Have a working knowledge of how route of administration

Understand the tenets of the “gap hypothesis” and how it could impact the overall risk/benefit ratio for cancer.

Describe the current status/outcomes of the WHI, KEEPS, to:

Upon completion of this lecture, participants will be able to:

- Describe the current status/outcomes of the WHI, KEEPS, ELITE and other current hormone therapy (HT) and estrogen therapy (ET) trials, and have a contextual understanding of their clinical implications to date.
- Understand the tenets of the “gap hypothesis” and how it applies differentially to cardiovascular disease vs. breast cancer.
- Have a working knowledge of how route of administration could impact the overall risk/benefit ratio for postmenopausal systemic HT or ET, and how these differences have been incorporated into treatment guidelines.

Learning Objectives:

In the Era of WHI, KEEPS, and ELITE

Background, Update & Perspective

Menopause Prevalence and Duration
- More than 50 million women in the United States are beyond 50 years of age
- The average age of natural menopause is 51.3 years
- 75% of women between the ages of 50 and 55 are postmenopausal
- Premature or early menopause
- 1% of women under the age of 40 experience premature menopause
- 5% of women between 40-45 years of age experience early menopause
- Surgical Menopause
- 267,000 US women age 45 and over undergo hysterectomies each year
- Ovaries are removed in more than 80% of these women
- Among women who have hot flashes (HFs):
- 25% report that these symptoms remain for longer than 5 years
- 10% report that they remain for longer than 10 years
- Vaso motor symptoms (VMS) may last for up to 10 years or longer in some women
- Among women who have hot flashes (HFs):
- 25% report that these symptoms remain for longer than 5 years
- 10% report that they remain for longer than 10 years
- Vaso motor symptoms (VMS) may last for up to 10 years or longer in some women

Advancing Health After Hysterectomy: (AHAH)

As a result of all these factors, an idea became deeply rooted world-wide- the idea that estrogen is dangerous and harmful.

This idea persists among doctors, other health care providers and the public in spite of the plethora of evidence to the contrary

Information and evidence has so far been unable to kill off the idea – it walks among us – like a zombie – seemingly impervious to our best efforts.

“Estrogen is Dangerous and Harmful”

Disclosures 2015

Dr. James A. Simon has served (within the last year) or is currently serving as a consultant to or on the advisory boards of: AbbVie, Inc. (North Chicago, IL), Actavis, PLC. (Dublin, Ireland), Amgen Inc. (Thousand Oaks, CA), Amnitech Pharmaceuticals (Bridgewater, NJ), AstraZeneca, Inc. (Toronto, Canada), Asend Therapeutics (Herndon, VA), Dr. Reddy Laboratories, Ltd. (Hyderabad, India), Exelixis Laboratories, Inc. (West Orange, NJ), JDS Therapeutics LLC (Purchase, NY), Merck & Co., Inc. (Whitehouse Station, NJ), Novo Nordisk Pharmaceuticals, Inc. (New York, NY), Nuelle, Inc. (Bagsvaerd, Denmark), Nuelle, Inc. (Mountain View, CA), Perfini Company, LLC (Duluth, Minnesota), Radius Health, Inc. (Westham, MA), Reprogen Pharmaceuticals, Inc. (Tarrytown, NY), Sandi S.A. (Paris, France), Shionogi Pharmaceuticals, Inc. (Columbus, OH), Shionogi Inc. (Flushing Park, NJ), Sprout Pharmaceuticals (Raleigh, NC), TherapeuticsMD (Boca Raton, FL).

In the last year he has received or is currently receiving grant/research support from: AbbVie, Inc. (North Chicago, IL), Actavis, PLC. (Dublin, Ireland), Agile Therapeutics (Princeton, NJ), Bayer Healthcare LLC. (Tarrytown, NY), New England Research Institute, Inc. (Watertown, MA), Novo Nordisk (Bagsvaerd, Denmark), Pelatin Technologies ( Cranbury, NJ), and TherapeuticsMD (Boca Raton, FL).

He has also served or is currently serving on the speaker’s bureaus of: Amgen Inc. (Thousand Oaks, CA), Bristol-Myers Squibb Co. (Princeton, NJ), Merck (Whitehouse Station, NJ), Nuelle, Inc. (Bagsvaerd, Denmark), Nuelle, Inc. (Mountain View, CA), Novo Nordisk (Bagsvaerd, Denmark), Nuelle, Inc. (Flushing Park, NJ).

Dr. Simon served as chief medical officer (CMO) of Sprout Pharmaceuticals until April 2013.

Have You and Your Patients Been Getting Mixed Signals about Hormone Therapy?
**Zombie Idea**

“An idea that should have been killed by evidence, but refuses to die”

Paul Krugman, Nobel Prize in Economics, 2008
NYT. March 30, 2014

Slide by Voelker EE and Sarrel PM

N.B.: “Zombies” tap into deep-rooted, irrational human fears

---

**Decline in the Use of Postmenopausal HT In the US 1999-2010***

<table>
<thead>
<tr>
<th>HT Use in Women &gt; 40 years (%)</th>
<th>1999-2000</th>
<th>2009-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any formulation</td>
<td>22.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Estrogen only</td>
<td>13.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Estrogen + Progestogen</td>
<td>8.3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

p< 0.01 for all comparisons 1999-2000 vs 2009-2010


---

**Use of Estrogen and Estrogen/Progestin Has Dropped Since the WHI: Results From NHANES**

![Graph showing decline in the use of estrogen and estrogen/progestin](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAA...)

Data from 13,177 women aged 40 years in the National Health and Nutrition Examination Survey (NHANES), Sarrel et al. Obstet Gynecol. 2012;120:595-603.

---

**Vasomotor Symptoms and Related Psychosocial Impairment During the Menopausal Transition**

- Hot flushes
- Night sweats
- Sleep disturbances
  - Insomnia
  - Sleep apnea
- Mood swings
  - Irritability
  - Sadness
  - Tension
- Cognitive deficits
  - Poor concentration
  - Verbal memory problems
- Social impairment
  - Disruption of family relationships
  - Social isolation
- Work-related difficulties
- Reduced productivity
- Other quality-of-life impairment
  - Embarrassment
  - Anxiety
  - Fatigue
- Social impairment
  - Disruption of family relationships
  - Social isolation
- Work-related difficulties
  - Reduced productivity
- Other quality-of-life impairment
  - Embarrassment
  - Anxiety
  - Fatigue

---

**Impact and Costs of Untreated Vasomotor Symptoms**

![Graph showing incidence and costs of untreated vasomotor symptoms](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAA...)

---

**Causes of Death Among U.S. Women**

![Graph showing causes of death](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAA...)

### Observational Studies of CVD Risk: ET Compared with HT

<table>
<thead>
<tr>
<th>Event</th>
<th>Overall Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>Absolute Risk per 10,000 Women/Year</th>
<th>Absolute Benefit per 10,000 Women/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.29</td>
<td>1.02–1.63</td>
<td>0.85–1.97</td>
<td>7</td>
</tr>
<tr>
<td>CHD-Revised</td>
<td>1.24</td>
<td>1.00–1.54</td>
<td>0.87–1.90</td>
<td>6</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.26</td>
<td>1.00–1.56</td>
<td>0.97–1.90</td>
<td>7</td>
</tr>
<tr>
<td>Strokes</td>
<td>1.60</td>
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<td>0.93–1.84</td>
<td>7</td>
</tr>
<tr>
<td>VTE</td>
<td>1.00</td>
<td>0.95–1.07</td>
<td>0.96–1.05</td>
<td>7</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.67</td>
<td>0.47–0.96</td>
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<tr>
<td>Hip fractures</td>
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</tr>
</tbody>
</table>

ET = unopposed estrogen
HT = sequential estrogen + progestin

### WHI received enormous media coverage – more than 400 newspaper stories and 2500 television-radio stories...

- "The Truth About Hormones – Hormone Replacement Therapy is Riskier Than Advertised: What's a woman to do?" July 22, 2002
- "The End of the Age of Estrogen" July 22, 2002
- "Hormone Therapy: The Danger Assessed" May 27, 2003
- "Another Study Slams Hormone Pills; The Replacement Regimen Doesn't Help Improve Women's Memory or Mood, Researchers Said" March 18, 2003
- "Hormone Hazards" July 29, 2002
- "Study Dismissed HRT As Clinically Useless" March 18, 2003
- "A New Blow to Hormone Therapy," June 24, 2003
- "And what about the embargo?" July 30, 2002

### WHI-E: Relative and Absolute Risk

<table>
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<tr>
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</table>

### WHI-E+P: Relative and Absolute Risk

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<tr>
<th>Event</th>
<th>Overall Hazard Ratio</th>
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<td>0.65–1.10</td>
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</tr>
</tbody>
</table>
WHI E-Alone Substudy

**Risk by Age**

<table>
<thead>
<tr>
<th>Age 50-59</th>
<th>Age 60-69</th>
<th>Age 70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>CER (Relative Breast Cancer)</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>CEC (Relative Endometrial Cancer)</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>VTE</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**WHI – CAC**

**Coronary Artery Calcium Score in Women on ERT alone in WHI aged 50-59**

- 1,064 women aged 50-59 with hysterectomy on ERT alone who had screening for coronary calcium
- CAC reflects progression from simple fatty streak to complex plaque
- Mean CAC/ERT, 83.1 vs placebo CAC/placebo, 123.1 (P=0.02)
- Among women with 80% adherence
  - CAC of 0 OR .64
  - CAC 10-99 OR .55
  - CAC >100 OR .46

**WHI : Estrogen Alone**

**Cardiovascular Outcomes Ages 50-59**

- MI, coronary death, CABG, PCI, and confirmed angina

**WHI-EP Trial and WHI Observational Study of Estrogen and Progestin**
WHI Post-Intervention Reports: ET+P 2010 and ET 2011

Results of the WHI After More Than a Decade of Follow-up

Enrolled More Than 27,000 Menopausal Women, Aged 50 to 79 Years

Women who had a hysterectomy

CEE (n=5710) Placebo (n=5691)

CEE vs placebo:
No significant change in risk of coronary heart disease (CHD)
Persistence of decreased risk of breast cancer

CEE + MPA (vs placebo):
Increased risk of breast cancer and breast cancer mortality

Women with an intact uterus

CEE (n=5310) Placebo (n=5292)

CEE vs placebo:
No significant change in risk of coronary heart disease (CHD)
Persistence of decreased risk of breast cancer

CEE + MPA (vs placebo):
Increased risk of breast cancer and breast cancer mortality

Major outcomes after 10.7 years (mean intervention 7.3 years)

Major outcomes after 11.0 years (mean intervention 5.6 years)

Women with an intact uterus

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Increased risk of breast cancer and breast cancer mortality

Major outcomes after 11.0 years (mean intervention 5.6 years)

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Persistence of decreased risk of breast cancer

CEE + MPA (vs placebo):
Increased risk of breast cancer and breast cancer mortality

Major outcomes after 10.7 years (mean intervention 7.3 years)

HRT and CV Risk by Age: WHI Second Arm (Estrogen Alone after Hysterectomy)

<table>
<thead>
<tr>
<th>Age</th>
<th>CHD</th>
<th>MI</th>
<th>Mortality</th>
<th>Breast Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>.59</td>
<td>.54</td>
<td>.73</td>
<td>.80</td>
</tr>
<tr>
<td>60-69</td>
<td>1.0</td>
<td>1.05</td>
<td>1.04</td>
<td>.73</td>
</tr>
<tr>
<td>70-79</td>
<td>1.06</td>
<td>1.26</td>
<td>.81</td>
<td>.81</td>
</tr>
</tbody>
</table>

LaCroix AZ et al. JAMA. 2011;305(13):1305-14

ET and HT vs. Placebo and Breast Cancer in The WHI

E+P

Mortality

Breast Ca

LaCroix AZ et al. JAMA. 2011;305(13):1305-14

WHI E-alone post-intervention study

<table>
<thead>
<tr>
<th>Menopause Status</th>
<th>CHD</th>
<th>MI</th>
<th>Mortality</th>
<th>Breast Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal</td>
<td>.59</td>
<td>.54</td>
<td>.73</td>
<td>.80</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>1.0</td>
<td>1.05</td>
<td>1.04</td>
<td>.73</td>
</tr>
<tr>
<td>Menopausal</td>
<td>1.06</td>
<td>1.26</td>
<td>.81</td>
<td>.81</td>
</tr>
</tbody>
</table>

LaCroix AZ et al. JAMA. 2011;305(13):1305-14

WHI Post-Intervention Reports: ET+P and ET 2013

Estrogen + Progestin Therapy and Risk of MI in WHI: Results According to Age and Time Since Menopause

<table>
<thead>
<tr>
<th>Age</th>
<th>HR</th>
<th>Time Since Menopause Onset</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>1.32*</td>
<td>&lt;10 yrs</td>
<td>0.91</td>
</tr>
<tr>
<td>60-69</td>
<td>1.05</td>
<td>10-19 yrs</td>
<td>1.16</td>
</tr>
<tr>
<td>70-79</td>
<td>1.46*</td>
<td>≥ 20 yrs</td>
<td>1.99*</td>
</tr>
</tbody>
</table>

P, interaction 0.55 *P, interaction 0.01*

*based on 5 events
*N enrollment
*P-value <0.05
*P-value for trend by age group


Other Miscellaneous Findings From WHI 2013 (1)

- For CEE alone, younger women (aged 50-59 years) had more favorable results for all-cause mortality, myocardial infarction, and the global index (nominal P < .05 for trend by age).
- Following stopping of the interventions, fewer than 4% of women reported personal use of hormone therapy.
- RE: Breast cancer—
  - women assigned to CEE alone had an HR of 0.79 (95% CI, 0.61-1.02) compared with placebo and the HRs did not differ by time since randomization.
  - The HR for invasive breast cancer with CEE plus MPA remained statistically significantly elevated during the post-intervention and cumulative follow-up compared with placebo (HR for cumulative follow-up, 1.28 [95% CI, 1.11-1.48]; a detailed time dependent analyses identified risk attenuation with time since cessation of hormone therapy use.


Kronos Early Estrogen Prevention Study (KEEPS): Design

- N=727 menopausal women aged 42-59 (mean age, 52.7, within 3 years of LMP)
- Trial Duration: 48 months
- Design: Multicenter double blind, placebo controlled RCT
- Treatment Arms:
  - Oral conjugated equine estrogens (o-CEE) given as Premarin®, 0.45 mg/d (lower dose than WHI)
  - Transdermal estradiol (t-E2) given by Climara® patch, 0.05 mg/d
  - Placebo

(active arms received cyclical micronized progesterone [Prometrium®] 200 mg/d x 12 d/mo; placebo arm received placebo Prometrium®)

Wharton M, Glaser CL, Miller VM, Astorina S, Stefanick and Design of the Kronos Early Estrogen Prevention Study (KEEPS) and the KEEPS Cognitive and Affective Sub-Study (KEEPSCog). Brain Res. 2013 June 13; 1514:12-17.

Women’s Health Initiative (WHI) Estrogen-Alone Trial: MI, CABG/PCI Results According to Age at Randomization

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total MI</th>
<th>CABG/PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>0.55 (0.31-1.00)</td>
<td>0.56 (0.35-0.88)</td>
</tr>
<tr>
<td>60-69</td>
<td>0.95 (0.68-1.30)</td>
<td>1.13 (0.86-1.46)</td>
</tr>
<tr>
<td>70-79</td>
<td>1.24 (0.88-1.75)</td>
<td>1.07 (0.79-1.43)</td>
</tr>
</tbody>
</table>

P, interaction = 0.02 *P, interaction = 0.06

*P, trend by age group


Other Miscellaneous Findings From WHI 2013 (2)

- A reduced risk of endometrial cancer with CEE plus MPA emerged post-intervention. HR of 0.58 (95% CI, 0.40-0.86) compared with placebo.
- Women in both the CEE + MPA and CEE alone groups had statistically significant 33% reductions in hip fracture compared to placebo.
- In both trials, women assigned hormone therapy had significantly lower rates of treated diabetes than women assigned to placebo. HR, 0.81 (95%CI, 0.70-0.96) for CEE plus MPA and 0.85 (95% CI, 0.76-0.98) for CEE alone; these reductions in diabetes dissipated post-intervention in both trials.
- Rates of gallbladder disease were approximately 50% higher among women assigned to hormone therapy in both trials; HRs for gallbladder disease were attenuated, but still elevated for CEE plus MPA and became neutral for CEE alone.
- Health-related quality of life (RAND 36-Item Short Form Health Survey) with CEE plus MPA compared with placebo was associated with a small but statistically significant benefit for physical functioning, role physical, bodily pain, and general health, and neutral results for the other subscales.


KEEPS: Directions of Changes in CHD* Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>O-CEE</th>
<th>T-E2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>Favorable</td>
<td>Neutral</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Adverse</td>
<td>Neutral</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>Favorable</td>
<td>Neutral</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>Neutral</td>
<td>Favorable</td>
</tr>
<tr>
<td>HOMA-IR*</td>
<td>Neutral</td>
<td>Favorable</td>
</tr>
</tbody>
</table>

o-CEE is Premarin® 0.45mg/d
T-E2 is Climara® 0.05 mg/d
*CHD: Coronary Heart Disease; HOMA-IR: homeostasis model assessment estimated insulin resistance

Wharton M, Glaser CL, Miller VM, Astorina S, Stefanick and Design of the Kronos Early Estrogen Prevention Study (KEEPS) and the KEEPS Cognitive and Affective Sub-Study (KEEPSCog). Brain Res. 2013 June 13; 1514:12-17.

**KEEPS Overall Summary & Conclusions**

- **Similarities:** Both o-CEE and t-E2 had:
  - neutral→favorable effects on CVD biomarkers (differences related to first-pass liver metabolism).
  - neutral effects on CIMT and CAC (ns trend for CAC benefit).
  - neutral effects on cognition; favorable effects on VMS.
- **Differences:**
  - o-CEE improved mood
  - t-E2 improved HOMA-IR and some advantages on sexual function.
- **Conclusions:**
  - KEEPS highlights the need for individualized decision making about HT, by treatment priorities and risk factor status.
  - Additional research on HT in newly menopausal women (i.e. formulations/doses/routes of delivery) is needed.

*Presented by JoAnn E. Manson, MD, Dr.PH, NCMP at NAMS Annual Meeting October 11, 2013*

---

**Effects of Different Hormone Therapies on Breast Pain in Recently Postmenopausal Women: Findings from the Mayo Clinic KEEPS Breast Pain Ancillary Study**

Julia A. Files, MD, Virginia M. Miller, PhD, Stephen S. Che, MS and Sandhya Pruthi, MD

Conclusion: Four years of treatment with o-CEE at a lower dose than that studied in the WHI with cyclic m-P or transdermal E2 with cyclic m-P did not increase breast pain in healthy, recently menopausal women.

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**Timing Hypothesis**

The “timing hypothesis” posits that there is a differential effect on atherosclerosis and clinical events according to when postmenopausal HRT is initiated in relation to menopause.

---

**Impact of Timing of Hormone Therapy?**

**Early initiation**

(+) Heart

(-) Breast

**Later initiation**

(-) Heart

(+) Breast
The Early versus Late Intervention Trial with Estradiol (ELITE)

- 643 healthy postmenopausal women—no clinical evidence of CVD or diabetes mellitus
- Stratified by time since menopause
  - <6 years, n=271 (median, 2.5 years)
  - >10 years, n=372 (median 14.3 years)
- Primary end point: progression of carotid artery intima media thickness (CIMT).
- Women randomized to oral 17β-estradiol 1 mg/d with or without vaginal micronized progesterone gel 4% (45 mg) 10 days per month or to placebo

The rate of CIMT progression was significantly reduced with HT relative to placebo (approx 40%) in the early postmenopausal group but not in the late postmenopausal group (p = 0.007).

When HT is initiated at or within 6 years of menopause: significant reduction in CVD
When initiated >10 years after menopause, no change.

Hodis H et al, Am Heart Assoc 2014

Are Transdermal Preparations Safer?

CHD
- In a Danish national registry, significantly lower risk of MI was found with the transdermal route than with oral unopposed estrogen (P=0.04).

STROKE
- In a nested case-control study from the UK General Practice Research database (n=15,710), the risk of stroke was not increased with low-dose transdermal estrogen (≤50 mcg) but did increase with higher transdermal doses and oral therapies.

VTE
- In a French systematic review and meta-analysis, the risk of first-time VTE was increased in oral estrogen users, but not in transdermal estrogen users (OR 2.5 [1.9–3.4] for oral; 1.2 [0.9–1.7] for transdermal).

Transdermal estrogen and change in body weight or BMI

• "One crossover study noted greater fat gain with oral vs. transdermal estrogen, results that are supported by clinical data."

— Santen RJ. Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement. JCEM. 2010;95:S1:S1-S66

Transdermal Estradiol Absorption From Hydroacholic Gels (i.e. Estrogel® 0.06%, Elestrin® 0.06%, Divigel® 0.1%) Impact From Other Transdermals

- Repeated daily application of moisturizer placed on the skin 1 hour after application of 0.06% estradiol gel (Estrogel®), increased the mean AUC 0-24h and Cmax of estradiol by 38% and 73%, respectively.
- Repeated daily application of sunscreen for 7 days placed on the skin 1 hour after application of 0.06% estradiol gel (Estrogel®), decreased the mean AUC 0-24h and Cmax of estradiol by 13%.
- If the application site was washed 1 hour after application, there is a 22% decrease in average 24-hour serum concentrations of estradiol.
- There have been no studies to assess the impact of moisturizer, or sunscreen if applied before the application of 0.06% estradiol gel (Estrogel®). 0.06% estradiol gel-Estrogel®, prescribing information.
- Sunscreen application 10 minutes before application of 0.06% estradiol gel (Elestrin®), increased the exposure to estradiol by approximately 55%.
- No significant change in estradiol exposure was observed when sunscreen was applied 25 minutes after application of 0.06% estradiol gel (Elestrin®).
- Prolonged (7 days) concurrent application of sunscreen to the site of 0.06% estradiol gel (Elestrin®) application increased exposure to estradiol by about 2.6-fold.
- 0.06% estradiol gel-Elestrin®, prescribing information.
- The effect of sunscreens and other topical lotions on the systemic exposure of 0.1% estradiol gel (Divigel®) has not been evaluated in clinical trials.
- 0.1% estradiol gel-Divigel®, prescribing information.

How Might You Explain the Cardiovascular and Breast Cancer Results of the WHI (The Gap or Timing Hypothesis), and keep them in clinical perspective?

The Gap or Timing Hypothesis (earlier “better”, later “worse”)

This Gap Hypothesis also seems to apply to:
- Mood
- Dementia
- Ischemic Stroke
- Mild cognitive impairment
- Parkinson’s Disease

• How might you explain the cardiovascular and breast cancer results of the WHI (The Gap or Timing Hypothesis), and keep them in clinical perspective?

Breast Cancer

The Headlines: The Women’s Health Initiative Results (E + P)

- 41% Increase in Strokes
- 29% Increase in Heart Attacks
- 100% Increase in Venous Thromboembolism
- 22% Increase in Total CV Disease
- 26% Increase in Breast Cancer (3.3/1000 increased to 4.1/1000 for each year)
- 37% Decrease in Colorectal Cancer
- 33% Decrease in Hip Fracture
- 24% Decrease in Total Fractures
- No Difference in All Cause Mortality
**WHI Breast Cancer by Years of Prior Use (E + P)**

<table>
<thead>
<tr>
<th>YRS</th>
<th>N</th>
<th>HT vs PBO</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>12304</td>
<td>114 vs 102</td>
<td>1.06</td>
<td>0.81-1.38</td>
</tr>
<tr>
<td>&lt;5 yrs</td>
<td>3005</td>
<td>32 vs 15</td>
<td>2.13</td>
<td>1.15-3.94</td>
</tr>
<tr>
<td>5-10 yrs</td>
<td>783</td>
<td>11 vs 2</td>
<td>4.61</td>
<td>1.01-21.02</td>
</tr>
<tr>
<td>&gt;10 yrs</td>
<td>515</td>
<td>9 vs 5</td>
<td>1.81</td>
<td>0.60-5.43</td>
</tr>
</tbody>
</table>

*Writing Group for Women’s Health Initiative Investigators. JAMA. 2002; 288*

---

**HT and Breast Cancer Risk**

- Initial WHI data suggested that CEE + medroxyprogesterone acetate (MPA) was associated with increased breast cancer risk.
- Adjusting for breast cancer risk factors at baseline, there was no statistically significant increase in breast cancer risk in the combined arm vs placebo (RR=1.20; 95% CI, 0.94-1.53) at 5+ years of treatment.
- Tremendously good news for women.

Hodis HN, Mack WJ. Menopause. 2007;14:944-957.*

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**The Other Gap or Timing Hypothesis (earlier “worse”, later “better”)**

*This Gap Hypothesis also seems to apply to: Breast Cancer*

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**WHI E+P Trial: No Effect of E+P on Risk of In Situ Breast Cancer**


---

**Route of Administration and Type of Progestin:**

- Breast cancer was not elevated within the first 3 years of use, but it rose to 1.31 (95% confidence interval 1.20-1.42) for the use from 3-5 years and to 2.07 (1.84-2.30) with 10 or more years of use.
- Sequential progestogen for 5 years or more was accompanied with a lower risk elevation (1.78, 1.64-1.90) than exposure to continuous use (2.44, 2.17-2.72).
- Oral and transdermal use of E2-progestogen therapy was associated with comparable risk elevations for breast cancer.

Comparison of VTE, DVT and PE in RCTs

<table>
<thead>
<tr>
<th>Therapy Placebo</th>
<th>WHI-EP</th>
<th>WHI-E CEE+MPA</th>
<th>WEST</th>
<th>WHI-E CEE alone</th>
<th>WHI-E ECE alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk</td>
<td>2.06 (1.57-2.70)</td>
<td>1.95 (1.43-2.61)</td>
<td>2.15 (1.49-3.07)</td>
<td>1.32 (0.99-1.75)</td>
<td>1.37 (0.99-2.27)</td>
</tr>
<tr>
<td>Absolute Risk</td>
<td>17 35</td>
<td>15 35</td>
<td>10 34</td>
<td>17 35</td>
<td>12 34</td>
</tr>
<tr>
<td>(Events per 10,000 Women per Year)</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>No. Additional Cases per 10,000 Women per Year of Therapy</td>
<td>17 26</td>
<td>13 26</td>
<td>10 26</td>
<td>17 26</td>
<td>12 26</td>
</tr>
</tbody>
</table>
| WHI-E in Perspective

<table>
<thead>
<tr>
<th>Outcome</th>
<th>WHI-E</th>
<th>RUTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. cases/10,000 women/year of treatment</td>
<td>n=10,739</td>
<td>n=10,101</td>
</tr>
<tr>
<td>mean age</td>
<td>63.6 years</td>
<td>67.5 years</td>
</tr>
<tr>
<td>mean follow-up</td>
<td>6.8 years</td>
<td>5.6 years</td>
</tr>
<tr>
<td>CHD -5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Stroke 12 (8)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>VTE 7</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>PE 4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>DVT 6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bone fracture</td>
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</tr>
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Primary Prevention of CHD with Lipid-Lowering Therapy in Women

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<th>WHI-E CEE+MPA</th>
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<tr>
<td>Relative Risk</td>
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<tr>
<td>Absolute Risk</td>
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Breast Cancer in Randomized Controlled Trials of Hormone and Statin Therapy

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CONCLUSIONS:

The synthesis of data using Bayesian meta-analysis indicates a reduction in mortality in younger postmenopausal women taking hormone therapy compared with no treatment. This finding should be interpreted taking into account the potential benefits and harms of hormone therapy.
Take Home message

- The synthesis of pooled data indicates that hormone therapy reduces total mortality by 25% in younger postmenopausal women.
- A similar reduction in mortality is seen with randomized trials and observational studies.
- The probability that hormone therapy reduces total mortality in younger women is almost 1.
- This finding of reduced mortality should be interpreted taking into account the potential benefits and harms of hormone therapy.


Conclusions of S. Salpeter...

- CONCLUSIONS: Hormone therapy for 5 to 30 years in younger postmenopausal women increases quality adjusted life-years and is cost-effective. Hormone therapy started in later years results in a loss of quality-adjusted life for several years before a net gain can be realized.


Does the type of progestogen matter?

Relative risks for invasive breast cancer by type of HRT and type of progestagen, compared with HRT never-use (E3N cohort study, N=80,377)

- E2 alone: 1.00
- E2 + mic P4: 1.10
- E2 + DHG: 1.60
- E2 + synth. Prog.: 1.30

E2: estradiol; mic P4: micronized progesterone; DHG: dydrogesterone; syn. Prog.: synthetic progestins (mainly nomegestrol acetate, promegestone, chlormadinone acetate, cyproterone acetate, medrogestone)


Is There a Difference Among Progestins?

- Comparative data is insufficient
- Current research is ongoing in light of WHI findings that suggested possible harm from progesterone (EPT compared with ET)
- PEPI, a large RCT, suggested micronized progesterone has less negative impact on lipids.
- Small trials suggest ↓ VTE with micronized progesterone
  - Caveat: formulated in a peanut oil suspension so ask about peanut allergies!


Progestin Routes of Administration

- Oral
  - Medroxyprogesterone
  - Micronized progesterone
- Transdermal progestin (combined with estrogen)
- IUD with levonorgestrel
Levonorgestrel IUD HT for Endometrial Protection

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Journal</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon 2015</td>
<td>2015</td>
<td>JAMA</td>
<td>Additional sections: 1. 2011</td>
</tr>
</tbody>
</table>
### And What if You Stop…?

<table>
<thead>
<tr>
<th>Period</th>
<th>Mortality Ratio</th>
<th>95% Confidence Interval</th>
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</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First year</td>
<td>1.26</td>
<td>1.16–1.37</td>
</tr>
<tr>
<td>Beyond 1 year</td>
<td>0.75</td>
<td>0.72–0.78</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First year</td>
<td>1.63</td>
<td>1.47–1.79</td>
</tr>
<tr>
<td>Beyond 1 year</td>
<td>0.59</td>
<td>0.55–0.64</td>
</tr>
</tbody>
</table>


### Suggested Reading
- Lobo RA. Where Are We 10 Years After the Women’s Health Initiative? J Clin Endocrinol Metab. 2013 May;98(5):1771-80.
- Simon JA. What if the Women’s Health Initiative had used transdermal estradiol and oral progesterone instead? 2014 Jul;21(7):769-83.

### Questions?