Menopausal Hormone Therapy and Breast Cancer
Disclosures

• **Current Grant Funding:** Pfizer
• **This presentation represents my research and does not present the views of the Endocrine Society in my role as President**
I will first examine data on the effects of Menopausal Hormone Therapy (MHT) as reported from the only randomized controlled trial
Women’s Health Initiative Study in USA

- 27,000 healthy women entered
- Average age 63
- Two arms
  - Placebo versus estrogen (E)
  - Placebo versus estrogen plus progestin (E+P)
- Randomized Controlled Trial
- Treatment for 6 years
WHI E+P
ages 50-79
2002

Benefits

Risks

RR 1.23

RR 2.05

RR 1.26

RR 2.06
Average Age 63

Benefits

Risks

Risks

RR 2.05

RR 2.06

RR 1.23

RR 1.26
Women make a decision about menopausal hormone therapy shortly after menopause and commonly plan to use for about five years.
Reanalysis of WHI
Post-hoc Reanalysis WHI

Post-hoc Reanalysis WHI

• October 2, 2013 Manson JA et al JAMA 310:1353-1368, 2013
• Recognized that relative risk data can be misleading
Relative vs Absolute Risk

• Example of relative risk
  – One flight by plane from Lima to New York City---one chance in 10 million of death in a plane crash
  – Five flights from Lima to New York City---five chances in one million of death in a plane crash

  – This is a 500% increase in relative risk

• Example of absolute risk
  – One in five 10 million chance of dying with five flights
  – absolute risk is very small even though relative risk is 500 %
Post-hoc Reanalysis WHI

- Recognized that relative risk data can be misleading
- Reported excess risks and benefits
Post-hoc Reanalysis WHI

- Recognized that relative risk data can be misleading
- Reported excess risks and benefits
- Calculated the difference in rates between placebo group and CEE plus MPA or CEE alone
Example of Calculation of Excess Risk

- Without menopausal hormone therapy the incidence of breast cancer is 4 per 1000 women.
- With hormone therapy the incidence is 7 per 1000 women.
- The excess risk would be 3 per 1000.
Post-hoc Reanalysis WHI

- Recognized that relative risk data can be misleading
- Reported excess risks and benefits
- Calculated the difference in rates between placebo group and CEE plus MPA or CEE alone
- Analyzed subgroup of women ages 50-59
Postmenopausal women (50-59 years of age)

Risks

- Coronary heart disease
- Invasive breast cancer
- All fractures
- Hip fractures
- All-cause mortality
- Diabetes

Benefits

- Stroke
- Pulmonary embolism
- Deep vein thrombosis
- Colo-rectal cancer
- Endometrial cancer (N/A)
- Lung cancer

Primary End points

Secondary end points

Self-reported End point

Number of women per 1,000 per 5 years of use

2.5

7.5

12.5

15
Number of women per 1,000 per 5 years of use

Risk

Benefit
How can E+P increase the risk of breast cancer and E alone reduce the risk?
We developed a biologically based and a computer based models to address the question.

Life History of a Breast Tumor

Start of mutation cascade through initiation events
Start of mutation cascade through Initiation events

Average of 11 mutations

HELU, ADH, DCIS, IBC
For diagnosis, the tumor must exceed the detection threshold.
What determines the detection threshold?
Influence of Age on Detection Threshold

- <40: 1.63 cm
- 40-49: 1.44 cm
- 50-59: 1.25 cm
- 60-69: 1.07 cm
- >70: 0.88 cm

Average for the WHI age 50-69: 1.16 cm
Change in mammographic density with age
Change in mammographic density with age
Change in mammographic density with age
How long does it take for a de novo tumor to reach the detection threshold?
Depends on the doubling time
It takes 30 doublings for a tumor to go from one cancerous cell to a tumor of a billion cells, the number needed to reach a size of 1 cm in diameter.
The average tumor doubling time in post-menopausal women is 200 days.
How many de novo tumors would have reached the diagnostic threshold within the 5.6 year duration of the WHI E+P study?
Only tumors with a doubling time of 50 days or less
94% of tumors were pre-existing and only 6% de novo.
Therefore nearly all of the effects of menopausal hormone therapy in the WHI were on pre-existing occult tumors.
What was prevalence of pre-existing, occult tumors at start of WHI Study?
Occult breast cancers diagnosed at autopsy
Ages 40-80

TABLE 9. Incidence of breast cancer in autopsy studies of women not known to have breast cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cases</th>
<th>Autopsy setting</th>
<th>% Occult DCIS (all ages)</th>
<th>% Occult IBC (all ages)</th>
<th>% Occult DCIS or IBC (age ≥40 yr)</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryan</td>
<td>200</td>
<td>Hospital</td>
<td>0</td>
<td>0</td>
<td>0% (40–100 yr)</td>
<td>214</td>
</tr>
<tr>
<td>Kramer</td>
<td>70</td>
<td>Hospital</td>
<td>4.3</td>
<td>1.4</td>
<td>4.3% (DCIS), 1.4% (IBC) (all &gt;70 yr)</td>
<td>211</td>
</tr>
<tr>
<td>Wellings</td>
<td>67</td>
<td>Hospital</td>
<td>4.5</td>
<td>0</td>
<td>10% (DCIS) (50–70 yr)</td>
<td>206</td>
</tr>
<tr>
<td>Nielsen</td>
<td>77</td>
<td>Hospital</td>
<td>14.3</td>
<td>1.3</td>
<td>Not available</td>
<td>212</td>
</tr>
<tr>
<td>Alpers</td>
<td>101</td>
<td>Hospital</td>
<td>8.9</td>
<td>0</td>
<td>13% (DCIS) (40–70 yr)</td>
<td>208</td>
</tr>
<tr>
<td>Bhathal</td>
<td>207</td>
<td>Forensic</td>
<td>12.1</td>
<td>1.4</td>
<td>Not available</td>
<td>210</td>
</tr>
<tr>
<td>Bartow</td>
<td>221</td>
<td>Forensic</td>
<td>0</td>
<td>1.8</td>
<td>7% (IBC) (45–54 yr)</td>
<td>209</td>
</tr>
<tr>
<td>Nielsen</td>
<td>109</td>
<td>Forensic</td>
<td>14.7</td>
<td>0.9</td>
<td>39% (DCIS) (40–49 yr)</td>
<td>213</td>
</tr>
</tbody>
</table>

In Situ 6%  Invasive 1%  Total 7%
This is the same situation as for prostate cancer. At age 50, about 15% of men have prostate cancers too small to detect.
We then used our model to re-analyze the WHI data
Effect of estrogen plus a progestogen on these occult tumors
Estrogen plus a progestogen

- We assumed that this combination caused occult, pre-existing tumors to grow more rapidly
- We used our growth model to examine
- We examined the effects of tumor doubling times of 180 days, 150 days, and 120 days
150 day doubling time

200 day doubling time
How do we explain the effects of estrogen alone?
CEE alone arm of the WHI
23% reduction in breast cancer incidence.

Ages 50-79

HR 0.77 (CI 0.62-0.95)
Hypothesis

- Conjugated equine estrogens caused apoptosis of occult tumors
- Long term deprivation of estrogen causes breast cancer cells to undergo apoptosis in response to estrogen
- The average age of women in the WHI was 63, 12 years after the average age of menopause
In Vitro Model of Long Term Estrogen Deprivation

MCF-7

>6 months

LTED

Estrogen deprived media
Wild Type Cells

Apoptosis (fold of induction)

E2 concentration (M)
Long term anti-estrogen treated xenografts

Data of VC Jordan
Percent apoptosis

Jordan et al

$E_2$ (5 days)

$P < .00014$

*
Model based on apoptosis used to predict effect of estrogen alone on breast cancer risk
Historical Footnote

- High dose estrogen was used to treat metastatic breast cancer
- Only effective in women at least 5 years postmenopausal
- Recent studies indicate that physiologic doses of estradiol also cause tumor regression in 30% of postmenopausal women with metastatic breast cancer
Implications

- Need to treat these occult breast cancer lesions before they become clinically detectable.
- A form of hormone therapy for menopausal women which prevents these occult lesions from growing but relieves menopausal symptoms would be ideal.
Treatment before diagnostic threshold reached
Emerging approach

New class of hormonal agents
TSEC
(tissue selective estrogen complex)
A combination of a SERM (selective estrogen receptor modulator) plus an estrogen

A new combination approved in USA – the SERM bazedoxifene in combination with conjugated equine estrogen

Treats symptoms of menopause but is breast neutral

7000 women studied in clinical trials
BZA/CEE

- Avoids need to use a progestogen
- Treats hot flashes, vulvovaginal atrophy, osteopenia/osteoporosis
- No uterine stimulation
- In underpowered trials, no cardiac disease or CVA and low incidence VTE
- Preclinical data—decrease in breast cancer
How does the TSEC work?
Gene Transcription

Estrogen-Estrogen

Estrogen receptor complex

E₂

E₂
Gene Transcription

Estrogen-Estrogen

7000 genes

Estrogen receptor complex
Gene Transcription

Estrogen receptor complex

SERM-SERM

Estrogen-Estragon

SERM complex

Estrogen receptor complex

$E_2$
Gene Transcription

Estrogen-receptor complex

SERM - TSEC Complex (Tissue Selective estrogen complex)
Wardell SE and McDonnell D
Mol Endo 26:1235-1248, 2012
Effects on immature mouse breast
The effects of the TSEC on breast are anti-estrogenic.
Carcinogen Induced Tumor Model

(Sprague Dawley Rats, 50 days of age)
Tumor incidence

- OVX
- Intact
- CEE 3 mg
- CEE 10 mg
- E₂ implant

BZA
Summary

- Menopausal hormone therapy with E + P does not cause breast cancer but stimulates the growth of pre-existing small occult tumors.
- E alone reduces risk of breast cancer due to apoptosis.
- Emerging therapies are being developed to improve safety with respect to the breast.
Conclusions

• The benefits of menopausal hormone therapy outweigh the risks in most women just entering menopause
• Before recommending menopausal hormone therapy, determine the underlying risk of breast cancer and don’t recommend if a woman is at moderate or high risk of breast cancer
• TSECs may be used to eliminate the need for a progestogen and may be safer on the breast
Thank you for your attention