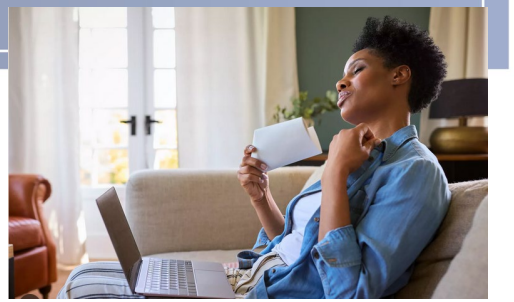
Systemic Menopausal Hormone Therapy
An Evidence-Based Strategy



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SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS • EST. 1938

UF UNIVERSITY of FLORIDA

Menopausal Hormone Therapy: Changing the Conversation

JoAnn V. Pinkerton, MD, FACOG, MSCP
Women's Midlife Health Endowed Professor
University of Virginia
Medical Director Emeritus, NAMS
President Emeritus, SAAOG

- Well informed clinicians can change the conversation, *removing fear from discussions re HT*, and help our patients make sound, *evidence-based* choices regarding treatment of menopausal symptoms

Pinkerton JV. Clin Obstet Gynecol 2018

Andrew M. Kaunitz, MD FACOG MSCP
Menopause-related Disclosures

Clinical Trials

(Funding to University of Florida Research Foundation):

- Bayer
- Mylan
- Estetra

Advisory Boards

- Estetra
- Mylan

Royalties

- UpToDate

Editorial Board:

- *Menopause* (the journal of The Menopause Society)

Abbreviations

- HT = hormone therapy
- ET = estrogen therapy
- CE = conjugated equine estrogen, E2=estradiol
- EPT = combination estrogen-progestin therapy
- VMS= vasomotor symptoms
- CHD= coronary heart disease
- VTE= venous thromboembolism

= Women's Health Initiative (WHI)

= Menopause Society (formerly known as NAMS)

Safety of Systemic Hormone Therapy

Learning Objectives I…

- Describe evidence regarding the safety of oral conjugated estrogen with or without medroxyprogesterone, focusing on WHI data
  - breast cancer, coronary heart disease, venous thromboembolism (VTE)
- Detail risk of breast cancer with:
  - estrogen-only therapy
  - progesterone vs. synthetic progestins
- Review risk of VTE with oral vs. transdermal estrogen

Learning Objectives II:

- Discuss practical issues related to initiating systemic menopausal hormone therapy
- Detail safety of menopausal HT in *BRCA* mutation carriers with intact breasts who have undergone risk-reducing BSO

Up to date OB/GYNs can change the conversation, providing evidence-based guidance, thereby helping our patients make good choices regarding HT

Treatment of Menopausal Symptoms: Systemic Hormone Therapy

- Appropriate when VMS or other symptoms, including joint pain, present
  - Disrupt daytime activities and/or sleep
  - Impair quality of life
- Estrogen used for many decades used to treat VMS
  - Most effective treatment
    - Numerous randomized, placebo-controlled trials
    - ~75% reduction in VMS frequency
    - Significant reduction in VMS severity
    - Oral and transdermal estrogen have similar efficacy

Systemic Hormone Therapy

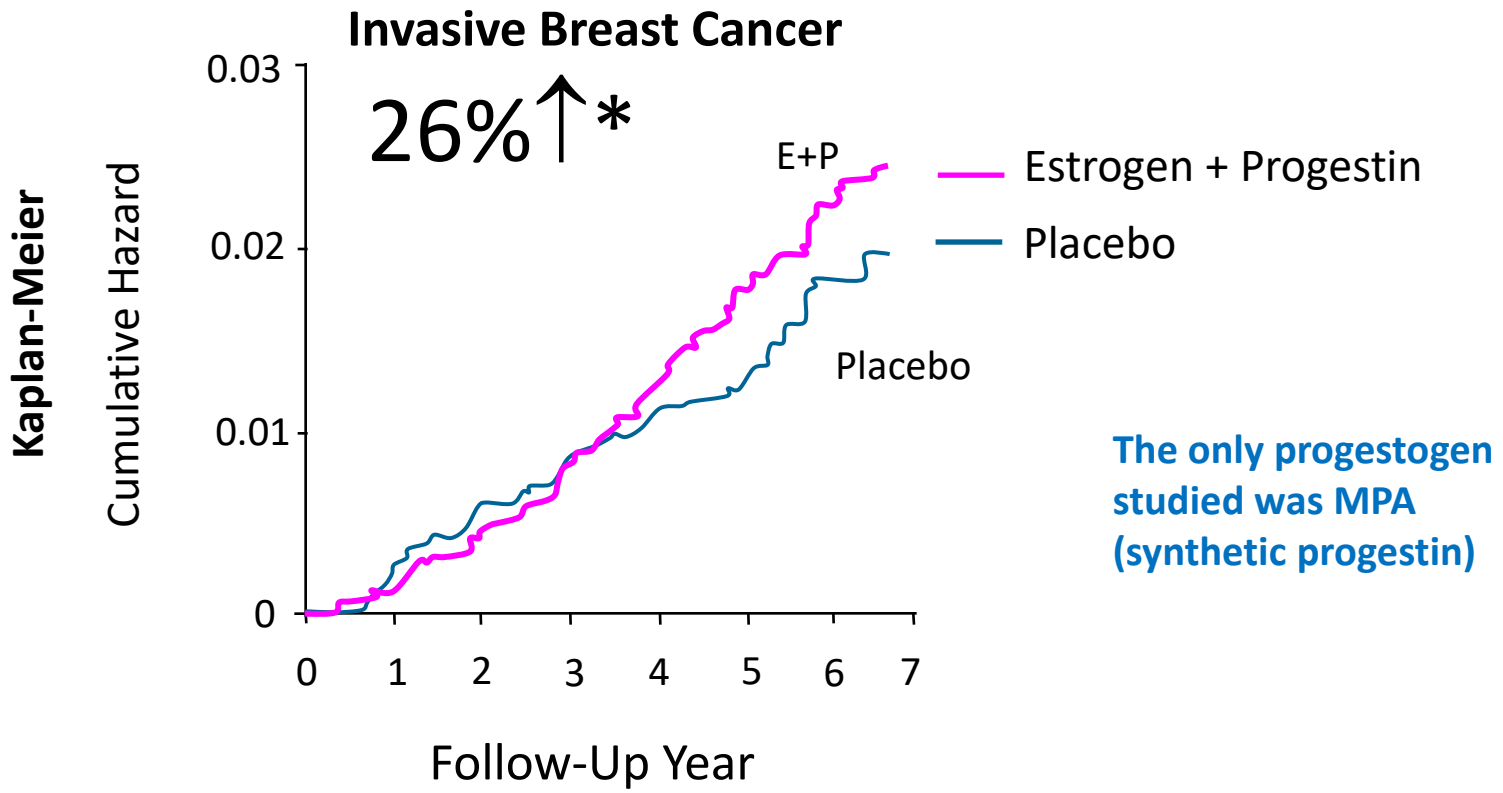
- Clear
  - VMS: most common indication for HT
  - HT's efficacy in treating VMS well-established
- Controversial
  - Our understanding of HT's safety….

WHI: Women's Health Initiative

- NIH-sponsored multicenter, double-blind, placebo-controlled trial of women **age 50-79 years at baseline**, designed to assess HT's impact on cardiovascular and other chronic diseases
- **Mean age at screening 63-64 years**
- Planned 10-year trial; stopped early
  - Oral CE/Medroxyprogesterone acetate (MPA) v. placebo: N ~ **17,000** , stopped Summer '02, mean follow-up 5.2 years
  - Oral CE v. placebo: N ~ **11,000** , stopped Spring '04, mean follow-up 6.8 years

Writing Group WHI. JAMA 2002 WHI Steering Committee. JAMA 2004

EPT: Invasive Breast Cancer

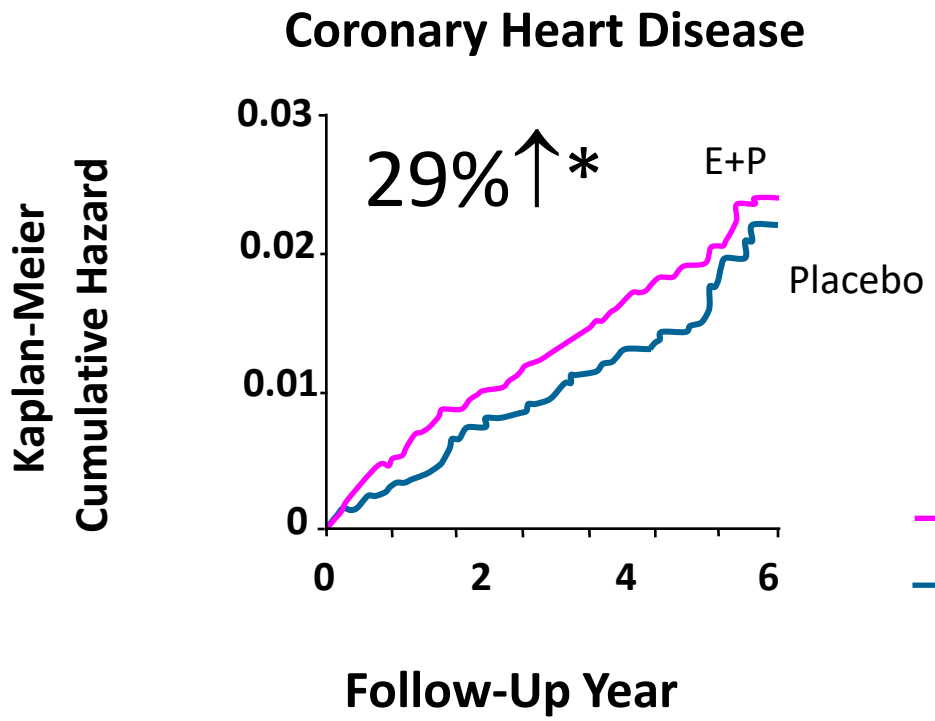


The only progestogen studied was MPA (synthetic progestin)

*95% nominal CI Hazard Ratio = **1.26 (1.00-1.59)**

Adapted from: Writing Group WHI. JAMA 2002

EPT: Coronary Heart Disease (CHD)



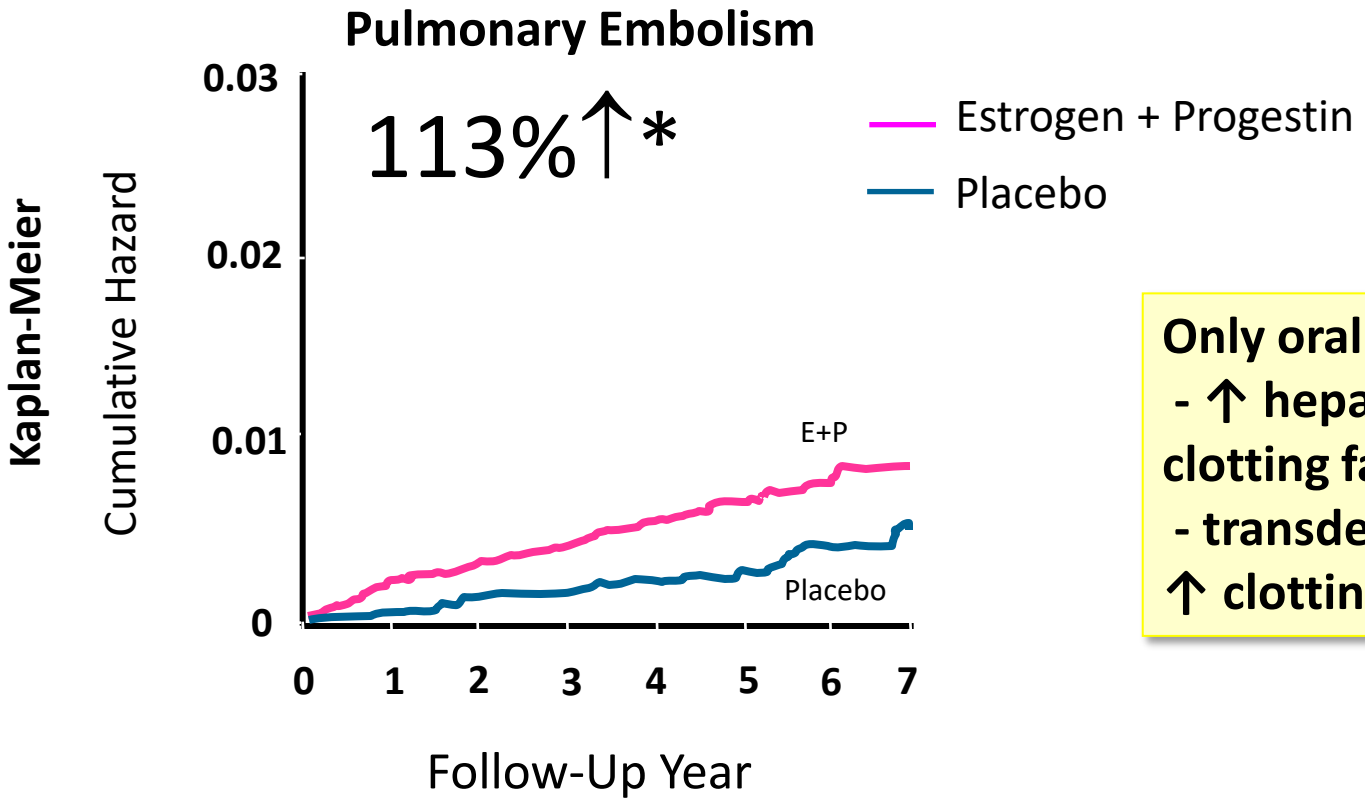
-Initially, no age-stratified analysis presented…

Hazard Ratio = **1.29**

*Statistically significant based on 95% nominal CI on Hazard Ratios

Adapted from: Writing Group WHI. JAMA 2002

EPT: Pulmonary Embolism

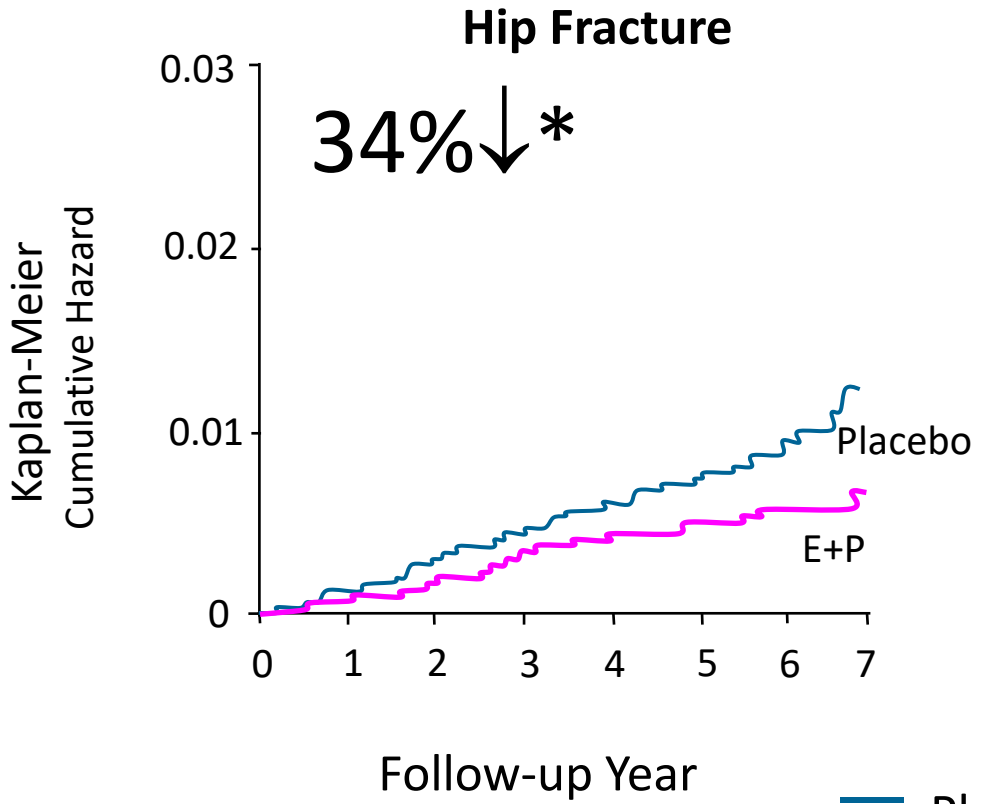


Only oral estrogen used in WHI
- ↑ hepatic production of clotting factors
- transdermal estradiol does <u>not</u> ↑ clotting factors

*95% nominal CI Hazard Ratio = **2.13 (1.39-3.25)**

Writing Group WHI. JAMA 2002

Standard Dose EPT Prevents Fractures

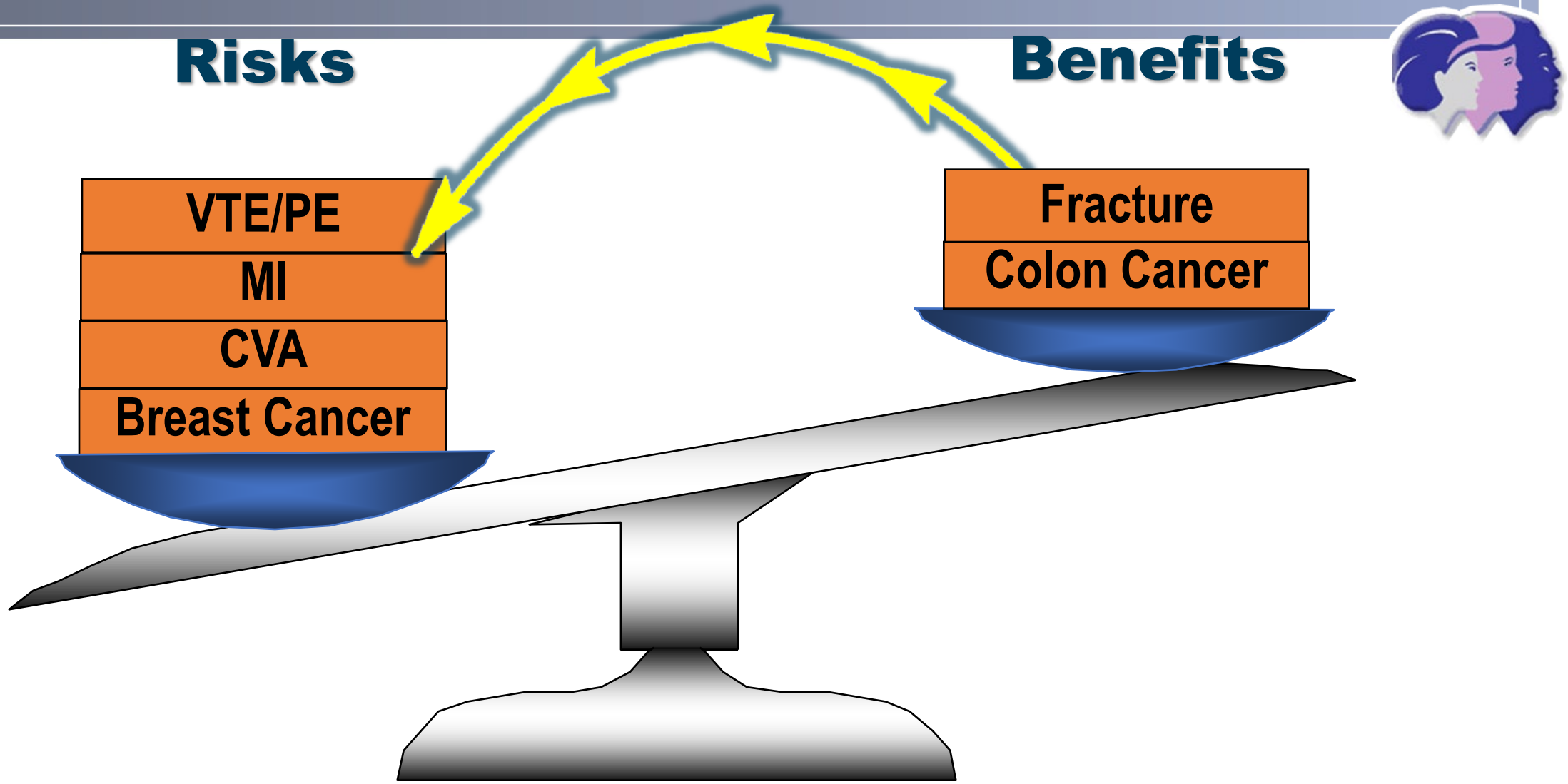


EPT also reduced risk colorectal cancer by 37%

*Statistically significant based on 95% nominal CI on Hazard Ratios

Adapted from: Writing Group WHI. JAMA 2002

WHI EPT Study: Findings at Early Interruption Summer 2002



Adapted from: Writing Group WHI. JAMA 2002

WHI ET Initial (short-term) Findings: Summary as of 2004

- ET **not** found to significantly impact risk of CHD, PE, or colorectal cancer
  - significant reduction in risk of breast cancer and osteoporotic fractures
- Overall safety of ET appears greater than EPT
- ET component of study also stopped early
  - after 6.8 years of follow-up
- 2004 findings received less attention than 2002 report

WHI Steering Committee. JAMA 2004

WHI's Impact on Use of HT in US Women

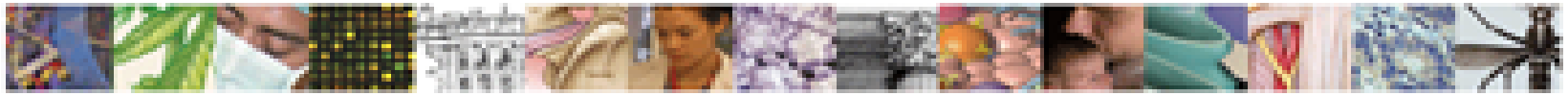
- Since 2002, use of HT has decreased substantially
- Many clinicians, including OB/GYNs, remain reluctant to treat women with bothersome menopausal symptoms

Pendulum swung to a fear-based perspective

Most women with bothersome symptoms are not treated…

PI Jewett, et al. Obstet Gynecol 2014

The NEW ENGLAND JOURNAL of MEDICINE



Perspective

Menopause Management — Getting Clinical Care Back on Track

JoAnn E. Manson, M.D., Dr.P.H., and Andrew M. Kaunitz, M.D.

N Engl J Med 2016; 374:803-806 | March 3, 2016 | DOI: 10.1056/NEJMp1514242

WHI: Long-term 13,18, and 20-Year Follow-up: EPT and ET…

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JE Manson, et al. 2013, 2017 RT Chlebowski, et al. 2020

Risk of Breast Cancer @13 Years Cumulative f/u in Participants OVERALL (all ages at randomization)

- EPT Hazard Ratios (HRs):
  - **Persistent, significant but modest ↑ risk breast cancer: 1.28**

- ET Hazard Ratios:
  - **WHI: Persistent, significant but modest ↓ risk breast cancer: 0.79**

JE Manson, et al. JAMA October 2, 2013

JAMA® The Journal of the American Medical Association

EPT and Elevated Risk of Incident Breast Cancer

- **What does an 1.28 HR for breast cancer mean?**
  - <1 additional case per 1,000 EPT users annually can be attributed to HT (WHI)
    - Per WHO: 'rare'
  - Breast cancer common with or without use of HT
    - Only 1 in 5 breast cancers occurring in women using EPT can be attributed to HT (WHI)

JE Manson, et al. 2013

JAMA®
The Journal of the American Medical Association

Breast Cancer Incidence and Mortality with 20+ Years Median Cumulative f/u*

- EPT Hazard Ratios (HRs):
  - Persistent significant ↑ risk <u>incident</u> breast cancer**:**

    HR 1.28
  - Breast cancer <u>mortality</u> not significantly ↑ed**:** HR 1.35
    - Small #s of breast cancer deaths
- ET Hazard Ratios:
  - Significantly lower <u>incidence</u> of breast cancer: **HR 0.78**
  - Significantly lower <u>mortality</u> from breast cancer: **HR 0.60**

*Statistically significant HRs **bolded**

JAMA®
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RT Chlebowski, et al. JAMA 2020

Breast Cancer Incidence and Mortality with 20+ Years Median Cumulative f/u*

- ET Hazard Ratios:
  - Significantly lower incidence of breast cancer: **HR 0.78**
  - Significantly lower mortality from breast cancer: **HR 0.60**

Might these findings be a fluke, applying only to conjugated estrogen and WHI?

JAMA®
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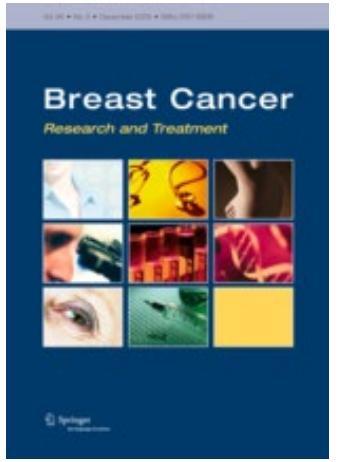
RT Chlebowski, et al. JAMA 2020

ET (CEE or E2) and Risk of Breast Cancer: Meta-analysis of Randomized Trials

- 10 randomized trials of ET vs placebo, including WHI
  - 14,282 post-hysterectomy participants
  - 591 participants diagnosed with (incident) breast cancer
  - ET: 3.6% vs. Placebo: 4.7% diagnosed with breast cancer:
  - Overall RR 0.77 (95% CI 0.65–0.91, *P* = 0.002)

- **Authors' conclusion:** "The totality of randomized clinical trial evidence supports a conclusion that estrogen-alone use significantly reduces breast cancer incidence."

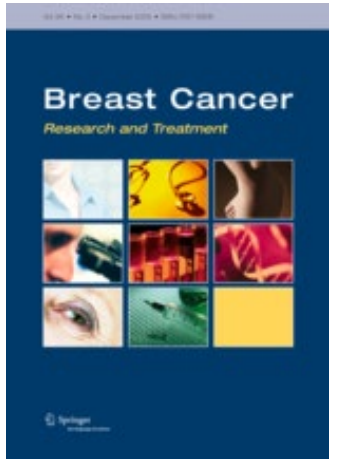


RT Chlebowski…J Manson. Breast Cancer Research and Treatment 2024

ET (CEE or E2) and Risk of Breast Cancer: Meta-analysis of Randomized Trials: Does Type of Estrogen Matter?

- Most of the study participants randomized to ET in trials included in this meta-analysis used **conjugated equine estrogen**

- Although the number of participants randomized to estradiol was small, findings re reduced risk of breast cancer were congruent with the CEE participants and the overall meta-analysis



RT Chlebowski…J Manson. Breast Cancer Research and Treatment 2024

Hormone Therapy and Risk of Young-onset Breast Cancer: 2025 report

- Pooled data from 13 prospective (observational) cohort studies
  - North America, Europe, Asia and Australia
  - ~450,000 women age < 55 years of age
  - Invasive and in-situ cancers diagnosed < 55 years of age
  - Median f/u 7.8 years
  - Mean duration of ET use 4.7 years
  - No information regarding type of estrogen provided

THE LANCET Oncology

KM O'Brien, et al. Lancet Oncol 2025

Estrogen-only Therapy and risk of young-onset Breast Cancer: 2025 report

- No use of hormone therapy
  - HR=1.0, Cumulative risk: 4.1%
- EPT
  - HR 1.05 (NS) Cumulative risk: 4.5%
- Estrogen-only
  - **HR 0.75 (0.67-0.83)** Cumulative risk: 3.6%
- Reduction of breast cancer risk with ET:
  - Stronger if ET started < age 45 years
  - Stronger if ET used > 2 years
  - This 'dose effect' adds credibility to study's findings
- Similar HRs with this report and meta-analysis of RCTs also adds credibility to findings

KM O'Brien, et al. Lancet Oncol 2025

A provocative question …

- Should our new knowledge with respect to ET and prevention of breast cancer change how we counsel patients who have completed childbearing regarding pros and cons of hysterectomy?
- Examples:
  - facing surgery for benign adnexal disease
  - considering surgical vs medical management of AUB
  - making decisions re myomectomy vs. hysterectomy

All-cause Mortality

Many would consider <u>all-cause mortality</u> the most important outcome of clinical trials assessing safety of HT…

Risk of All-cause Mortality @18 Years Cumulative f/u in Participants (all ages at randomization)

- With EPT (HR 1.02) and ET (HR 0.94), **all-cause mortality** similar with HT and placebo
  - Mortality from CVD and Cancer (all types) similar with HT and placebo
  - **WHI recruited women age 50-79 years**
- Above findings refer to all participants (mean age at screening 63-64 years)

Age stratified results…

JE Manson, et al. JAMA September 2017

JAMA® The Journal of the American Medical Association

All-cause Pooled (EPT+ET) Mortality Hazard Ratios at 18 Years Cumulative f/u Stratified by Age at Randomization

70-79 years
1.03

60-69 years
0.98

50-59 years
0.89

Risks ⇧ with age at randomization

JE Manson, et al. JAMA September 2017

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HT, CHD and the 'Timing Hypothesis'

- If initiated **early** in the menopausal transition, HT does not increase coronary heart disease risk
  - May reduce morbidity/mortality if initiated early
  - **'Early':** Age 50-59 years, or < 10 years after menopause onset
  - If initiated later, HT increases CHD risk
- Timing hypothesis may also apply to type II diabetes and dementia

J Hsia. Arch Int Med 2006
JE Rossouw. JAMA 2007
RI Pereira, et al. JCEM 2015
JE Manson. N Eng J Med 2007
S Toh. Annals Int Med 2010
B Imtiaz. Neurology 2017
Stram DO. Menopause 2011
HN Hodis,. N Engl J Med 2016
MA Allison, JE Manson. Editorial. Menopause 2011
P Tuomikoski. Obstet Gynecol 2014

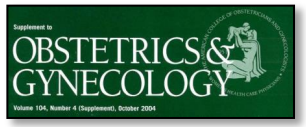
Moving Beyond WHI…

- Type of progestational agent
- Route of estrogen delivery

Risk of Breast Cancer: Is Bioidentical Progesterone Safer than MPA or NETA?

- No randomized trial has compared safety of progesterone with progestins medroxyprogesterone acetate or norethindrone acetate
- However, two observational studies provide reassurance re progesterone
  - 2022 large case-control study (>43,000 breast cancer cases) based on UK Family Practice data
    - E+ progestin (mostly MPA): **RR 1.28** (relative risk similar to WHI findings)
    - E+ progesterone: RR **0.99** (risk ~identical to that of non-users)
- Findings from this large UK study similar to those from an earlier smaller French cohort study (< 1,000 case of breast cancer)

From perspective of breast cancer risk, progesterone appears to be safest progestogen



HA Abenheim, et al. Obstet Gynecol 2022 A Fournier, et al. Int J Cancer 2005 JV Pinkerton, C Wilson, AM Kaunitz. Menopause 2022

Disadvantages of Progesterone

- Micronized oral progesterone formulated with peanut oil
  - Not appropriate for women with peanut allergy

- Endometrial suppression with progesterone less potent than with synthetic progestins including norethindrone acetate and medroxyprogesterone acetate
  - Consider 200 mg Progesterone HS daily dose rather than 100 mg in women using standard dose estrogen
  - Women using higher than standard dose estrogen should routinely use 200 mg Progesterone
  - In women who experience bleeding with E + Progesterone (including those with fibroids and adenomyosis), synthetic progestins (oral and/or intrauterine) often appropriate
    - Consider CEE/bazedoxifene in women with bleeding

Risk of VTE: Is Transdermal Estrogen Safer than Oral?

- No randomized trial data comparing benefits and risks
  - 8 observational studies: VTE risk increased with oral, but not with transdermal ET
- Given consistency and biologic plausibility of observational data, we should counsel patients: **transdermal estrogen safer re risk of VTE**
- Transdermal route particularly appropriate when obesity or other risk factors for VTE present
  - Appropriate also for women with hypertriglyceridemia

PY Scarabin. Lancet 2003 M Canonico. Arterioscler Thromb Vasc Biol 2010 A Bergendal. Menopause 2016 JA Simon . Menopause 2016
C Renoux. J Thromb Haemost 2010 C Renoux,. BMJ 2010
L Laliberté. Menopause 2011 RE Roach. J Thromb Haemost 2012 **Y Vinogradova. BMJ 2019**

Treatment of Menopausal Symptoms: Practical Issues

- One clinician’s approach to HT initiation

Initiating HT in Symptomatic Young/Recently Menopausal women: Evidence-based statements (I)

'Script' examples: *'HT is highly effective in treatment of symptoms and prevention of osteoporosis, including fractures…'*

- **Uterus absent:** *'estrogen therapy does not increase, and in fact, reduces risk of breast cancer'*
- **Oral vs. TD ET:** *'Oral ET increases risk of blood clots, similar to what is seen with younger women using oral contraceptives.' 'Patch ET does not increase clot risk'*
- **Uterus present, E+Progesterone:** *'EPT does not appear to impact risk of breast cancer'*
- **Uterus present, E+Progestin:** *'After 3 or more years of use, EPT slightly increases risk of being diagnosed with breast cancer, underscoring the importance of continuing regular mammograms.'*

Initiating HT in Symptomatic Young/Recently Menopausal women: One Clinician's Approach (II)

- Start HT using **standard** dose of estrogen*
  - **Oral estradiol (E2) 1 mg; Oral conjugated equine estrogen (CE) 0.625 mg**
  - **Transdermal (TD) E2 0.0375 mg or 0.05 mg patch**
    - For overweight/obese women, smokers and other women with ↑ risk VTE/CVD, consider TDE2
- After VMS have resolved for several years on initial dose of estrogen, encourage trial of lower dose
  - If bothersome VMS or loss of sense of wellbeing occur on the lower dose, patients can resume prior higher dose

***Some clinicians start with lower doses**

AM Kaunitz. Clin Obstet Gynecol 2018

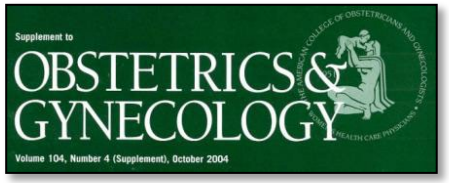
Cho, Kaunitz, Faubion, et al. Circulation 2023

Safety of Menopausal Hormone Therapy in *BRCA* Carriers with Intact Breasts Who Have Undergone Risk-reducing BSO…

- Concerns re safety of HT prevent some mutation carriers from undergoing risk-reducing (lifesaving) BSO

- However, literature review (6 observational reports) reveals that among mutation carriers **with intact breasts** who had RR BSO prior to age 45…

AMK Kaunitz, C Reese, JV Pinkerton. Obstet Gynecol 2025

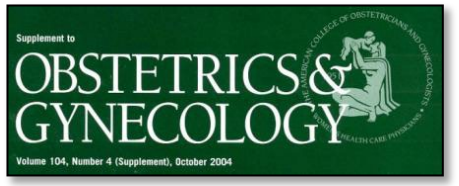


Safety of Menopausal Hormone Therapy in BRCA Carriers Who Have Undergone Risk-reducing BSO

- HT does not elevate risk of breast cancer

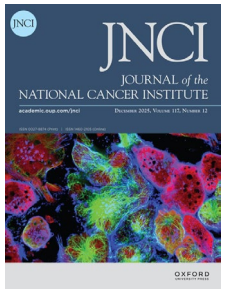
- 'Given the emerging data on the potential of ET to reduce breast cancer risk, clinicians caring for women with *BRCA ½* mutations could consider offering hysterectomy along with BSO as part of risk-reducing surgery.'

AM Kaunitz, C Reese, JV Pinkerton. Obstet Gynecol 2025



Safety of Menopausal Hormone Therapy in BRCA Carriers with Intact Breasts Who Have Undergone Risk-reducing BSO: Largest Study to Date

- A 2025 matched prospective cohort study which assessed breast cancer risk in 676 *BRCA1/2* carriers found, compared with those not using HT, EPT did not elevate risk, while ET significantly reduced risk (by >60%)
- TDET was most common ET: HR 0.46 (P=0.08)
- While numbers were small, none of the 43 users of CEE/bazedoxifene developed breast cancer after a mean follow-up of 6·2 years



Kotsopoulos…Narod. JNCI 2025

Steven Narod, MD

Safety of Menopausal Hormone Therapy in BRCA Carriers with Intact Breasts Who Have Undergone Risk-reducing BSO: Largest Study to Date

- Authors' conclusions:
  - 'Given our finding that MHT use does not increase breast cancer risk in *BRCA* carriers, we believe that these young women need not suffer physical, psychological, and emotional disturbances of abrupt menopause (post-BSO) due to misinformation regarding the safety of estrogen therapy.'
  - 'The observed protective effect of E alone on breast cancer risk suggests that a hysterectomy might be considered at the time of oophorectomy so that women can avail themselves of the potential benefit of unopposed estrogen.'

Kotsopoulos…Narod. JNCI 2025

Steven Narod, MD

Summary: Treating Menopausal Symptoms: an Evidence-based Strategy

- Pendulum has swung from a fear-based towards an evidence-based perspective
- Transdermal ET safer than oral route with respect to risk of clot
- Regarding breast cancer
  - Estrogen-only therapy reduces risk
  - Using progesterone appears to reduce or eliminate the modest increased risk with synthetic progestins…