Estrogen Metabolism

Jim Paoletti, Pharmacist, FAARFM
ZRT Laboratory
• The following potential conflict of interest relationships are germane to my presentation:
  – Equipment: None
  – Speaker Bureau: ZRT Laboratory
  – Stock Shareholder: none
  – Grant/Research Support: none
  – Consultant: ZRT Laboratory

• Status of FDA devices used for the material being presented: N/A
• Status of off-label use of devices, drugs, or other materials that constitute the subject of this presentation: N/A
Disclaimer

Employee of ZRT Laboratory

ZRT Laboratory is a testing Laboratory for hormones, cardiometabolic risks factors, Vitamin D
Objectives

• Explore estrogen production, metabolism and choices for therapy
Three Stages of Breast Cancer

- **Initiation** - DNA Damage
  - Estrogen metabolites involved
- **Promotion** - Tumor Growth
- **Progression** - Invasion/Metastasis
The three major estrogens produced by our bodies:

- Estrone (E1)
- Estradiol (E2)
- Estriol (E3)

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## Bio-identical Estrogens

### Original Formulations (80% Estriol)

<table>
<thead>
<tr>
<th>Human Estrogen</th>
<th>Tri-Est (original) 1.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>Estradiol 0.1 mg (10%)</td>
</tr>
<tr>
<td>Estrone</td>
<td>Estrone 0.1 mg (10%)</td>
</tr>
<tr>
<td>Estriol</td>
<td>Estriol 0.8 mg (80%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bi-est (original) 1.0mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol 0.2 mg (20%)</td>
</tr>
<tr>
<td>Estriol 0.8 mg (80%)</td>
</tr>
</tbody>
</table>
# Bio-identical Estrogens

## 50% Estriol Formulas

<table>
<thead>
<tr>
<th>Human Estrogen</th>
<th>Tri-Est 0.2 mg</th>
<th>Bi-est 0.2mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol 6%</td>
<td>Estradiol 0.05 mg (25%)</td>
<td>Estradiol 0.1 mg (50%)</td>
</tr>
<tr>
<td>Estrone 60%</td>
<td>Estrone 0.05 mg (25%)</td>
<td></td>
</tr>
<tr>
<td>Estriol 34%</td>
<td>Estriol 0.1 mg (50%)</td>
<td>Estriol 0.1 mg (50%)</td>
</tr>
</tbody>
</table>
The Influence of Estriol
The Influence of Estriol

ER E2
ER E2
ER E3
ER E3
ER E3

E2
E2
E2
E3
E3
The Influence of Estriol

<table>
<thead>
<tr>
<th>E3:E2</th>
<th>E2 Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mg Bi-est 80:20</td>
<td></td>
</tr>
<tr>
<td>0.4 mg Bi-est 50:50</td>
<td></td>
</tr>
</tbody>
</table>
ESTROGEN METABOLISM AND BREAST CANCER INITIATION

PROGESTERONE

E1-S04

Sulfotransferase

Sulfatase

17β-HSD-Type II

17β-HSD-Type I

CYP-1B1

I3C

4-OH-E1

2-OH-E1

16-OH-E1

E3

INACTIVE ESTROGEN METABOLITES

COMT
SAMe

GSH Transferase

POLLUTANTS

DNA ADDUCT FORMATION

DNA DAMAGE MUTATION

PROTEIN BINDING

NO FURTHER EFFECT

DNA ADDUCT FORMATION

DNA REPAIR

NO FURTHER EFFECT

David Zava, PhD
ESTROGEN METABOLISM AND BREAST CANCER INITIATION

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16-OH-E2

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4-QUINONE

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DNA REPAIR

NO FURTHER EFFECT

PROTEIN BINDING

2-OH-E2

2-QUINONE

INACTIVE ESTROGEN METABOLITES

GSH Transferase

COMT SAMe

David Zava, PhD (modified)
• Cavalieri EL, Rogan EG. Depurinating estrogen-DNA adducts in the etiology and prevention of breast and other human cancers. Future Oncol 2010;6(1):75-79.

Estrogen Meabolites

• Estrone and Estradiol are initially metabolized by two major pathways

  1. Formation of catechol estrogens at the 2- or 4-position
     • Cytochrome P450 (CYP) 1B1 almost exclusively metabolizes formation of 4-OHE1 or 4-OHE2
     • Cytochrome P450 (CYP) 1A1 preferentially hydroxylates E1 and E2 at the 2 position

  2. 16α hydroxylation
Estrogen Metabolites

• 4-hydroxyestrogens
  • Can form quinone metabolite and DNA adduct formation that binds tightly to DNA and is carcinogenic
  • 4-OH Es have greater carcinogenic potency than 2-OHEs
    – Due to formation of depurinating adducts with DNA
• 2-hydroxyestrogens bind tightly to DNA, but in a stable form that is eventually repaired
  – Increased with onions, garlic, broccoli, cauliflower, I3C and DIM
• 16-hydroxyestrogens–
  – Undergoes protein binding in vivo – no further effect
  – Evidence it may be carcinogenic – *in vitro* testing
  – Decreases proportionally with increase in 2-OHE1
Figure 1. Major metabolic pathway in cancer initiation by estrogens.
Figure 2. Formation, metabolism and DNA adducts of estrogens. Activating enzymes and depurinating DNA adducts are in red and protective enzymes are in turquoise. N-acetylcyesteine (NACys, shown in blue) and resveratrol (Resv, purple) indicate the various points where NACys and Resv could improve the balance of estrogen metabolism and minimize the formation of deourinating DNA adducts.
Figure 2. Formation, metabolism and DNA adducts of estrogens. Activating enzymes and depurinating DNA adducts are in red.
Catechol Estrogen Metabolism

- Catechol estrogens are inactivated by conjugating reactions
  - Glucuronidation and sulfation
    - Occurs primarily in the liver
    - Proper liver metabolism is critical to safe estrogen metabolism
Catechol Estrogen Metabolism

- Catechol estrogens are inactivated by conjugating reactions
  - \(O\)-methylation of the hydroxyl group
    - The most common pathway of conjugation in extrahepatic tissues
    - Catalyzed by catechol-\(O\)-methyltransferase (COMT)
    - Inactivity of COMT results in increased competitive oxidation of 2-OH and 4-OH estrogens to semi-quinones and quinones
  - Methoxyestrogens have feedback inhibition on the expression of CYP1A1 and CYP1B1
    - Help regulate level of catechol estrogens
ESTROGEN METABOLISM

PROGESTERONE

E1-S04 → Sulfotransferase (Sulfatase)
E1 → 17β-HSD-Type II
E2 → 17β-HSD-Type I

E1 → CYP1B1

4-OH-E1 → 4-QUINONE
DNA ADDUCT FORMATION

2-OH-E1 → DNA DAMAGE MUTATION

16-OH-E1 → Safe Metabolites

Conjugation or Methylation

E3

CYP1A1

I3C

DNA DAMAGE FORMATION

CANCER

David Zava, PhD (modified)
4-OH Quinone Production

• Exposure to environmental pollutants such as PCBS or dioxins activate enzyme conversion that favors formation of 4-OHE1

• Molecular iodine (I2) induces CYP-1A1 and also inactivates oxidized peroxilipids
ESTROGEN METABOLISM

PROGESTERONE

E1-S04

Sulfotransferase

Sulfatase

E1

17 β-HSD-Type II

17β-HSD-Type I

E2

POLLUTANTS

CYP-1B1

I3C

Iodine

CYP1A1

4-0H-E1

2-OH-E1

16-OH-E1

E3

4-Quninone

DNA ADDUCT FORMATION

DNA DAMAGE MUTATION

CANCER

David Zava, PhD (modified)
Redox Cycling

• Semi-quinones are oxidized to quinones
• Quinione are reduced to semi-quinones
  – Catalyzed by CYP reductase
• Molecular oxygen is reduced to superoxide anion radical, which is converted to $\text{H}_2\text{O}_2$
  – In presence of Fe++, $\text{H}_2\text{O}_2$ yields hydroxyl radicals
  – Hydroxyl radicals cause formation of lipid peroxidases, which increase the oxidation of catechol estrogens to quinones
• Too much redox cycling increase carcinogens
ESTROGEN METABOLISM

PROGESTERONE

E1-S04 + Sulfotransferase + 17β-HSD-Type II -

Sulfatase

E1 + 17β-HSD-Type I

E2

4-OH-E1 + CYP1B1 + I3C + CYP1A1

2-OH-E1

16-OH-E1 → E3

Iodine

4-QUINONE

LIPID PEROXIDES

DNA ADDUCT FORMATION

4-QUINONE

DNA DAMAGE MUTATION

CANCER

David Zava, PhD (modified)
Cancer Initiation

• “It is the imbalance in estrogen metabolism leading to relatively high levels of estrogen-DNA adducts that may be a critical determinant of breast cancer initiation.”

Initiation of Cancer

• Estrogen metabolism in which the homeostatic balance between activating (oxidation) and deactivating (blocking of oxidation) pathways.
• Factors include lifestyle, diet, environment and supplementation which create an imbalance in the pathways
• If pathways are balanced, adduct formation is low and conjugates high.

Prevention of Risk

• Always balance estrogen with progesterone
• Never supplement any more E1 or E2 than necessary
• Encourage 2-OH formation along with conjugation
  – Liver function – phase one and phase two enzymes
  – Methylation – COMT support and methyl donor
• Support immune system function, including physiologic level of DHEA
Prevention of Risk, cont’d

• Reduce CYP-1B1 activity
  – Avoid pollutants and toxic chemicals

• Reduce lipid peroxidase activity
  – Avoid trans-fats
  – Antioxidants
    • N-Acetyl-Cysteine and Resveratrol

• Support Glutathione conjugation

• Support quinone reductase activity
Estrogen Metabolism & Elimination:

- **Indole-3-carbinol (I3C) or DIM**
  - Indole-3-carbinol: 100 mg TID (≤500 mg)
  - Found in cruciferous vegetables
  - Modulates estrogen metabolism
  - Has other anti-cancer properties
    - Induces Quinone reductase

- **Liver detox program**
  - Milk thistle (Silybum Marianum)
    - Clears estrogen and metabolites from the body
    - 250 mg TID (Standardized to contain 70-80% silymarin)
Estrogen Metabolism & Elimination:

• Keep estrogen doses physiologic
  – Higher estradiol and estrone levels increase risk of forming harmful metabolites

• Fiber
  – Eliminates conjugated steroid hormones
  – Increases SHBG
  – Absorbs and eliminates bile toxins

• B-Complex
  – Enzyme cofactors
**Estrogen Metabolism & Elimination:**

- **Progesterone**
  - Affects enzymes that metabolize estradiol

- **Decrease beta-gluronidase activity**
  - Beta-gluronidase causes re-absorption of estrogens that were conjugated for elimination
  - Elevated beta-glucuronidase activity is associated with an increased risk for various cancers, particularly hormone-dependent cancers
  - Probiotic supporting *Bifidobacterium* *bifidium*
  - Calcium-D-Glucarate: inhibits beta-glucuronidase
Methylation of Catechol Estrogens

- 99% of catechol estrogens metabolized with (COMT) catechol ortho-methyltransferase
- Renders estrogens inactive
- Some methylated metabolites may help protect against cancer, and have antioxidant properties
Methylation of Catechol Estrogens

- Ways to increase COMT methylation
  - B1, B6, B12 and folic acid
    - Enzyme Cofactors
  - Methyl donor:
    - MSM (MethylSulfonylMethane) (organosulfur cpd)
      - Methyl donor and sulfur donor – 1-2 Gm daily
      - Great anti-inflammatory - 3-4 gm QD for pain (up to 10-15 Grams/day)
    - SAMe
      - 200-1600 mg QD
      - For methylation and depression
  - Trimethylglycine (Betaine) or Dimethylglycine
Estrogen Metabolism

• Lower quinone formation
  – Antioxidants to lower lipid peroxidase
  – Avoid transhydrogenated fats
Estrogen Metabolism

• Safely metabolize quinones: increase Glutathione activity
  – Avoid toxins that stress the liver
    • Excess hormones & alcohol
  – Supplement garlic capsules or MSM
    • Source of sulfur, which is needed to maintain high levels of glutathione
    • Garlic 300-1800 mg
  – Cysteine (especially for smokers)
    • 1 gm TID
  – Glutathione
    • 1-2 gm QD oral, topical, or IV
    • N-acetylcysteine 500-3000 mg to produce glutathione
Estrogen Metabolism

• Increase Quinone Reductase Activity
  – Return structure to hydroxyl group
  – Sulforaphane (broccoli sprouts)
  – EGCG (green tea)
  – Resveratrol
  – A-Lipoic acid
  – Cruciferous vegetables
Thanks For Listening!!!

Jim Paoletti
ZRT Laboratory
503-597-1865
jepaoletti@zrtrlab.com