Peri-Menopause and Menopause

Gary S. Donovitz, M.D., F.A.C.O.G
Peri-Menopause

• Perimenopause means "around menopause" and refers to the time period during which a woman's body makes its natural transition toward permanent infertility (menopause).
Menopause

- Menopause is defined as occurring 12 months after your last menstrual period and marks the end of menstrual cycles. Menopause can happen in your 40s or 50s, but the average age is 51 in the United States.

**Traditional Definition But Not Practical**
Why Does Menopause Matter?

- 100 years ago menopause was the end of lifespan
- 50 years ago women lived 20 years after menopause
- Now the post-menopause life has increased by 30+ years
- How do we optimize those 30+ years

Same for Andropause
HEALTHY LIFE EXPECTANCY

22/23

Industrialized Nations
Hopkins Medicine

• Wen Shen M.D.
• Graduated 1987 Johns Hopkins

• “Too Few doctors are prepared to help guide women through menopause......”
• “Hopkins never prepared me for the problems her patients were facing...”
“In response to recent media attention being given to so-called bioidentical hormones, The American College of Obstetricians and Gynecologists (ACOG) reiterates its position that there is no scientific evidence supporting the safety or efficacy of compounded bioidentical hormones.”
Endocrine Society Advises Against Compounded Hormone Use April 01, 2016 Journal of Clinical Endocrinology and Metabolism.

• "Custom-compounded hormones should be reserved for situations in which a patient is allergic to or does not tolerate any of the FDA-approved therapies and treatment is necessary for his or her health,“
• of all menopause therapy prescriptions custom-compounded products, garnering about $1 billion in annual sales. "This to us seems somewhat absurd when we have a large variety of what are technically the same bioidentical hormones that are FDA approved....It's kind of unfortunate that we live in an era where this has become so widespread it's a very big business."
“The risk of side effects (such as heart attack, stroke, blood clot, or breast cancer) with HT in healthy women ages 50 to 59 is low. In contrast, using HT for a long time or starting HT when you are a number of years beyond menopause is associated with a higher risk of these side effects.”
ET Group from W.H.I.

<table>
<thead>
<tr>
<th>Outcome by Age, y</th>
<th>No. of Cases (Annualized %)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
<th>Favors CEE</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td></td>
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<tr>
<td>50-59</td>
<td>16 (0.14)</td>
<td>29 (0.24)</td>
<td>0.56 (0.30-1.03)</td>
<td>.14</td>
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<tr>
<td>60-69</td>
<td>87 (0.54)</td>
<td>98 (0.59)</td>
<td>0.92 (0.69-1.23)</td>
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<td>.59</td>
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<tr>
<td>70-79</td>
<td>74 (0.88)</td>
<td>72 (0.84)</td>
<td>1.04 (0.75-1.44)</td>
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<td>.39</td>
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<td>Stroke</td>
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<td>50-59</td>
<td>19 (0.16)</td>
<td>19 (0.16)</td>
<td>1.08 (0.57-2.04)</td>
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<td>60-69</td>
<td>79 (0.49)</td>
<td>50 (0.30)</td>
<td>1.65 (1.16-2.36)</td>
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<tr>
<td>70-79</td>
<td>60 (0.71)</td>
<td>49 (0.57)</td>
<td>1.25 (0.85-1.82)</td>
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<td>Venous Thromboembolism</td>
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<td>50-59</td>
<td>18 (0.15)</td>
<td>15 (0.13)</td>
<td>1.22 (0.62-2.42)</td>
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<tr>
<td>60-69</td>
<td>49 (0.31)</td>
<td>30 (0.23)</td>
<td>1.31 (0.86-2.00)</td>
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<tr>
<td>70-79</td>
<td>34 (0.40)</td>
<td>24 (0.28)</td>
<td>1.44 (0.86-2.44)</td>
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<tr>
<td>Invasive Breast Cancer</td>
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<td>50-59</td>
<td>25 (0.21)</td>
<td>35 (0.29)</td>
<td>0.72 (0.43-1.21)</td>
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<tr>
<td>60-69</td>
<td>42 (0.26)</td>
<td>60 (0.36)</td>
<td>0.72 (0.49-1.07)</td>
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<tr>
<td>70-79</td>
<td>27 (0.32)</td>
<td>29 (0.34)</td>
<td>0.94 (0.56-1.60)</td>
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</tbody>
</table>
BHRT Cardio protective

- Transdermal E2 does not increase risk of VTE like oral E2
- Cardioprotective, decreased risk of AMI
- Decreased risk of T2DM
- Micronized P4 reduces risk of T2DM, does not increase risk of VTE, reduces BP

Best Outcome!

• Right Hormone (Bio-Identical)

• Right Dose (BioTE® Dosing Site)

• Right Route Of Administration (Sub Q)
W. H. I.- Worst Outcome!

- ✗ Wrong Estrogen
  - CEE is not a human hormone
  - Mostly Equilllin
    - Low Estradiol (E2)

- ✗ Wrong “Progesterone”
  - MPA blocks progesterone receptors and is not a human hormone. MPA reverses benefits of E2

- ✗ Wrong route
  - Oral Estrogens increase inflammation

Wrong women
- Older (mean 63 years) who may already have established CV disease or breast cancer
Conventional HRT
Women's Health Initiative Trial

- 41% increase in stroke
- 29% increase in heart attacks
- 26% increase in breast cancer
- Twice the rate of blood clots
- 76% Increase in Alzheimer’s Dementia

**Note:**

After this trial many women were left with NO alternative for hormone balance and symptom relief. Sadly, there have been safe, alternative methods available for years.
WALL STREET: LOSING SAVINGS—AND TRUST

IS THIS OUR FIRST ANCESTOR?

THE TRUTH ABOUT HORMONES

Susan Peirce, 60, of Miami, has been on hormones for 15 years. She is angry and confused but not yet ready to stop taking them.

Hormone-replacement therapy is riskier than advertised. What's a woman to do?
The new Mayo Clinic study combines the data from 43 randomized, controlled trials on hormone therapy. The trials included more than 52,000 women. All were 50 or older. The researchers found that neither of the main hormone therapies – estrogen alone, or estrogen combined with progesterone – affected a woman's risk of dying from any cause, or specifically from a heart attack, stroke, or cancer.
Conventional HRT
Women's Health Initiative Trial

In less than 2 years, half of the women who were using systemic hormone therapy stopped the treatment. Compared with 2001, use of oral estrogen-only among women aged 50-59 years with no uterus dropped by almost 60% in 2004, 71% by 2006, and 79% in 2010 and 2011, the authors noted.

In 2004 and 2011, they restated their data and said the mortality was lower in Estrogen users but the trend continues.

JAMA 2011;305:1305-14
The Mortality Toll of Estrogen Avoidance- Yale Study

Analysis of the 2011 WHI-ET (Women’s Health Initiative Estrogen-Alone Trial) data, showing that a minimum of 18,600 and as many as 91,600 excess deaths occurred between 2002 and 2011 among hysterectomized women aged 50-59 years due to ET avoidance

Am. J. Public Health 2013
Which Diseases Has HRT Been Shown to Be Protective Of?

- Coronary Artery Disease
- Alzheimer’s Disease
- Dementia
- Strokes
- Degenerative Arthritis
- Osteoporosis
- Sexual Dysfunction
- Macular Degeneration
- Breast Cancer
- Colon Cancer
- Prostate Cancer
Positive Effects of Bio-identical Testosterone

WOMEN

- Enhanced libido
- Heart Protection
- Lower cholesterol and LDL
- Increased energy
- Enhanced sleep
- Feeling of overall well-being
- Reducing body fat
- Stronger bones and muscles
- Depression relief
- Reduced “brain fog”

Minimal side effects for either men or women
Tx the Patient NOT the Lab

“Clinical manifestations of testosterone deficiency do not occur at a definitive threshold value”
Women with Low T

- Increased risk for Alzheimer's Disease
- Increased Risk for CVD
- Increased Risk for ORF
- Increased Risk for DM
- Possibly Breast Cancer
Top Ten Myths about Testosterone in Women

- **Testosterone is a Male Hormone**
  - Where is the AR located???

- **Testosterone’s only role in women is sex drive and libido**

- **Testosterone masculinizes women**
  - Requires 30x dose we use

- **Testosterone causes hoarseness and voice changes**
  - Only true of anabolics

- **Testosterone causes hair loss**
Top Ten Myths about Testosterone in Women (cont.)

• **Testosterone has adverse effects of the heart**
• **Testosterone causes liver damage**
  • 3 reported cases hepatocellular carcinoma from oral synthetic T
• **Testosterone causes aggression**
• **Testosterone may increase the risk of breast cancer**
• **The safety of testosterone use in women has not been established**
Effect on Lipids
Time-course on lipids.

Effects of low-fat diets on TC, HDL-C and LDL-C only showed significant reductions in premenopausal women.

Liping Wu, MS, RN, Di Ma, MS, Benita Walton-Moss, DNS, Zhong He, PhD, RN
Menopause. 2014;21(1):89-99
The Bones
Osteoporosis

• Approximately one in seven women over age 50 has osteoporosis
• About one half of all women over age 50 can be expected to suffer an osteoporosis-related fracture during their lifetime
• After a hip or vertebral fracture, direct and indirect mortality can be as high as 25–30%
• All postmenopausal women should be advised to consume adequate amounts of calcium and vitamin D
• Treatment is recommended if the T-score is less than -2.5
• DXA screening should start at age 65
1. Testosterone: “Bone Builder”
2. Demonstrated Four-fold Increase in Bone Density vs. Oral Estrogen and 2.5x Greater than Patches
   • 8.3% per/year for Pellet Therapy
   • 3.5% per/year for Patches
   • 1-2% per/year for Oral Estrogen

Am Journal OB/GYN 163, 1474-1479
Vertebral Fracture Risk Reduction Proportional to Hip BMD Change*

Total Hip BMD Change at 24 Months

* Analysis of summary statistics from the FIT Trial

Hochberg M, Arthritis & Rheum. 1999;42:1246-54
Bisphosphonates

- Slow the natural resorption and remodeling process, making bones super hard and break easier
- Cell and bone mineral depletion are actually accelerated if you are using bisphosphonates and minerals are not being adequately replaced.
- There are cases of jaw bone necrosis has caused the teeth to fall out.
- Increased risk of a fib lead leading to blood clots

Bad Medicine
**Bisphosphonates**

- Fosamax is the third most frequently prescribed drug to seniors.
- It does not prevent fractures when used to prevent osteoporosis.
- Actonel significantly reduces hip fx in women over 70 only if they already have spinal fx.
Romosozumab May Be the Next Big Treatment for Osteoporosis

- Monoclonal Antibody
- Increase BMD at spine 11%
- Increase BMD Hip 4.1%
- Minimal S.E.
- Injections...Injections...Injections
- Not here till 2021
- How does it work????
### SSRIs and Fractures

#### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
<th>Weight, % (random effect)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td></td>
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<tr>
<td>Ensrud, et al. 2003$^8$</td>
<td>4.95</td>
<td>1.44 (0.93-2.24)</td>
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<tr>
<td>Schneeweiss and Wang 2004$^{19}$</td>
<td>9.89</td>
<td>1.80 (1.54-2.10)</td>
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<tr>
<td>Richards, et al. 2007$^9$</td>
<td>4.47</td>
<td>2.10 (1.30-3.40)</td>
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<tr>
<td>Lewis, et al. 2007$^{11}$</td>
<td>3.53</td>
<td>1.65 (0.93-2.94)</td>
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<tr>
<td>Ziere, et al. 2008$^{10}$</td>
<td>3.54</td>
<td>2.35 (1.32-4.18)</td>
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<tr>
<td>Spangler, et al. 2008$^{20}$</td>
<td>10.99</td>
<td>1.30 (1.20-1.41)</td>
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<tr>
<td><strong>Case Control</strong></td>
<td></td>
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<tr>
<td>Liu, et al. 1998$^7$</td>
<td>10.50</td>
<td>2.40 (2.13-2.70)</td>
<td></td>
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<tr>
<td>Hubbard, et al. 2003$^{12}$</td>
<td>10.66</td>
<td>1.42 (1.28-1.58)</td>
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<tr>
<td>Vestergaard, et al. 2006$^{13}$</td>
<td>11.35</td>
<td>1.40 (1.34-1.46)</td>
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<tr>
<td>Bolton, et al. 2008$^{14}$</td>
<td>10.86</td>
<td>1.45 (1.32-1.59)</td>
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<tr>
<td>van den Brand, et al. 2009$^{15}$</td>
<td>9.24</td>
<td>2.35 (1.94-2.84)</td>
<td></td>
</tr>
<tr>
<td>Verdel, et al. 2010$^{21}$</td>
<td>10.01</td>
<td>1.95 (1.68-2.26)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>100.00</td>
<td>1.72 (1.51-1.95)</td>
<td></td>
</tr>
</tbody>
</table>

*Osteoporosis Intl. 2012.23:365-375*
NOTE: The 1988–1994 estimates for men are considered unreliable because the estimates have relative standard errors of 20%–30%.

SOURCE: CDC/NCHS, Health, United States, 2013, Figure 25. Data from the National Health and Nutrition Examination Survey.
The Brain
Early MCI

- Dementia takes 15-20 years to develop and begins with MCI (Mild Cognitive Impairment)
- MCI begins in the 30s-40s
- By 80-85, 50% of Americans have dementia
- Dementia may be accelerated by hormonal and neurotransmitter imbalances
HRT and Neurodegenerative Conditions

- HRT and particularly ERT plays an efficacious role in preventing neurodegenerative conditions
- E2 (17B Estradiol) can reduce the risk for Alzheimer’s disease and minimize cognitive decline in otherwise healthy women
- E2 can protect against B-amyloid induced degeneration
- Progestins may actually dampen this affect
- Compared to non-users E2 used for avg. 15 years had increased cerebral blood flow

Silverman et al looked at 17B Estradiol vs C.E.E. vs C.E.E. plus progestin on cerebral metabolic activity!

Which one performed the best especially on verbal memory? 17B Estradiol 3 s.d. higher

Verbal Memory is predominant symptom of Early A.D.

Psychoneuroendocrinology 2010;36:502-513
Alzheimer's Disease

- Number of Alzheimer’s cases will triple by 2050
- Cost will increase 500% to 1.1 trillion dollars
- Alzheimer’s patients spend 3x more on health care cost than other patients
- Several Trials are under way to try and prevent the disease (SERM, SARMS)

Neurology 2/2013
Journal of Alzheimer’s and Dementia 2/2013
Alzheimer's Disease

- Both Estrogen and Testosterone have Neuroprotective role
- Women have a higher incidence of AD 8:1 over men
- Women with lower E2 levels have even greater risk of AD
- There is overwhelming evidence that E and T helps decrease apoptosis
- This protective effect of both hormones decreases the beta amyloid deposition

Gonadal Sex Steroids

• ANTIOXIDANT
• ANTI-INFLAMMATORY
• ANTI-AMYLOIDGENIC
Alzheimer's disease and HRT
THE HEART
Cardiovascular Disease

• Leading cause of morbidity and mortality in the United States
• Affects 12 million people
• 1 million deaths per year

JCEM 2005;90:6257-62
1 in 7 Premenopausal Women Die from HEART DISEASE

For POSTMENOPAUSAL WOMEN That Number RISES to 1 in 3
More Fatal Than Any Other Disease

- Heart disease is the leading cause of death of American women, killing more than a third of them.
- More than 200,000 women die each year from heart attacks, five times as many women as breast cancer.

www.cdc.gov/women/lcod/2010
Women on Statins and HRT and CVD

• Classic case of perception vs reality
• Extrapolation of data from studies on men
• No evidence that statins reduce all cause mortality or are beneficial for primary prevention
• All cause mortality rates from 1992-1996 to 2002 to 2006 increased in 42% of U.S. counties, but increased in only 3.4% of U.S. counties for men.
• Among women on HT and satins 5/10,000 CV events if on statins only 18/10,000

Menopause 2015. 22:363-64
Menopause 2015.22: 369-76
Women on Statins and HRT and CVD

“It is important to be clear that HT reduces all cause mortality, whereas statin therapy does not in primary prevention. Avoidance of HT is associated with excess morbidity and mortality.”

Menopause 2015. 22:363-64
Estrogen Replacement and Coronary Artery Disease

Effect on Survival in Postmenopausal Women

Jay M. Sullivan, MD; Roger Vander Zwaag, PhD; Jeff P. Hughes, MA; Virginia Maddox; Frank W. Kroetz, MD; K. B. Ramanathan, MD; David M. Mirvis, MD

Arch Intern Med—Vol 150, December 1990

Fig 3.—Ten-year survival of group 2 patients with left main coronary stenosis of 50% or greater or other stenosis of 70% or greater.
Effects of HRT on CV Events in Recent Post-Menopausal Women: Randomized Trial

• 1006 women, 45-58 y.o., recently post-menopausal
• Treated with 17 Beta Estradiol and norethindrone if they had uterus
• After 10 years: 16 women had CV event in treatment group vs 33 in control group (HR .48, C.I. .26-.87)
• No increase risk of Breast cancer or DVT or stroke
• After 16 years the protection was still present

BMJ 2012;345:e6409
Trajectories of Estradiol- European J Preventative Cardiology-2015
Trajectories of FSH- European J Preventative Cardiology-2015
Differential Effects of 17β Estradiol, CEE, and Raloxifene
Dr. D Can You Help Sort This Out?

- Estrogen responses can be cell type-specific.
- Due to variance in estrogen receptor isoform expression and variable recruitment of coregulatory molecules.
- The balance of estrogen isoforms changes with age, which has been shown to influence the vascular response to oxidative stress, nitric oxide production, and the process of atherosclerosis.
Aromatase Extremes and CV Mortality in Older Women

• Prospective Study 809 women over 50 y.o. not using Estradiol
• Aromatase Index (estrone /androstenedione) measured and patients followed for 14 yr
• 49% of deaths due to CV Disease
• Highest and Lowest Quintiles were positively associated with CVD mortality (nearly double the middle quartiles)
• Age and B.M.I. are positively associated with aromatase activity

Clinical Endocrinology
2012;77:391-98
BREAST CANCER
Breast Cancer

- Most Common female cancer
- Median age 61 y.o.
- 400,000 deaths annually worldwide
- 75% occur in postmenopausal women
- 80% are hormone receptor positive
- How long do they use adjuvant therapy?
- What percent reoccur in years 5-15 after dx?
### WHI Estrogen Alone

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>Nominal CI</th>
<th>Adjusted CI</th>
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</thead>
<tbody>
<tr>
<td>CHD&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.95</td>
<td>0.79-1.16</td>
<td>0.76-1.19</td>
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<tr>
<td>Stroke&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.39</td>
<td>1.10-1.77</td>
<td>0.97-1.99</td>
</tr>
<tr>
<td>Breast Ca&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.77</td>
<td>0.59-1.01</td>
<td>0.57-1.06</td>
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<tr>
<td>Total Fx&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.70</td>
<td>0.63-0.79</td>
<td>0.59-0.83</td>
</tr>
</tbody>
</table>

*Final, centrally adjudicated data*

Review of Studies Published From 1975-2000: Lack of Consistent Results ET and Breast Cancer Risk (45 Studies)

- 82% of studies reported risk estimates not significantly different from 1.0
- 13% of studies reported risk estimates > 1.0, but none > 2.0
- 2% of studies reported risk estimates < 1.0

Reduced breast cancer incidence in women treated with subcutaneous testosterone, or testosterone with anastrozole: A prospective, observational study

<table>
<thead>
<tr>
<th>Table 4</th>
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</thead>
<tbody>
<tr>
<td>Breast cancer cases in women using testosterone (T) or T with anastrozole (A) without estrogen compared with major studies using estrogen (E), progestin (P) therapy, E/P/T, E/T, past users, never users and SEER incidence rates.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N patients</th>
<th>Age, years</th>
<th>Cases/100,000 person-years</th>
<th>Years observed</th>
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</thead>
<tbody>
<tr>
<td>WHI (E/P)</td>
<td>8,506</td>
<td>63.2</td>
<td>380</td>
<td>5.2</td>
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<tr>
<td>Placebo</td>
<td>8,102</td>
<td>63.3</td>
<td>300</td>
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<tr>
<td>MWS current users</td>
<td>394,697</td>
<td>55.1</td>
<td>501</td>
<td>14</td>
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<tr>
<td>Past users</td>
<td>221,056</td>
<td>56.7</td>
<td>337</td>
<td></td>
</tr>
<tr>
<td>Never users</td>
<td>513,272</td>
<td>57.7</td>
<td>325</td>
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<td>Adelaide (E/P/T, E/T)</td>
<td>508</td>
<td>56.4</td>
<td>238</td>
<td>5.9</td>
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<td>Dayton (T, T/A)</td>
<td>1,268</td>
<td>52.2&lt;sup&gt;a&lt;/sup&gt; 56.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>142</td>
<td>5.0</td>
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<td>ITT</td>
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<td>Adherent</td>
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<td>73</td>
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<tr>
<td>SEER incidence rates</td>
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<td>50-54</td>
<td>234</td>
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<td>55-59</td>
<td>293</td>
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<td></td>
<td></td>
<td>60-64</td>
<td>358</td>
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</tbody>
</table>

<sup>a</sup> Mean age at first T insertion

<sup>b</sup> Age at time of analysis, for comparison to SEER data
Dayton Experience-82 month data-January 2015

• 4 cases of invasive BCA in 5231 p-y of therapy
• Incidence of 76/100 000 p-y
• SEER expected incidence 297/100 000 p-y

10th European Congress on Menopause and Andropause
5/2015
Dr. Donovitz 2008-2015

- 41,000 insertions
- 20% males
- 80% females
- Total Females = 32,800 insertions
- Avg Frequency 3.6 months
- Therefore 9,111 female patients
- Total 10 breast cancers, 0 mortality
38 developed breast cancer each year, compared to 30 breast cancers for every 10,000 women taking a placebo each year.

There was no difference in the development of breast cancer during the first 4 years among women taking estrogen plus progestin, compared to those taking a placebo. After that time, the numbers began to increase. After an average of 5.2 years, there was an increased risk of breast cancer in women taking estrogen plus progestin compared to those taking placebos.

34 had blood clots in the lungs or legs, compared to 16 out of every 10,000 women taking a placebo.
Hormone Replacement Therapy After a Diagnosis of Breast Cancer in Relation to Recurrence and Mortality

- 2755 women age 35-74
- The rate of breast cancer recurrence was 17 per 1000 person-years in women who used HRT
- 30 per 1000 person-years in nonusers
- Breast cancer mortality rates were five per 1000 person-years in HRT users and 15 per 1000 person-years in nonusers
- Total mortality rates were 16 per 1000 person-years in HRT users and 30 per 1000 person-years in nonusers

Journal of the National Cancer Institute, Vol. 93, No. 10, May 16, 2001
Hormone Replacement Therapy After a Diagnosis of Breast Cancer in Relation to Recurrence and Mortality----

Confounding facts

- Tamoxifen has anti-estrogenic effects on the breast and reduces risks of recurrence and death
- Ovarian ablation by bilateral oophorectomy, pelvic irradiation, or drugs improves survival in young women with breast cancer
- Postmenopausal patients with breast cancer who are obese experience worse survival than those who are lean

Journal of the National Cancer Institute, Vol. 93, No. 10, May 16, 2001
But are These Confounding Facts???

- Tamoxifen is an estrogen blocker at the level of the breast. In pre-menopausal women when estradiol levels are higher, it blocks estrogen at the level of the ER α receptor so BCL-2 is reduced, telomerase activity is reduced, and cell proliferation is reduced.

Whether a cell should live or die is largely determined by the Bcl-2 protein

- Estradiol Erα ↑
- Estradiol Erβ ↓
- Testosterone ↓
- Progesterone PRβ ↓
- Progesterone PRα ↑
But are These Confounding Facts???

• Ovarian ablation by bilateral oophorectomy, pelvic irradiation, or drugs improves survival in young women with breast cancer. Young women with or without ovaries will have mutation in the DNA of epithelial cells allowing for proliferation with high levels of tissue estradiol. Breast tissue aromatase also plays a factor.

But are These Confounding Facts???

• Postmenopausal patients with breast cancer who are obese experience worse survival than those who are lean. Note that estrone has $5\times$ the binding affinity of ER $\alpha$. So there is increase BCL-2, telomerase activity is increased, and cell proliferation is increased.

Matrix Metalloproteinase-9

- If MMP-9 is increased in stroma worse prognosis
- Degrades extracellular matrix enabling tumor invasion
- Increased metastatic disease
- Increased angiogenic activity

Clin Cancer Res 2004;10: 7621
Breast Ca Res Treat 2007;102:253-61
Management (a.k.a. Traditional Therapy)

**WOMEN**

- Premarin, Enjuvia, Estradiol, etc.
- Vivelle
- Synthetic Estrogen and Testosterone injections
- Sub-cutaneous Pellet Both E2 and T
Potential and Unnecessary Effects of Oral Estrogen Therapy Continued

- SHBG
- CBG
- TBG
- CRP, IL-6, MMP-9
Provocative Thoughts of the Day

- Is lowering BP to extremely low levels good for the patient?
- Where is the data that lowering cholesterol is so beneficial?
- Do mammograms save lives or increase mastectomies?
- Is hormone optimization the key to improving quality of life?
- If we continue to over-diagnose won’t we make people sicker not healthier with drugs and tx we use?
THANK YOU