range in %)[a]: I. o-CEE + o-seqMPA baseline 46% (0–90), after 2 months 27% (0–80) (n.s.); II. t-E2 + o-seqMP baseline 49% (0–100%), after 2 months 26% (0–80) ($p = 0.06$) *Microarray analysis* I. o-CEE + o-seqMPA: 2500 altered genes (fold change ≥1.5); II. t-E2 + o-seqMP: 300 altered genes (fold change ≥1.5); I + II. 300 commonly altered genes
Söderqvist (abstract)[6]	RCT in healthy postmenopausal women	77/8 (microarray) and 30 (rtPCR)	2 months	Group 1: o-MPA 5 mg/day on 14 days out of 28 days per cycle; group 2: o-MP 200 mg/day on 14 days out of 28 days per cycle	Group 1: o-CEE 0.625 mg/day; group 2: t-E2 gel 1.5 mg/day Core needle biopsy (upper outer quadrant of left breast) at baseline and at end of second treatment cycle; endpoints: microarray analysis and rtPCR of 16 genes	*Microarray analysis* 225 genes involved in mammary tumor development (group 1: $n = 198$, group 2: $n = 34$); rtPCR: MKi-67: group 1 significant increase from baseline to study end (group 2 n.s.); PRL and bcl-2: group 2 significant decrease from baseline to study end (group 1 n.s.)

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RCTs: MHT with MP and Breast Cancer

Author (year)	Study design	Sample size; cohort characteristics	Study duration/follow-up, duration of MHT use	Reproductive stage; age of participants	Progestogen dosage; application regimen	Estrogen dosage; application regimen	Endpoints	Results
De Lignières (2002)[18]	Cohort study	3175 women with ≥1 year of follow-up; 1739 MHT users (systemic ET for ≥1 year), 1545 EPT users (89%)	Follow-up: mean 8.9 (range 1–24) years	Postmenopause (or ≥50 years); mean age 50 (range 20–59) years	MHT regimen and dosage not specified; EPT users: 58% MP, 10% DYD, 32% other progestogens (promegestone, lynestrenol, CMA, NOMAC, MPA) < 3%	Dosage not specified; EPT users: 83% t-E2 gel, 17% t-E2 patch, o-E2 or o-CEE	I. BC incidence during follow-up or since menopause; II. SIR; III. Relative risk for BC by Cox's proportional hazards regression; IV. Risk for BC according to duration of use	I. 105 women with BC (43 MHT nonusers, 59 EPT, 3 ET users); II. SIR (95% CI): nonuser 1, EPT 1.19 (0.81–1.79); III. RR[a] (95% CI): nonuser: 1, EPT 1.1 (0.73–1.66); IV: no significant increase in RR[b] with the duration of MHT use (≥10 years: RR 1.15 (95% CI 0.64–2.05))
Espié (2007)[8]	Prospective cohort study (MISSION)	4949 women; 2693 with MHT exposure (current systemic MHT use or MHT stop ≤5 years ago), 2256 with MHT non-exposure (never MHT use or stop >5 years ago), 31.2% MHT use >10 years	Mean follow-up 2.5 years; mean MHT duration 8.3 ± 5.3 years	Postmenopause; mean age 60.6 ± 6.3 years (MHT exposure) and 64.2 ± 8.3 years (MHT non-exposure)	MHT regimen and dosage not specified; EPT users: 43.7% MP, 56.3% synthetic progestogens (excluding MPA and 19-nortestosterone derivatives)	Dosage not specified; E2 alone 13.3%; ET and EPT: 77.7% t-E2, 22.3% o-E2	I. BC incidence; II. RR for BC compared with MHT non-exposure by Mann–Whitney test; III. RR according to MHT duration; IV. RR according to MHT type	I. 17/2662 women with BC in MHT-exposed group, 14/2004 women with BC in MHT non-exposed group; II. non-adjusted $RR_{exposed/non-exposed}$ 0.94 (95% CI 0.449–1.858); III. non-adjusted $RR_{\leq 5\ yrs\ >5yrs.}$ 1.23 (95% CI 0.45–3.35); IV. E2 alone: non-adjusted RR 0.40 (95% CI 0.05–3.00); E2 + synthetic progestogen non-adjusted RR 1.00 (95% CI 0.48–2.07); t-E2 + MP non-adjusted RR 1.07 (95% CI 0.50–2.27); o-E2 + synthetic progestogen non-adjusted RR 0.81 (95% CI 0.23–2.85)
Fournier (2005)[19]	Prospective cohort study (E3N)	54 548 women; 29 420 incident MHT users (systemic MHT ≥1 year but not prior to baseline)	Mean 5.8 (range 0.1–10.6) years; mean MHT duration 2.8 (range 2.4–3.1) years	Postmenopause; mean age 52.8 (range 40–66.1) years	MHT regimen and dosage not specified; main use[c] of oral progestogen in MHT users (EPT 83.3%): MP 20.1%, progesterone derivatives (retroprogesterone, pregnane, norpregnane derivatives) (main use 58.3%), testosterone derivatives) (main use 4.6%)	Dosage not specified; main use[c] of estrogens in MHT users: weak estrogens 4.5, CEE 1%, E2 93.2% (transdermal 59.9%)	I. BC incidence; II. RR for BC compared with MHT non-users by Cox's proportional hazards regression	I. 984 women with invasive BC; II. RR[d] (95% CI) compared with non-users: any MHT 1.2 (1.1–1.4), all EPT 1.3 (1.1–1.5), E2 + MP 0.9 (0.7–1.2), estrogens + synthetic progestogens 1.4 (1.2–1.7); III. No evidence of increasing risk with increasing duration of HRT exposure except for oral estrogens combined with synthetic progestogens (ns, $p = 0.07$)
Fournier (2008)[24]	Prospective cohort study (E3N)	80 377 women; 56 674 incident and prevalent MHT users; 23 703 MHT non-users	Mean 8.1 ± 3.9 years; mean MHT duration 7.0 ± 5.2 years	Postmenopause; mean age at MHT start 52.4 ± 4.6 years, mean age at follow-up start 53.1 (range 40–66.1) years	MHT regimen and dosage not specified; combined MHT using oral progestogen: MP, DYD, other progestogens = progesterone + testosterone derivatives	Dosage not specified; mainly oral and transdermal E2, 1.3% o-CEE	I. BC incidence; II. RR for BC compared with MHT non-users by Cox's proportional hazards regression	I. 2354 women with invasive BC; II. adjusted RR (95% CI): estrogen + MP 1.00 (0.83–1.11) (129 BC cases/40 537 person-years); estrogen + DYD 1.16 (0.94–1.43); for estrogen + other progestogens 1.69 (1.50–1.91 (527 BC cases/104 243 person-years); III. Significant trends of increased risk with increased duration of use of estrogen + MP and estrogen + other progestogens; IV. Risk of BC after treatment stopped: no significant increased BC risk for all EPT ≥2 years after last use
Fournier (2008)[23]	Prospective cohort study (E3N)	80 391 women; 2265 BC cases with histology; 1792 BC cases with hormone receptor status	Mean 8.1 ± 3.9 years	Postmenopause;mean age at follow-up start 53.1 (range 40–66.1) years	MHT regimen and dosage not specified; combined MHT using oral progestogen: MP, DYD, other progestogens (progesterone + testosterone derivatives)	Dosage not specified; mainly oral and transdermal E2, 1.3% o-CEE	I. BC histology (ductal, lobular, other); II. hormone receptor status (ER+/PR+, ER+/PR-, ER-/PR+, ER-/PR-, missing); III. RR for BC histology by Cox's proportional hazards regression; IV. RR for BC hormone receptor status by Cox's proportional hazards regression	I. 1560 ductal and 448 lobular carcinoma; II. 1054 ER+/PR+, 372 ER+/PR-, 64 ER-/PR+, 302 ER-/PR-; III. adjusted RR (95% CI) estrogens + MP: ductal carcinoma 1.0 (0.8–1.3); lobular carcinoma 1.1 (0.7–1.7); estrogens + other progestogens: ductal carcinoma 1.6 (1.3–1.8), lobular carcinoma 2.0 (1.5–2.7); IV. adjusted RR (95% CI): estrogens + MP: ER+/PR+ 1.2 (0.9–1.5), ER+/PR- 0.8 (0.5–1.5), ER-/PR+ 0.9 (0.3–2.6), ER-/PR- 1.0 (0.6–1.7); estrogens + other progestogens: ER+/PR+ 1.8 (1.5–2.1), ER+/PR- 2.6 (1.9–3.5), ER-/PR+ 1.0 (0.5–2.1) and ER-/PR- 1.4 (0.9–2.0)

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RCTs: MHT with MP and Breast Cancer

Fournier (2009)[20]	Prospective cohort study (E3N)	53 310 women; 21 232 MHT never users; 26 171 MHT ever users with gap time ≤3 years; 5908 MHT ever users with gap time >3 years	Mean 8.1 ± 3.9 years	Postmenopause; mean age at follow-up start 54.6 ± 4.5 years	MHT regimen and dosage not specified; combined MHT using an oral progestogen: MP, DYD, other progestogens = progesterone + testosterone derivatives; recent MHT = current use and use within the previous 12 months	Dosage not specified; mainly oral and transdermal E2, 1.3% o-CEE	I. BC incidence; II. HRs for BC by Cox's proportional hazards regression comparing time from menopause (gap time) ≤ 3 years and >3 years and partially duration of use	I. 1726 women with invasive BC; II. adjusted HR (95% CI)[e]: recent EPT use: gap time ≤3 years: 1.61 (1.43–1.81), gap time >3 years: 1.35 (1.13–1.63); estrogen + MP: gap time ≤3 years significantly increased BC risk when used for >5 years (p trend for duration = 0.002), gap time >3 years did not increase BC risk regardless of duration of use (≤2 to >10 years) (p trend for duration = 0.54); estrogen + other progestogen: gap time ≤3 years significantly increased BC risk regardless of duration of use (≤2 to >10 years) (p trend for duration = 0.18), gap time >3 years significantly increased BC risk when used for >2 to ≤10 years (p trend for duration = 0.27)
Fournier (2014)[21]	Prospective cohort study (E3N)	78 353 women; 21 601 MHT never users; 31 223 MHT past users (no MHT in preceding 3 months); 17 986 MHT current users,	Mean 11.2 years	Postmenopause; mean age at end of follow-up 67.1 ± 7.8 years (MHT never users), 67.0 ± 5.8 years (MHT past users), 63.1 ± 5.5 years (MHT current users)	MHT regimen and dosage not specified; combined MHT using oral progestogen: MP, DYD, other progestogens = progesterone + testosterone derivatives, tibolone	Dosage not specified; mainly oral and transdermal E2	I. BC incidence; II. HRs for BC by Cox's proportional hazards regression with respect to time since last use and comparing short-term MHT use (≤5 years) with long-term MHT use (>5 years)	I. 3678 women with invasive BC; II. adjusted HR (95% CI): current estrogen + MP/DYD: ≤5 years 1.13 (0.99–1.29), >5 years 1.31 (1.15–1.48), any past use, ns effect on BC risk; current estrogen + other progestogen: ≤5 years 1.70 (1.50–1.91), >5 years 2.02 (1.81–2.26); stop of treatment after short-term use: ns effect; long-term-use: significantly elevated BC risk up to 10 years
Cordina-Duverger (2013)[25]	Population-based case-control study (CECILE)	1555 women; 739 BC cases, 816 controls	–	Postmenopause; range 35–74 years (82.3% of women between 55 and 74 years)	MHT regimen and dosage not specified; combined MHT MP, progesterone derivatives, testosterone derivatives, tibolone	Type of estrogens not further specified; dosage not specified	Invasive and *in situ* BC risk in comparison to MHT non-user by unconditional logistic regression analysis with regard to duration of use	Adjusted OR[f] (95% CI), estrogens + MP: any duration 0.80 (0.44–1.43) (25 cases/34 controls), <4 years 0.69 (0.29–1.68), ≥4 years 0.79 (0.37–1.71); estrogens + synthetic progestogens: any duration 1.72 (1.11–2.65) (67 cases/48 controls), <4 years 1.17 (0.48–2.86), ≥4 years 2.07 (1.26–3.39)
Harman (2014)[22]	PC-RCT (KEEPS)	727 randomized women (79% never MHT use before)	48 months; mean MHT use: o-CEE 37.4 ± 16.6 months, t-E2 34.6 ± 18.3 months, placebo 37.6 ± 17.3 months	Postmenopause; mean age at study entry 52.7 (range 42–58) years	Oral MP 200 mg/day on days 1–12 of each month (all women with estrogens)	o-CEE 0.45 mg/day or t-E2 50 µg/day	Primary endpoint: annual change in CIMT; BC as adverse event (annual mammogram)	BC as adverse events: $n = 3$ o-CEE, $n = 3$ t-E2, $n = 2$ placebo
Hodis (2016)[5]	PC-RCT (ELITE)	643 randomized women; 271 early postmenopause (previous MHT use 49–53%); 372 late postmenopause (previous MHT use 85–90%)	Median 4.8 (range 0.5–6.7) years	Postmenopause; median age at study entry 55.4 years (early postmenopause) and 63.6 years (late postmenopause)	Vaginal MP 45 mg/day (4% gel) on 10 days during each 30-day cycle or placebo (only in women with intact uterus receiving estrogens)	o-E2 1 mg/day or placebo	Primary endpoint: rate of change in CIMT; BC as adverse event	BC as adverse events: $n = 10$ o-E2, $n = 8$ placebo
Asi (2016)[7]	Systematic review and meta-analysis (2 cohort studies[8,24]	86 881 women	Mean follow-up 2.5 years[8] and 8.1 years[24]; mean MHT duration not given	Postmenopause; MHT exposed group: 60.6 ± 6.3 years, MHT non-exposed group: 64.2 ± 8.3 years[8]; MHT ever-use: 52.3 ± 4.1 years, MHT never-use 55.0 ± 4.8 years[24]	Dosage and route of administration not specified	Dosage and route of administration not specified	Relative risk for BC	RR 0.67 (95% CI 0.55–0.81)
Yang (2017)[4]	Systematic review and meta-analysis (14 trials; 5 RCT, 6 cohort studies, 2 nested case-control studies, 1 case-control study) including 9 with combined MHT	14 475 women	Not given	Peri- and postmenopausal women (not further specified)	Dosage and route of administration not specified: MPA, NETA, LNG, DYD, MP	Not further specified	Odds ratio for BC	OR (95% CI): All EPT 1.48 (1.30–1.68); ET + MPA 1.19 (1.07–1.33); ET + NETA 1.44 (1.26–1.65); ET + LNG 1.47 (1.17–1.85); ET + DYD 1.10 (0.89–1.36); ET + MP 1.00 (0.83–1.20)

Stute P, et al. Climacteric. 2018 Apr;21(2):111-122.

Micronized Progesterone (MP) and BC Risk: A Systematic Review

- **14 studies**
- **Estradiol only shows no increased risk**
  - Pooled OR=0.90 (0.4-2.02) from RCTs
  - Pooled OR=1.11 (0.98-1.27) from observational studies
- **Estradiol-progestogen risk increased based on type of progestogen and duration>5y OR 2.43 (1.79-3.29) versus <5y 1.49 (1.03-2.15)**

Yang Z, et al. Gynecol Endocrinol. 2017 Feb;33(2):87-92.

HT + BC: Observational Lancet, 2019

108 647 postmenopausal women developed breast cancer at mean age 65 years (SD 7); 55 575 (51%) had used MHT.

Mean MHT duration=10y (SD 6) in current users, 7 years (SD 6) in past users; mean age 50y (SD 5) at menopause; 50y (SD 6) starting MHT.

Every MHT type, except vaginal estrogens, associated with excess breast cancer risks, which increased steadily with duration of use and were greater for estrogen-progestagen than estrogen-only preparations (CEE and E2).

“Risks did not differ substantially between the main estrogenic constituents, or by whether estrogens were administered orally or transdermally.”

Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019 Sep 28;394(10204):1159-1168.

HT + BC: Observational Lancet, 2019

If these associations are CAUSAL…

For women at average weight in developed countries on MHTx5y, breast cancer incidence increases by:

- 1 in 50 users on estrogen plus daily progestin
- 1 in 70 users of estrogen plus cyclic progestin
- 1 in 200 users of estrogen-only preparation
- Corresponding risk from MHTx10y approx. 2X

Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019 Sep 28;394(10204):1159-1168.

HT + BC: Sweden Prospective Cohort

- All women who received ≥1 HT prescription during the study period 2005-2012 (290 186 ever-users), group-level matched (1:3) to 870 165 never-users
- Current use of estrogen-only therapy was associated with a slight excess breast cancer risk [odds ratio (OR) = 1.08 (1.02-1.14)].
- Risk for current estrogen plus progestogen therapy was higher [OR = 1.77 (1.69-1.85)] and increased with higher age at initiation [OR = 3.59 (3.30-3.91) in women 70+ years].
- In contrast, past use was associated with reduced breast cancer risk.
- Current use 1.12 E2, 0.76 E3, 4.47 CEE, 1.68 tibolone (all significant)

Brusselaers N, et al. Different menopausal hormone regimens and risk of breast cancer. Ann Oncol. 2018 Aug 1;29(8):1771-1776.

HT + BC: UK in BMJ, 2020

- 2 UK primary care databases of 99,000 women with breast cancer diagnosed 1998-2018 (age 50-79, mean age at dx 63, 95% white)
- Matched to 450,000 controls without breast cancer
- Recent use >5y of ET OR 1.15 (1.09-1.21)* different than WHI
- Recent use >5y of MHT OR 1.79 (1.73-1.85)
- Past longterm use (>5Y) of ET and past short term (<5 years) use of EPT not associated with increased risk.

*BMI lower in UK compared to WHI

Vinogradova Y, et al. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. BMJ. 2020 Oct 28;371:m3873.

Conventional Guidelines

- Endocrine Society
- NAMS
- ACOG

Endocrine Society Guidelines (2015)

The Endocrine Society recommends that women with a uterus who decide to undergo MHT with estrogen and progestogen be informed about risks and benefits, including the possible increased risk of breast cancer during and after discontinuing treatment. Health care providers should advise all women, including those taking menopausal hormone therapy, to follow guidelines for breast cancer screening.

- Serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin or pregabalin are recommended for women who want medication to manage moderate to severe hot flashes, but either prefer not to take hormone therapy or have significant risk factors that make hormone therapy inadvisable.

Treatment of the Symptoms of the Menopause
***JCEM* | November 2015**

Endocrine Society Guidelines (2015)

- Women with breast cancer or high risk: try nonhormonal treatment first. Could use low-dose vaginal estradiol.
- For breast cancer, data suggest that progesterone may have a lower risk
- 30% relative risk reduction in all-cause mortality for women starting MHT<10y from menopause
- Current evidence does not justify MHT to prevent heart disease, breast cancer, or dementia
- Treat for the shortest duration. Women with premature ovarian insufficiency should take MHT until age of menopause.

Treatment of the Symptoms of the Menopause
JCEM | November 2015

2017 Hormone Therapy Position Statement

Key Points from the
2017 Position Statement of
The North American Menopause Society

Recommendations Grading

- Level I: Based on good and consistent scientific evidence
- Level II: Based on limited or inconsistent scientific evidence
- Level III: Based primarily on consensus and expert opinion

NAMS
The North American Menopause Society

Hormone Therapy and Breast Cancer

- The effect of hormone therapy (HT) on breast cancer risk is complex and conflicting
- The effect of HT on breast cancer risk may depend on
  - Type of HT, dose, duration of use
  - Regimen, route of administration
  - Prior exposure to HT
  - Individual characteristics

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

NAMS
The North American Menopause Society

A4M MMI
REDEFINING MEDICINE

Hormone Therapy, the Women's Health Initiative, and Breast Cancer

- Increased risk of invasive breast cancer after 3 to 5 years of conjugated equine estrogen 0.625 mg + medroxyprogesterone acetate 2.5 mg therapy
- No increased risk of breast cancer was seen with 7 years CEE 0.625 mg alone therapy
- Allows for more flexibility in duration of estrogen therapy use in women without a uterus

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

NAMS
The North American Menopause Society

A&M MMI
REDEFINING MEDICINE

Hormone Therapy and Family History of Breast Cancer

- Observational evidence shows use of hormone therapy does not alter risk for breast cancer in women with a family history of breast cancer
- Family history is one risk among many that should be assessed when counseling women on the use of hormone therapy (Level II)

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

NAMS
The North American Menopause Society

A&M MMI
REDEFINING MEDICINE

Hormone Therapy and Survivors of Breast Cancer

Systemic hormone therapy is not recommended for survivors of breast cancer

- Selected cases with compelling reasons may be discussed in conjunction with an oncologist
- After nonhormone options have been unsuccessful

NAMS
The North American Menopause Society

Hormone Therapy and Survivors of Breast Cancer

- Systemic hormone therapy is not recommended for survivors of breast cancer
  - Selected cases with compelling reasons may be discussed in conjunction with an oncologist
  - After nonhormone options have been unsuccessful

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

NAMS
The North American Menopause Society

A&M MMI
REDEFINING MEDICINE

Low-dose Vaginal Estrogen and Survivors of Breast Cancer with Bothersome Genitourinary Syndrome of Menopause

- **Low-dose vaginal estrogen therapy (ET)**
  - **Minimal systemic absorption**
    - **Blood levels in postmenopause range**
  - **Based on limited data, minimal risk for recurrence of breast cancer (Level II)**
- **For survivors of breast cancer with bothersome genitourinary syndrome of menopause symptoms, low-dose vaginal ET may be an option**
  - **After a failed trial of nonhormone therapies**
  - **In consultation with an oncologist**
  - **Concern even with low-dose vaginal ET for women on aromatase inhibitors because of suppressed estradiol levels (Level III)**

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

A4M MMI
REDEFINING MEDICINE

Special Populations

- Early menopause
- Primary ovarian insufficiency
- *BRCA* after oophorectomy
- Age older than 65 years

NAMS
The North American Menopause Society

Hormone Therapy, Early Menopause and Primary Ovarian Insufficiency

- Data regarding hormone therapy in women aged older than 50 years should not be extrapolated to younger postmenopausal women
- Observational studies suggest benefits outweigh risks on bone, heart, cognition, vulvovaginal atrophy/ genitourinary syndrome of menopause, sexual function, and mood
- Hormone therapy recommended until at least median age
  of menopause (52 y)
- Younger women may require higher doses for symptom relief or protection against bone loss

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

NAMS
The North American Menopause Society

A&M MMI
REDEFINING MEDICINE

Ovarian Conservation When Possible

- Women with early menopause and primary ovarian insufficiency have health risks that may include persistent vasomotor symptoms, bone loss, vulvovaginal atrophy, mood changes, and increased risk of heart disease, dementia, stroke, Parkinson disease, ophthalmic disorders, and overall mortality
- Ovarian conservation is recommended, if possible, when hysterectomy for benign indications is performed in premenopausal women at average risk for ovarian cancer

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

NAMS
The North American Menopause Society

A&M MMI
REDEFINING MEDICINE

Hormone Therapy and *BRCA* After Oophorectomy

- Limited observational evidence suggests that hormone therapy use does not further increase risk of breast cancer in women with a family history of breast cancer or in women after oophorectomy for *BRCA 1* or *2* gene mutation

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

NAMS
The North American Menopause Society

A&M MMI
REDEFINING MEDICINE

Area of Scientific Uncertainty: Breast

- Breast tissue recently exposed to endogenous estrogen and progestogen may react differently to exogenous hormones than if more distantly exposed, but this theory of estrogen-induced apoptosis of occult tumors remains unproven
- Different types of estrogen may have different effects on the breast, thus limiting the generalizability of the findings of reduced breast cancer cases with conjugated equine estrogen in the Women's Health Initiative

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

NAMS
The North American Menopause Society

A&M MMI
REDEFINING MEDICINE

New Areas of the NAMS Guidelines

- **No evidence for Beers criteria to recommend discontinuation of hormone therapy after age 65 if indication to continue remains and no contraindications**
- **Breast cancer risk does not increase appreciably with short-term use of estrogen-progestogen therapy and may be decreased with estrogen alone (conjugated equine estrogen in the Women's Health Initiative)**
- **No increased risk of breast cancer in women who are *BRCA*-positive on hormone therapy after risk-reducing bilateral salpingo-oophorectomy (observational studies)**

NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

The 2017 NAMS Hormone Therapy Position Statement Has Been Endorsed by

- Academy of Women's Health
- American Association of Clinical Endocrinologists
- American Association of Nurse Practitioners
- American Medical Women's Association
- American Society for Reproductive Medicine
- Asociación Mexicana para el Estudio del Climaterio
- Association of Reproductive Health Professionals
- Australasian Menopause Society
- Chinese Menopause Society
- Colegio Mexicano de Especialistas en Ginecologia y Obstetricia
- Czech Menopause and Andropause Society
- Dominican Menopause Society
- European Menopause and Andropause Society
- German Menopause Society
- Groupe d'études de la ménopause et du vieillissement Hormonal
- HealthyWomen
- Indian Menopause Society
- International Menopause Society
- International Osteoporosis Foundation
- International Society for the Study of Women's Sexual Health
- Israeli Menopause Society
- Japan Society of Menopause and Women's Health
- Korean Society of Menopause
- Menopause Research Society of Singapore
- National Association of Nurse Practitioners in Women's Health
- SIGMA Canadian Menopause Society
- SOBRAC and FEBRASGO
- Società Italiana della Menopausa
- Society of Obstetricians and Gynaecologists of Canada
- South African Menopause Society
- Taiwanese Menopause Society
- Thai Menopause Society

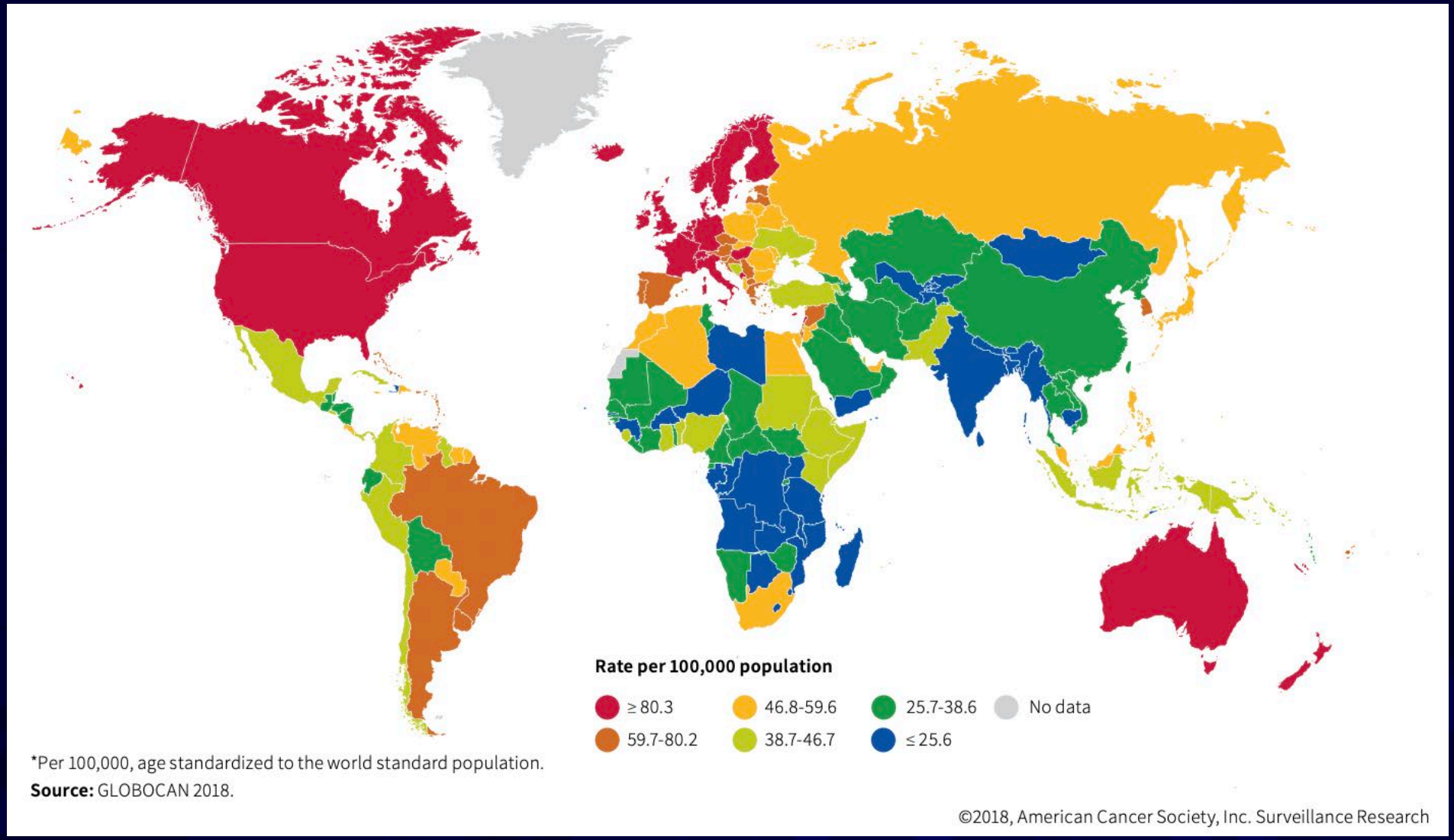
The American College of Obstetricians and Gynecologists supports the value of this clinical document as an educational tool, June 2017. The British Menopause Society supports this Position Statement.

ACOG Committee Opinion (2016)

- American College of Obstetricians and Gynecologists (ACOG) outlines the options and treatments for female-specific survivorship issues.
- For women with estrogen-dependent breast cancer or a history of estrogen-dependent breast cancer, non-hormonal options for vaginal atrophy should be the first choice.
- However, health practitioners may now consider topical estrogen therapy for patients with a history of estrogen-dependent breast cancer who are unresponsive to non-hormonal remedies. Although there is controversy related to the risk of topical estrogen therapy and breast cancer recurrence, ACOG notes that data show there is no increased risk of cancer recurrence with topical vaginal estrogen.

Committee Opinion #659, "The Use of Vaginal Estrogen in Women with a History of Estrogen-Dependent Breast Cancer," *Obstetrics & Gynecology* March 2016; Miller JG. Clinical Updates in Women's Health Care Summary: Gynecologic and Obstetric Care for Breast Cancer Survivors: Primary and Preventive Care Review. Obstet Gynecol. 2017 Jul;130(1):255.

Breast Cancer Global incidence, 2018



American Cancer Society, Global Cancer Facts & Figures. 3rd ed. Atlanta, GA: American Cancer Society, Inc; 2015.

Breast Cancer Update

- Breast cancer is the most common cancer in women worldwide
- One in 8 women (12.5%) in the United States will develop breast cancer throughout their lifetime.
- Genetic factors (WISDOM): ATM, BRCA1, BRCA2, CHEK2, CDH1, P53, PALB2, PTEN, STK11
- Meta-analysis of prospective cohort studies (N=22.7M) showed that every 5 kg/m^2 increase in BMI corresponded to 2% increase in breast cancer risk in women. However, higher BMI could be a protective factor in breast cancer in premenopausal women.

Liu K, et al. Cancer Manag Res. 2018; 10: 143–151.
https://www.thewisdomstudy.org/faqs/ accessed 10/30/21

Breast Cancer Mortality

In the US, mortality dropped across all ages 1989-2010 by 1.5-3.4%, then stalled for women <40 (nonsignificant, trend toward increase)

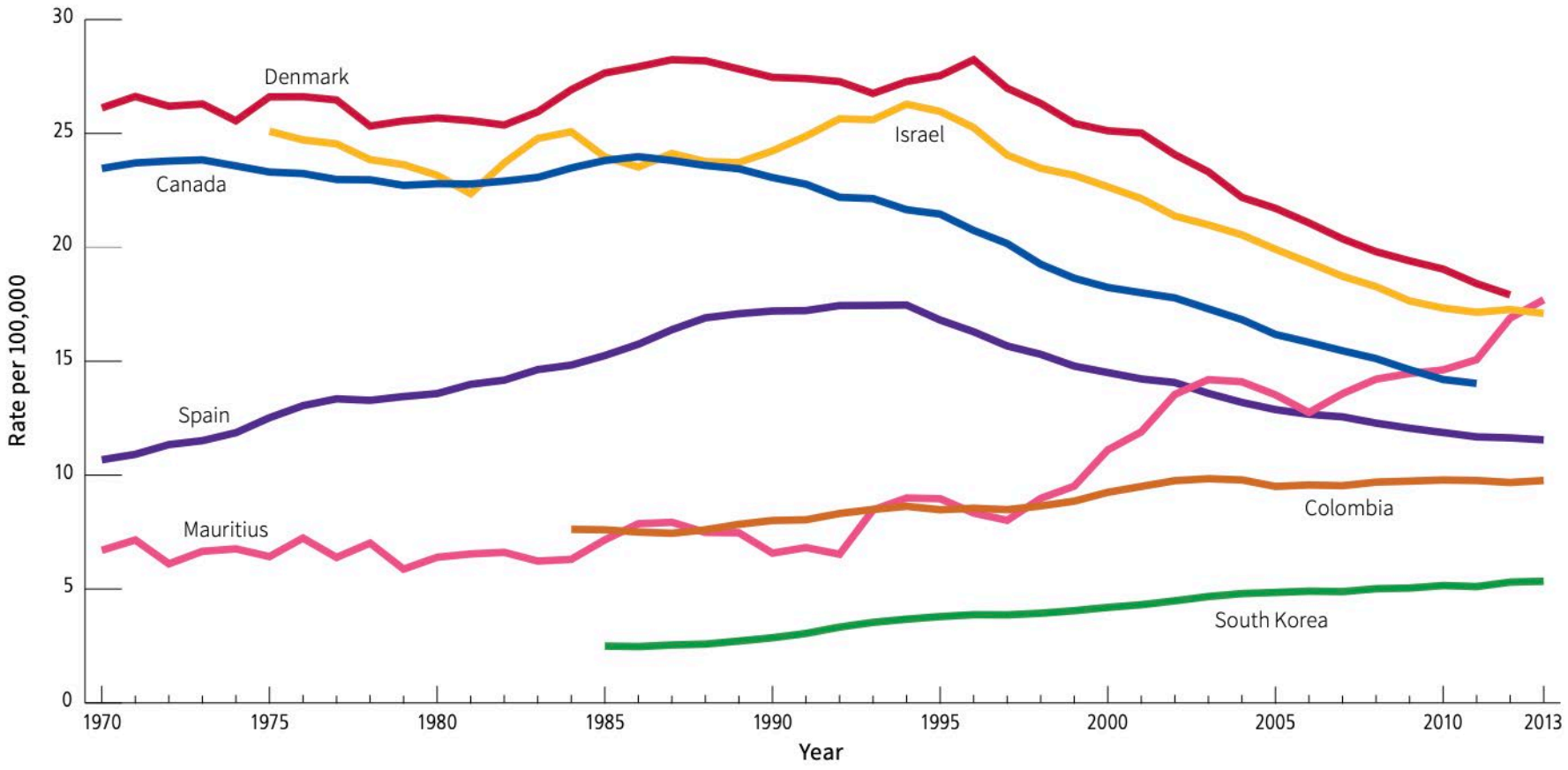
3/100,000 <40

30/100,000 40-69

80/100,000 >=70

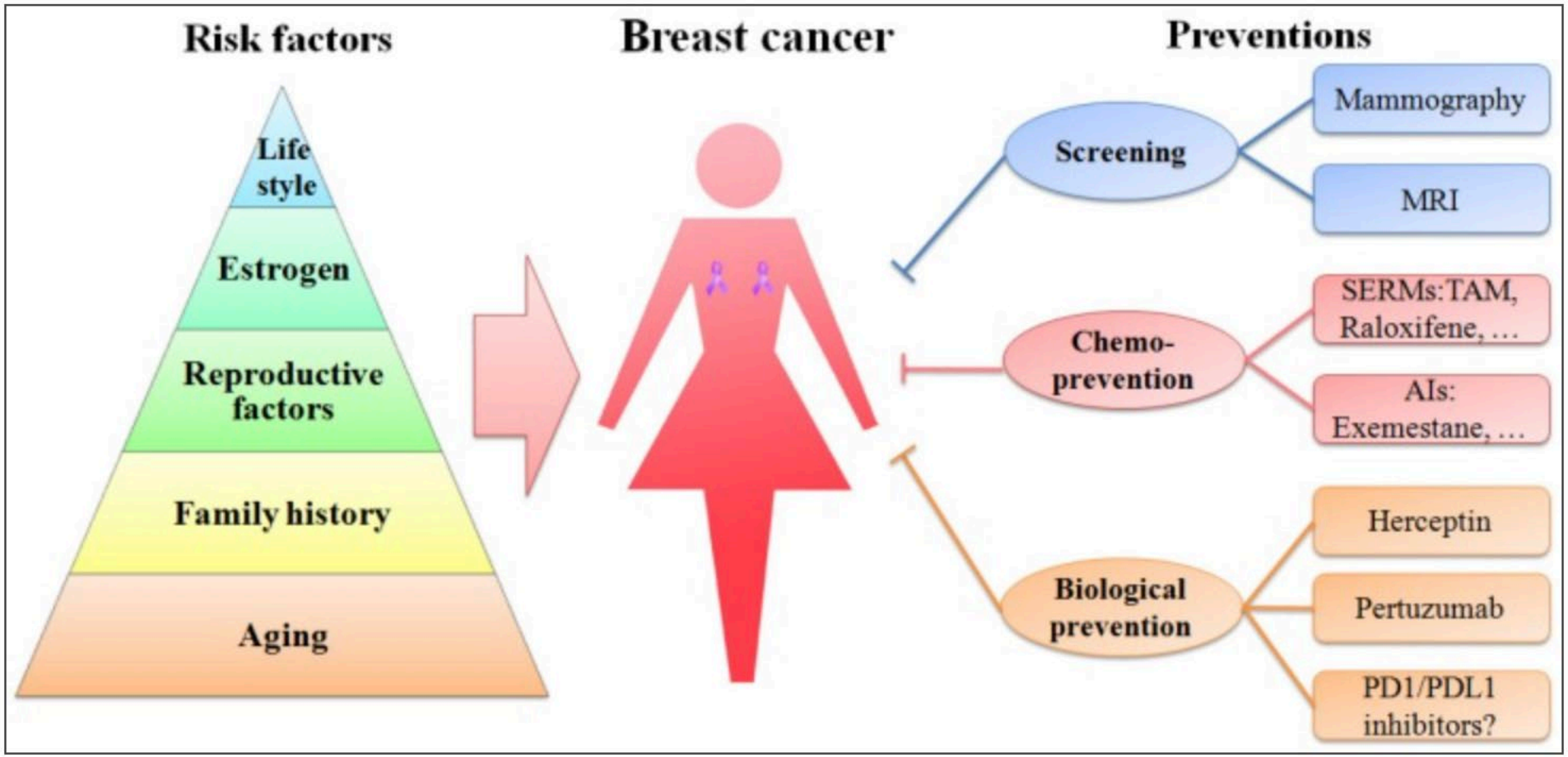
Hendrick RE, et al. Radiology. 2021 Apr;299(1):143-149.

Death Rates, 2018



American Cancer Society, Global Cancer Facts & Figures. 3rd ed. Atlanta, GA: American Cancer Society, Inc; 2015.

Breast Cancer Update



Sun Y-S, et al. *Int J Biol Sci* 2017 Nov 1;13(11):1387-1397.
American Cancer Society, Global Cancer Facts & Figures. 4th ed. Atlanta, GA: American Cancer Society, Inc; 2021.

Metabolic Landscape of Breast Cancer

N=503 women with breast cancer

As BMI increases, more hormones that can feed cancer

			BMI			
	<22	22-25	25-27.5	27.5-30	>30	P
Estrone (pg/mL)	19.7	22.3	21.2	22.7	26.5	0.005
Estradiol (pg/mL)	4.7	8.3	8.0	10.6	10.7	0.002
DHEAS (ng/dL)	50.5	53.2	55.6	60.0	59.3	0.21
SHBG (nmol/L)	73.9	66.2	52.1	43.4	38.1	.0001
Testosterone(pg/mL)	94.5	188.1	127.4	126.0	176.5	.0001
Free estradiol (pg/mL)	0.10	0.18	0.20	0.28	0.28	.0001
Free testosterone(pg/mL)	2.1	2.9	4.0	4.6	7.6	.0001

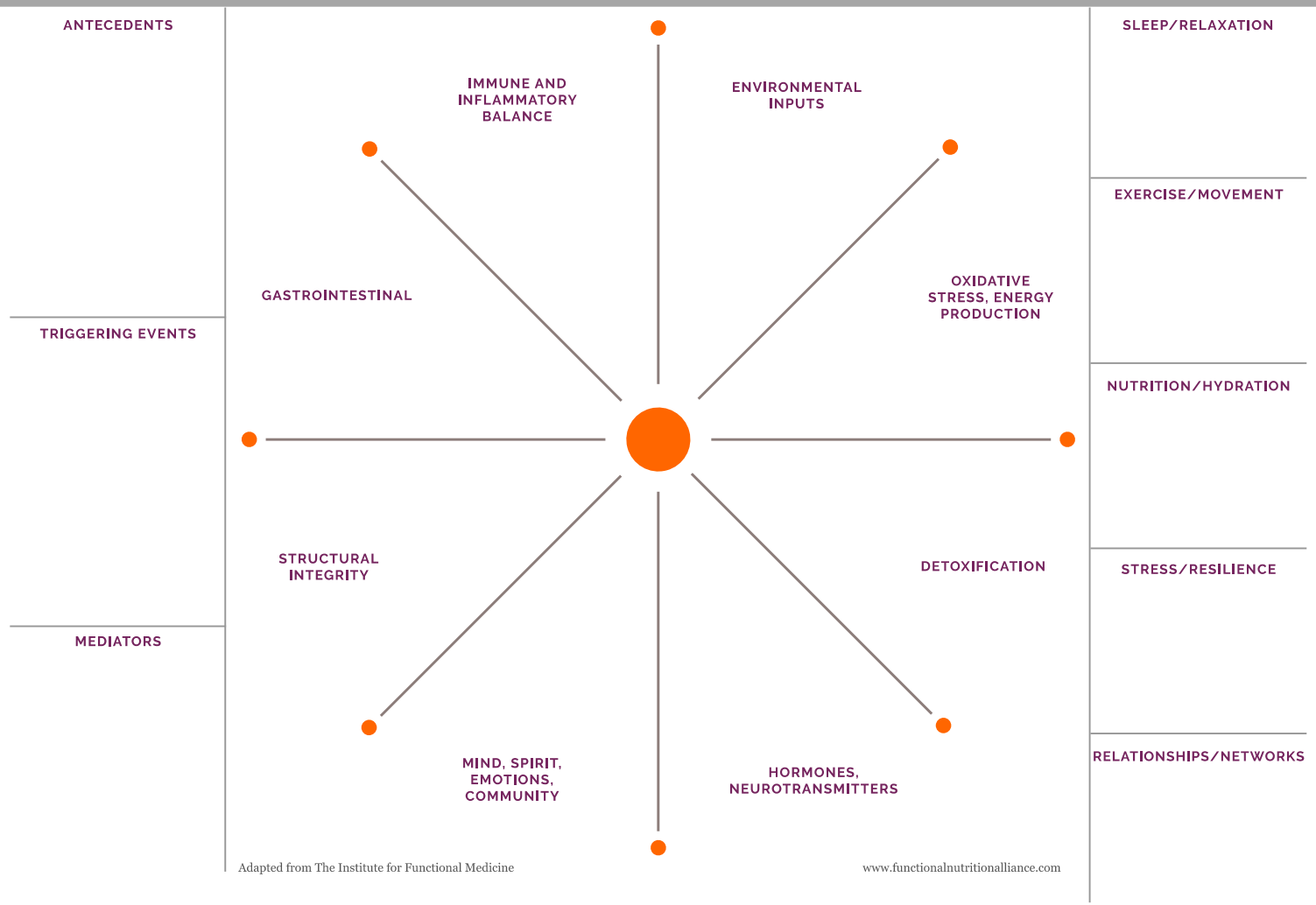
McTiernan A, J Clin Onc, 2003

Estrogen Regulation

functional nutrition alliance

functional nutrition matrix

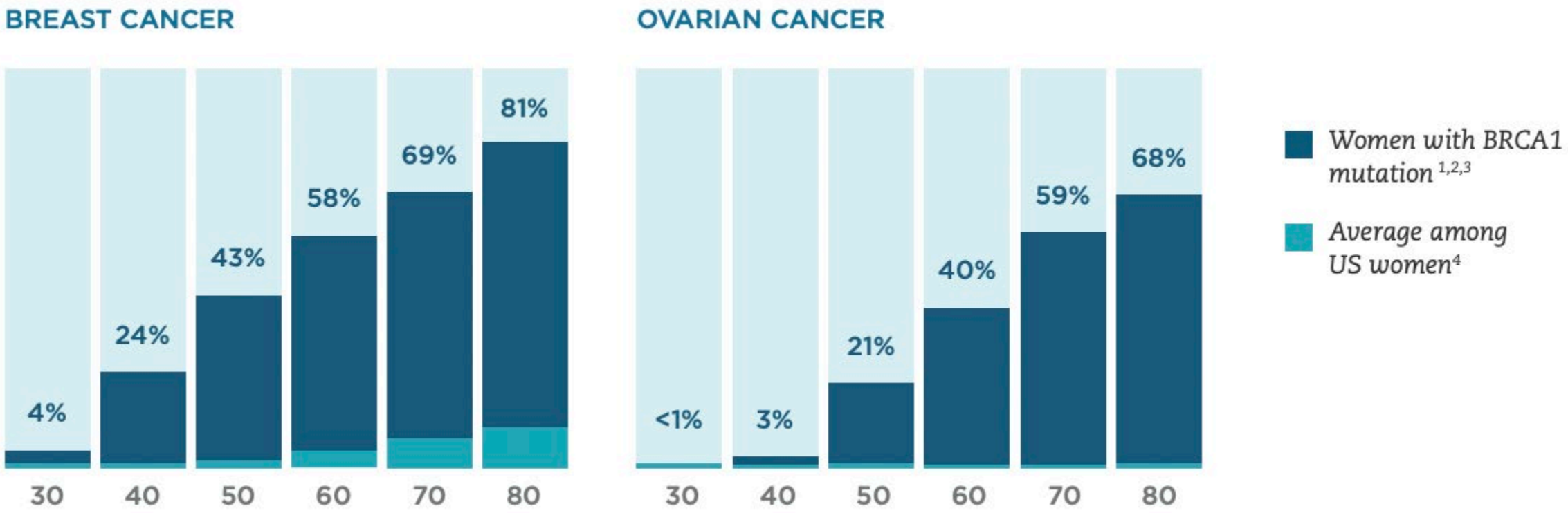
Name: Dr. Sara Gottfried Maps Estrogen Regulation on 15MM Date:



https://www.fxnutrition.com/15-minute-matrix-podcast/197-mapping-estrogen-regulation-with-dr-sara-gottfried/

A&M MMI REDEFINING MEDICINE

BRCA1



1 King MC, et al. Science. 2003;302(5645):643-6.
2 Mavaddat N, et al.. J Natl Cancer Inst. 2013;105(11):812-22.
3 Kuchenbaecker KB, et al. JAMA. 2017;317(23):2402-2416.
4 Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. Accessed May 2018.

BRCA + MHT Controversial

Birrer, 2018: Systematic Review & Meta-analysis

Results: Although there remains a paucity of data on this topic, these patients do benefit from treatment, especially as it relates to menopausal symptoms without an apparently increased risk of breast cancer.

Conclusions: Decisions regarding the use of HT in women who undergo BSO after detection of a BRCA mutation must be individualized based on careful consideration of the risks and benefits. However, the risks of a subsequent cancer diagnosis appear small, particularly in regards to the benefits of treatment afforded by HT.

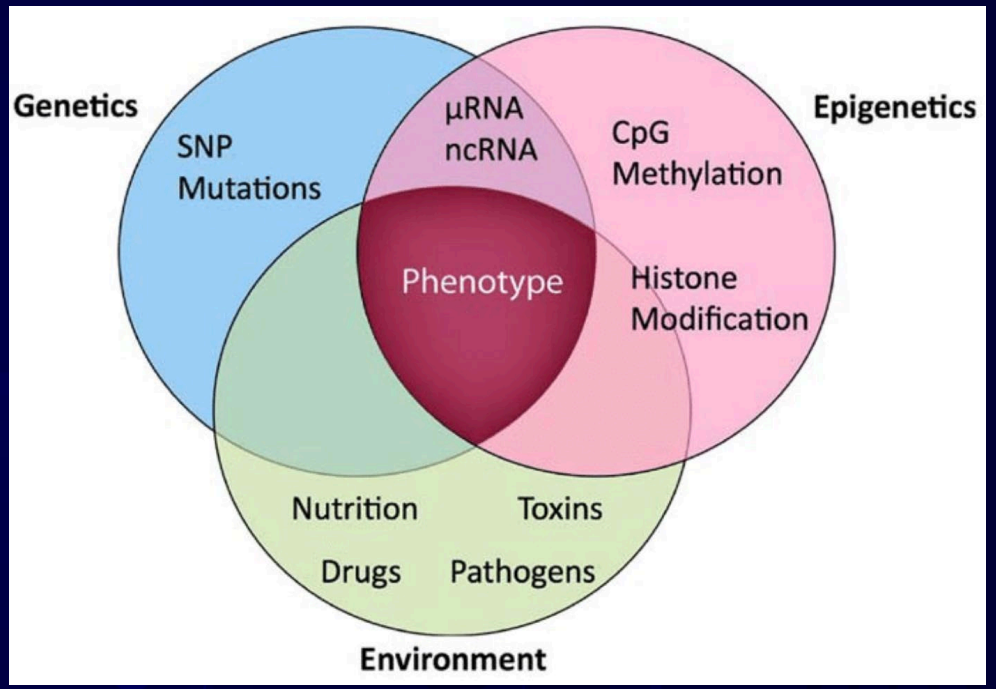
Gordhandas, 2019

Conflicting information has been published on HRT and breast cancer risk.

- For BRCA mutation carriers, potential augmentation of already elevated breast cancer risk is of great concern.
- Though evidence is limited, HRT after RRSO has a number of reported benefits and does not appear to impact breast cancer risk reduction in BRCA mutation carriers.
- This information is critical when discussing RRSO with patients, as providers should review risks of early menopause and treatment options.

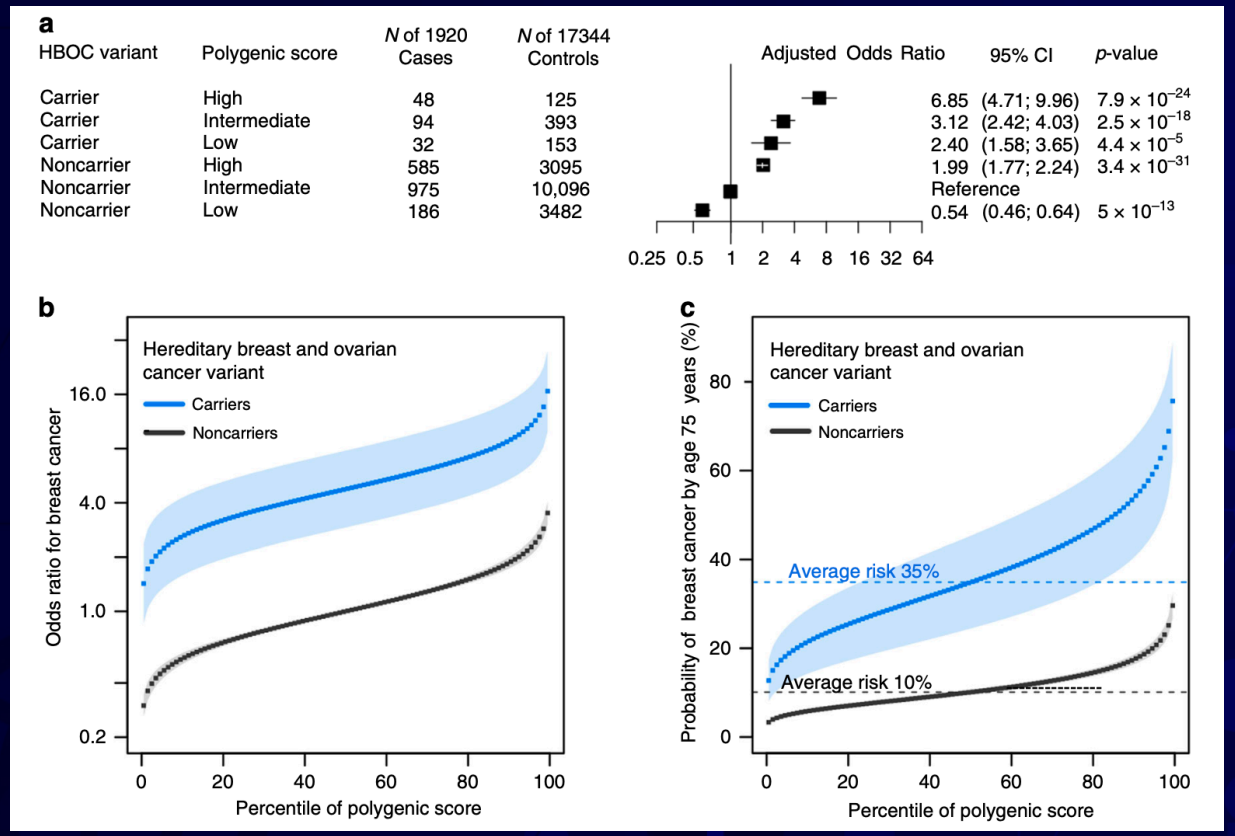
Birrer N, et al. Is Hormone Replacement Therapy Safe in Women With a BRCA Mutation?: A Systematic Review of the Contemporary Literature. Am J Clin Oncol. 2018 Mar;41(3):313-315; Gordhandas S, et al. Hormone replacement therapy after risk reducing salpingo-oophorectomy in patients with BRCA1 or BRCA2 mutations; a systematic review of risks and benefits. Gynecol Oncol. 2019 Apr;153(1):192-200.

Phenotype



Baye TM, et al. Per Med. 2011 Jan; 8(1): 59–70.

Interplay between Monogenic High-risk variants (BRCA) and Polygenic Background



Genetic variation can predispose to disease both through

- monogenic risk variants that disrupt a physiologic pathway with large effect on disease and (
- polygenic risk that involves many variants of small effect in different pathways.

80,928 individuals to examine whether polygenic background can modify penetrance of disease in tier 1 genomic conditions — familial hypercholesterolemia, hereditary breast and ovarian cancer (n=26,597), and Lynch

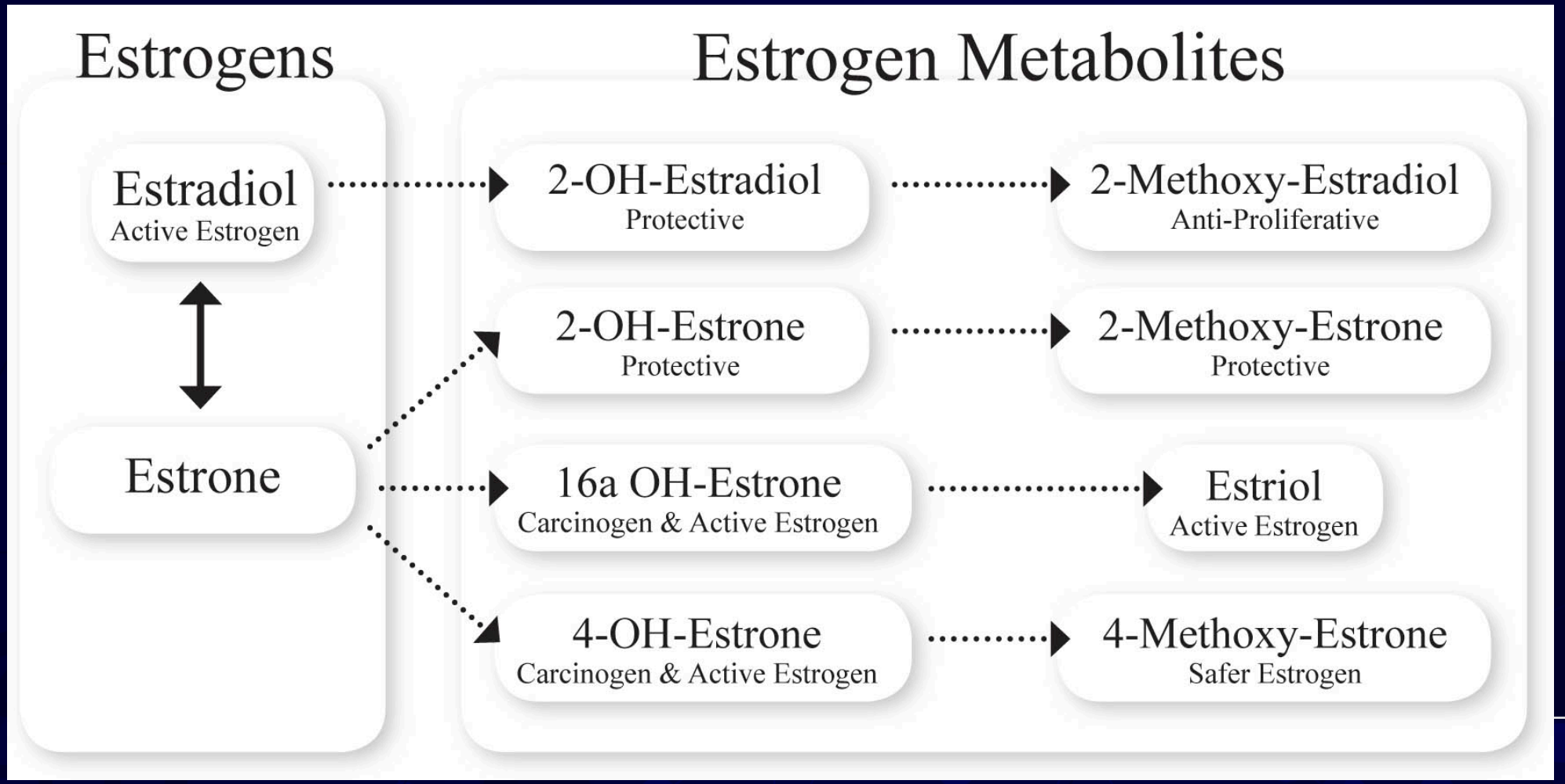
Probability of disease by age 75 years ranged from 17% to 78% for coronary artery disease, 13% to 76% for breast cancer, and 11% to 80% for colon cancer.

- First, we showed that risk conferred by monogenic risk var- iants, which act by perturbing a specific molecular pathway, can be substantially modified by polygenic background which appears to act by affecting a diverse set of physiological processes.
- Second, our findings indicate that accounting for polygenic background is likely to increase the accuracy of risk estimation for individuals who inherit a monogenic risk variant.

Fahed, Nature Communications 11, no. 1 (2020):3635

HORMONE SYNTHESIS

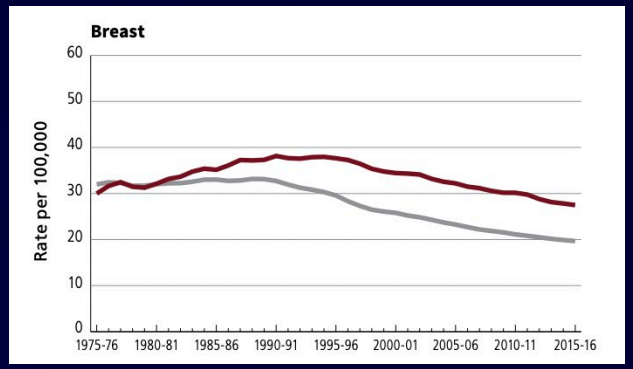
Estrogen Metabolism



Gottfried, Sara. *The Hormone Cure* (New York, Scribner, 2013)

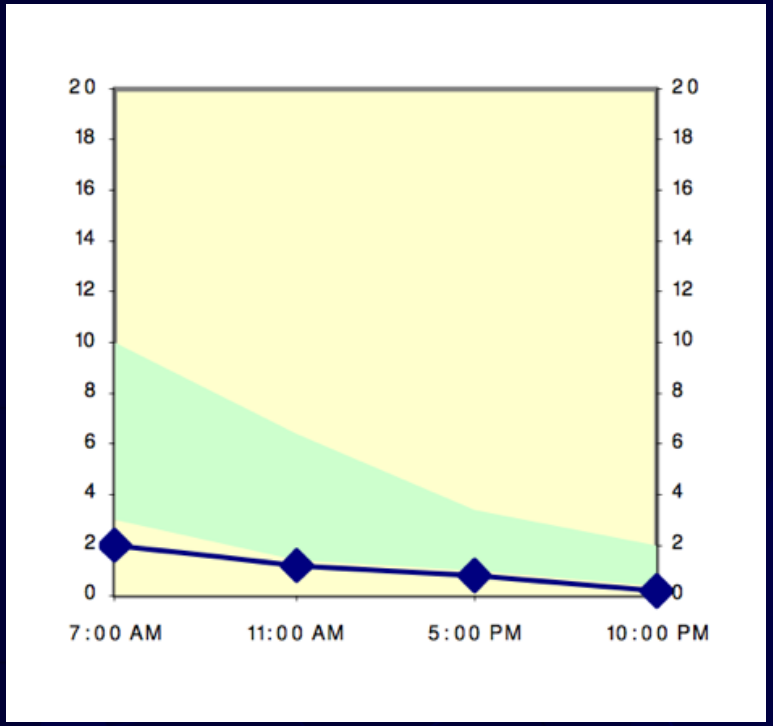
INCIDENCE: BLACK/WHITE IN US

- The overall 5-year relative survival **rate** for **breast cancers** diagnosed in 2008-2014 was 81% for **black women** compared to 91% for white women
- From NCI Surveillance Epidemiology and End Results (SEER) Database 1992-2014
  - Incidence highest for non-Hispanic white women (n=382,290), expected to increase 0.24% per year
  - Next highest non-Hispanic Black women (n=51,074), expected to decrease



Davis Lynn BC (2018) Black-White Breast Cancer Incidence Trends: Effects of Ethnicity. *Journal of National Cancer Institute* https://www.ncbi.nlm.nih.gov/pubmed/29982593;
https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-facts-and-figures-for-african-americans/cancer-facts-and-figures-for-african-americans-2019-2021.pdf

Flat Diurnal Cortisol Predicts Poor Survival



Diurnal Cortisol Rhythm as a Predictor of Breast Cancer Survival

Sandra E. Sephton, Robert M. Sapolsky, Helena C. Kraemer, David Spiegel

Background: **Abnormal circadian rhythms have been observed in patients**

marker of more rapid disease progression. [J Natl Cancer Inst 2000;92:994–1000]

Cancer poses numerous physical and emotional stresses. While disease and treatment exert a heavy physiological toll, accompanying anxiety about diagnosis and prognosis, taxing medical treatments, and disruption of social, vocational, and family functioning constitute a series of psychological stressors. Cancer patients repeatedly endure physical and emotional

N=104 metastatic breast cancer

"Women with breast cancer have flatter diurnal cortisol patterns than normal, and the loss of daily variation in cortisol predicts earlier mortality."

- David Spiegel MD, Stanford University

Sephton SE, et al. J Natl Cancer Inst. 2000 Jun 21;92(12):994-1000.

Intervention	Risk group	US women	Risk reduction	Time to benefit	Reference
Healthy diet	Few fruits/veg	5-11%	20-50%	5-20 years	Korde 2009 Jung 2013
No alcohol	> 4 drinks/w	15%	35%	5-20	Chen 2011 Smith 1998
No wt gain	All	100%	50%	10-20	Eliassen 2006
PA>30m/day	Sedentary	54%	20	10-30	Bernstein 2005
Breastfeed>1 year	Mothers	81%	18%	5	Collaboratve Group 2002
Hormone tx	current	2	10	1	IARC 2008
Hormone tx	longterm	1	50	2	IARC 2008
BSO	BRCA1&2	<1%	50	2	Rebeck 2009
Tam/Ralox	High risk	30	50	2	Visvanathan 2013

Colditz GA (2014) *CA Cancer J Clin* 64:186-94

Testosterone and Breast Cancer (BC)

- **T is breast protective and does not increase BC**
  - T is antagonistic to E2, inhibits ER-α, prevents E2 stimulation, and decreases breast proliferation as long as aromatization controlled
  - AR signaling exerts a pro-apoptotic, anti-estrogenic, growth inhibiting effect on normal and cancerous breast tissue
  - BC's, which are AR (+) are associated with a better prognosis
  - T/E2 ratio or balance is breast protective
  - T + an aromatase inhibitor (combined in a pellet) has been shown to not only decrease androgen deficiency symptoms in BC survivors, but decreases invasive BC incidence, and decreases tumor size when implanted directly in the breast

Dimitrakakis C, et al. Menopause. 2004; 11(5): 531-535.
Glaser RL, Dimitrakakis C. Maturitas. 2013; 74(3): 230-234.
Glaser RL, Dimitrakakis C. Maturitas. 2015; 82(3): 291-295.
Glaser RL, et al. BMC Cancer. 2019; 19(1): 1271

Slide adapted from Doreen Saltiel MD

Testosterone and Breast Cancer: The Dayton Study

Table 4 Incidence rates of IBC, comparison to published studies

	Cases per 100,000 p-y	Years Observed
Dayton Study		
T, T + AI	165	10
WHI RCT [29,30]		
Placebo	330	10.7
E alone	260	10.7
E + P	380	5.2

- Objective: 10-year prospective cohort study, assessing the long-term BC incidence in women treated with T pellets for hormone deficiency symptoms
- Study: 1267 pre/perimenopausal (23.2%) and PMP (76.8%) women, mean age 52.1 treated with T pellets or T + A pellets, 119 served as pseudo-control group
- Results: BC incidence compared to historical controls and age-matched Surveillance Epidemiology and End Results Data (SEER)
  - 39% decrease in invasive BC when compared to age-matched SEER data
    - T or T + A: 165/100,00 person-years vs SEER 271/100,00 person-years ($P < 0.001$)
  - T or T + A: 165/100,00 patient years vs "pseudo-control group:" 390/100,000 person-years ($P < 0.001$)
- **Conclusion: Long-term treatment with T implants did not increase invasive BC incidence, and should be investigated for hormone therapy and BC prevention**

Glaser RL, et al. BMC Cancer. 2019; 19(1): 1271.

Slide adapted from Doreen Saltiel MD

Summary: How I Counsel Patients

- **Aggregate data.** I review WHI, Fournier (2005), Mikkola (2016), and Liu (2020)
  - For transdermal E2 and oral PG, no association with increased risk of abnormal mammograms versus placebo (Liu, 2020)
  - Group that took transdermal estrogen and micronized progesterone had NO INCREASED RISK of breast cancer compared to controls who never took hormones RR 1.00 (0.83-1.22) (Fournier, 2005)
  - Estradiol decreased BC incidence and mortality up to 54%, even when MHT use was > 10 years (Mikkola, 2016)
  - There is substantial observational evidence that TD E2-alone not only decreases BC incidence, but decreases BC mortality up to 54%
- BIEST and estriol—lots of talk about E3 and lower risk of breast cancer theoretically, but there's no clinical studies.
- Full informed consent with risks, benefits, alternatives
- **Baseline testing, risk stratification, monitor levels and metabolites** q3-6m (I use serum and dried urine)
- Greatest benefit in women 50-59, pay attention to other aspects of breast cancer risk reduction.
- Even women using combined MHT had a mortality benefit when compared to the age-matched population, however, E2-alone users had the greatest mortality benefit.
- >60, 10+ years post menopause, restrictions on starting hormone therapy. Must risk stratify and metabolomics performed. Start low (I use 0.025 or 0.0125 mg patch). You will not get the same benefits as a woman aged 50-60, won't get the same breast cancer risk reduction, but they will get bone protection.

Mikkola TS, et al. Menopause. 2016; 23(11): 1199-1203.

Summary: Hormone Therapy and Breast Cancer Risk

- The relationship between menopausal hormone therapy (HT) and breast cancer risk is a complex and conflicting issue created in part by the data as well as by confusion surrounding interpretation of the findings themselves.
- Data aggregated from 2 trials: WHI (CEE, CEE + MPA) -- all other data are observational. WHI showed in 2017 reanalysis that for a woman s/p hysterectomy, decreased breast cancer mortality for CEE (0.625mg) alone x 7.1 years with 18 years follow up (HR 0.55, CI 0.33-0.92) though this finding was mostly overlooked.[3]
- When MPA added to the regimen, the decreased risk of CEE only was neutralized.[1,2]
- Meta-analysis of 108,647 women followed prospectively, 5 years of HT starting at age 50 increases incident breast cancer by 1 in 50 users of estrogen plus daily progestin, 1 in 70 users of estrogen with cyclic progestin, and 1 in 200 users of estrogen-only therapy. 10 years of HT about double these rates.[3]
- "The current state of science indicates that HT may or may not cause breast cancer but the totality of data neither establish nor refute this possibility. Further, any association that may exist between HT and breast cancer appears to be rare and no greater than other medications commonly used in clinical medicine."[2]
- Oral MP added to transdermal E2 is not associated with greater breast cancer risk even > 10 years[5]

[1] Mikkola TS, et al. Menopause. 2016; 23(11): 1199-1203;

[2] Hodis HN, et al. Climacteric. 2018; 21(6): 521-528.

[3] Manson JE et al. JAMA. 2017;318(10):927-938;

[4] Collaborative Group on Hormonal Factors in Breast Cancer, The Lancet 2019 394(10204):1159-1168,

[5] Stute P, et al.The impact of micronized progesterone on breast cancer risk: A systematic review. Climacteric. 2018 Apr;21(2):111-122

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