BREAST HEALTH

New Treatment Paradigms in Anti-Aging Medicine
Objectives

Objectives are to understand how we can advise patients so as to:

- maximize breast health
- minimize factors known to be associated with increased incidence of breast cancer

A clinical implementation tool will be provided so that each patient’s care can be individualized and personalized.
1 in 8

- Are we just “lucky” if we don’t develop breast cancer?

- What does the literature tell us about optimizing breast health and mitigating our risk?
Risk Models

“85% of women who develop breast cancer do not have an identifiable risk factor other than age, and, therefore, every woman must be considered at risk.”

The New Anti-Aging Paradigm is Prevention

- Lifestyle
- Toxicity
- Inflammation
- Diet
- Hormone Replacement Therapy
- Genetics
- Supplements
Lifestyle

- A review of 81 studies on breast cancer estimated that nearly 40% or more of breast cancer could be prevented with basic modification of lifestyle only Amin, AR et al. Perspectives for cancer prevention with natural compounds. J Clin Oncol.2009;27:2712-25.

- Recommendations included a healthy weight, less alcohol, more exercise and breastfeeding
Body Weight

Overweight women have a 3x greater risk of breast cancer...why?

- State of chronic inflammation in obesity?
- Increased insulin resistance/diabetes?
- Fatty liver?
- Adipocytes are storage sites for fat-soluble toxins?
- Adipose has more aromatase activity?
- Lack of exercise?

Anorectic women have 76% less breast cancers
NEW: Body Weight

- Risk triple negative breast cancer increased 35% with highest BMI
cancer Epidemiology Biomarkers and Prevention
- Adiponectin levels are less in obese people
  - Inhibits TNF-alpha
Pregnancy and Lactation

- Early pregnancy (<30yo) reduces the risk of breast cancer by 30%, possibly through mechanisms of final breast maturation as well as markedly increased levels of progesterone and estriol.

- Lactation reduces future breast cancer risk, potentially through release of oxytocin which clears ducts of pent-up inflammatory debris and is inhibitory to cancer cells.
NEW: Oxytocin and Breast Health

- Oxytocin is responsible for myoepithelial ductal cell (MEC) health in the breast (outer layer of the duct). These cells rarely get cancer which instead targets the luminal ductal cells (inner layer of the duct).
- Normal MEC function is to empty the duct during lactation.
- MEC’s are also involved in mammary cell morphogenesis in all stages, modulating the proliferation and differentiation of luminal cells.
- MEC’s are regarded as natural cancer suppressors due to actions due to stabilizing the normal structure of the breast, secreting suppressor proteins (maspin) and limiting cancer growth, invasiveness and neoangiogenesis.
- More research needs to be done to make this clear.
NEW: Oxytocin and Breast Health

- Oxytocin inhibits ER-alpha
- Alcohol decreases oxytocin
- Nipple stimulation increases oxytocin
Sleep

- Sleeping <6 hours, increase risk 10%
- Sleeping 6-8 hours does not change risk
- Sleeping >8 hours drops risk 72%

- Night shift work (just 3 nights per month) in nurses increases risk of DM II 20% after 3 years, 40% after 10 years and 58% after 20 years. Pan et al. PLoS Med. 2011 Dec;8(12):e10011
- “possible” association of night shift work with increased risk of breast cancer. IOM Report, Dec 2011
Melatonin

- Low melatonin levels are associated with breast cancer
- Melatonin levels at age 60 are $1/10^{th}$ of youthful levels
- Melatonin is a very potent antioxidant and immune activator.
Melatonin

- The breast has melatonin receptors

- Upregulates p53 and p21 tumor suppressor genes

- Slows cell replication rate (via calmodulin and gene inhibition)

- Upregulates detoxification
Stress

- Immune system function plummets when under excessive stress as manifested by persistent cortisol production from adrenal hyperactivity

- Inappropriately high nighttime cortisol and low DHEA with chronic severe stress are associated with increased risk of breast cancer
Stress

Stress

Chronic hypocortisolism (aka partial adrenal insufficiency or adrenal fatigue) can result in:

- Increased proinflammatory cytokines e.g. TNF-alpha and IL-6 which suppress lymphocyte function, disrupt T-cell signaling and inhibit NK cell activity
- Upregulation of inflammatory pathways increases susceptibility to the development of malignancies
- An increase in sympathetic tone and catecholamine activity

”Hypocortisolism – An Evidence-based Review” Integrative medicine, Sept/Oct 2011
Toxicity

How do toxins affect our risk for breast cancer?

- Direct mutagenic effects
- Compete for detox pathway enzymes
- Compete for nutrients needed in detox
- Bind the estrogen receptor (often irreversibly)
- Alter the local cell environment
- Reduce the effectiveness of the immune system
- Reduce/offset the nutritional value of foods
- Interfere with the action of the insulin receptor
Toxicity: IOM Report

- Institute of Medicine Report, December 2011
  - 100% funded by the Susan G. Komen for the Cure
  - Reviewed evidence on the link between breast cancer and environmental factors
  - Confirmed consistent associations between ionizing radiation exposure, taking estrogen-progestin hormone therapy and gaining excess weight after menopause
  - Confirmed a consistent link between physical activity and reduced risk of breast cancer
Toxicity: IOM Report

- Concluded that hair dyes, nonionizing radiation from cell phones, microwaves and other technologies do not increase breast cancer risk.
- Labeled the following as “probably human breast carcinogens”: ethylene oxide (medical sterilant, perfumes), benzene and 1,3-butadiene (vehicle exhaust).
- The first time an authoritative medical group has linked any specific environmental chemical to breast cancer.
- Found possible associations with secondhand smoke and nightshift work.
Toxicity: IOM Report

- For other risk factors, evidence was limited, contradictory or nonexistent.

- The IOM highlights chemicals with hormonal activity including PFOAs (nonstick cookware, food packaging), BPA (plastics) and atrazine (herbicide) as priorities for research because the evidence of plausible links to breast cancer is “provocative” but difficult to interpret so far.
Toxicity: IOM Report

- The IOM recommends that women “limit or eliminate workplace, consumer, and environmental exposures to chemicals that are plausible contributors to breast cancer risk while considering risks of substitutes”.

- The EPA maintains toxicity data on only 1% of the 83,000 chemicals used in the USA

- The Toxic Substances Control Act has not been updated since 1976
Toxicity: IOM Report

- Although headlines and major websites told women not to worry about consumer products, they ignored the reports explanation that definitive evidence is not attainable and lack of human evidence of harm doesn’t mean something is safe
Toxicity: IOM Report

• Because of the study and the revelation that so little is known about the environmental risks for breast cancer, the IOM has called on scientists to continue to study environmental factors and their influence on breast cancer, starting in utero.

• Emphasis is being placed on the timing of breast exposure to toxins, knowing that exposure to an adult may not have the same implications as exposure to an adolescent, for example.
Toxicity: Endocrine Disruptors

Rodents exposed to endocrine disruptors in utero or as newborns have mammary glands that:

- Do not develop normally
- Development can be sped up or slowed down
- Impaired breast feeding as adults
- Have increased tumors later in life

Included in the study were pharmaceutical estrogens, phytoestrogens in plants consumed as foods and synthetic compounds including BPA, flame retardants and pesticides.

Scientists say rodent breast development stages are similar to human breast development.

Environmental Health Perspectives
Toxicity

- Pesticides/Herbicides
  - 90% of the pesticides used in the USA are used on our food
  - 2007 study suggested that women exposed to DDT as adolescents were 5 times more likely to develop breast cancer during adulthood [Public health Institute, Berkeley, Ca]
  - DDT levels 700x higher in breast tissue than blood. Conferred a 4x increased risk of breast cancer from the 10 percentile to 90 percentile [Wolff et al. J Natl Cancer Inst 1993;85:648-52].
  - Long Island study of women with increased incidence of breast cancer were 3x more likely to live within 1 mile of an organochlorine-containing hazardous waste site and cancer-free women [Nature Review Cancer, 2005]
Toxicity

- Atrazine is the most commonly used herbicide in the nation.

- Rodents exposed to atrazine had delayed breast development when the dose was given 17-19 days after gestation, when the mammary buds are formed. [Environmental Health Perspectives](#)

- Women who live in areas where there is atrazine in small amounts (safe per federal standards) in the water are 5x more likely to suffer irregular menstrual cycles and 6x more likely to go 6 weeks between periods.
Toxicity

- Bisphenol A
  - Originally developed as a drug (synthetic estrogen) to have similar effects as DES, later it was polymerized and found to be useful to coat cans and make plastic bottles, etc (plastic no. 3 and no. 7)
  - Banned in Canada in 2010, declaring it toxic
  - California banned BPA in children’s food and drink
  - Endocrine disruptor and linked to obesity, insulin resistance, aggressive behavior, early onset of sexual maturation and cancer
  - BPA levels rise 1,221% after 5 days of eating canned soup

JAMA. 2011 Nov 23;306(20):2218-20
Toxicity

- **Bisphenol A**
  - Also found on receipts and 30% of the BPA from these receipts remains on the skin for 2 hours; it does not wash off
  - Environ. Sci. Technol., DOI:10.1021/es202507f
  - Individuals working in retail had 30% more BPA than average Americans
  - ewg.org/b-pa-in-store-receipts
  - We are estimated to absorb 25% of the topical dose of BPA
  - Chemosphere
  - Also found in lesser amounts in all products made from recycled paper
  - 90% of Americans have detectable levels of BPA
  - CDC
  - In human cell cultures, BPA has caused breast cancer cells to proliferate
Toxicity

- In 2010, more than 130 studies have linked BPA to breast cancer, obesity and other health problems. The United States’ President’s Cancer Plan.

- Perinatal exposure of low doses of BPA to rodent parents caused the daughters mammary tissue to manifest:
  - Perturbed estrogen-dependent transcriptional events
  - Change in the number of end-terminal buds (an estrogen-dependent proliferative structure) in a dose-dependent fashion
  - Mammary epithelial cell numbers increased (more than in DES trials)
  - Increased induction of NFKB by progesterone

NEW: Toxicity

- Tuesday July 17, 2012 FDA banned BPA in baby bottles and sippie cups
- New studies show common paper products many times the BPA of food containers; worst are newspapers and paper tickets, esp. if recycled
- New BPA-like (e.g. bisphenol s)plastics being used and can be labeled BPA-free
Toxicity

Breast cancer risk may begin in the womb aka estrogenic imprinting. More study needed but the concern is that maternal exposure to xenoestrogens can result in precancerous lesions which could be the genesis of adulthood cancers. Biomed and Phar, Landau, 2009 as well as Science News May 2010
Toxicity

- Phthalates
  - Plasticizer used in a huge variety of products such as PVC pipe, medical tubing, food packaging, children’s toys, personal care products and perfume
  - Found in over 100 prescription drugs and nutritional supplements (esp. controlled delivery mechanisms)
  - Banned in Europe since 2005 and many other countries have followed suit
  - Highest levels of phthalate MEP, higher odds ratio of developing Br. Ca
    - 2.2 postmenopausal
    - 4.13 premenopausal  

Lopez-Carillo, Env Hlth Per 2010
NEW: Toxicity

- Phthalates
  - DEHP and DiNP found in nearly 100% of decades-old amniotic fluid from the 1980’s and 1990’s
  - Study also found PFOS
  - First study to measure these contaminants in amniotic fluid
Toxicity

TCC (trichlorocarbanilide, similar to triclosan)

- antimicrobial used in soaps, rapidly metabolized by the body but persists in surface waters and sewage sludge that is used on agricultural fields

- Strongly affects aromatase expression in the hypothalamus of zebra fish embryos when introduced with estrogen
  Ruderman, Environmental Health Perspectives, 2011

- BPA also affects aromatase expression, even without estrogen present

- Together, TCC and BPA decrease aromatase action
Toxicity

Parabens (methyl-, propyl, butyl-)

- Preservative chemical found in everyday toiletry products (including deodorant), food (sausage, pies and pastries) and pharmaceuticals
- Study in 40 women with breast cancer Dr. Philippa Darbre, Univ of Reading, 2008
  - 160 specimens
  - 99% of specimens had 1 paraben
  - 60% of specimens had 5 parabens
  - Parabens were found even in women who didn’t use underarm deodorant
Toxicity

Other Xenoestrogens

- There are hundreds (?thousands?) of toxic chemicals that mimic estrogen and bind the estrogen receptor
- There are entire waterways in the US where there are no anatomically normal males of the fish species left
- Endocrine disrupting effects of toxins are very powerful and the knowledge of harms to humans is scarce.

“There are no safe doses for endocrine disrupting chemicals”
Laura Vandenberg, post-doc fellow at Tufts University, commentary following paper published in Endocrine Reviews 3/15/2012
Toxicity

- Electromagnetic frequencies and Radio-frequency radiation
- Synthetic fibers (textile industry): odds of breast cancer doubled with each 10-year increased exposure to acrylic or nylon fibers or organic solvents. Risk tripled with exposure to PAH’s from petroleum sources.
- Viruses (HPV and MMTV in mice)
- Cosmetics
- Cigarette smoke (Nurses Health Study)
  - 60 known carcinogens amongst 4000 chemicals
  - Damage cellular DNA, cause mutations, disrupt cellular repair mechanism, inhibit apoptosis
  - Worst risk if start smoking before giving birth to first child
NEW: Toxicity

- Endocrine Disruptor Screening Program
  - Established in 2009
  - Requires manufacturers to test pesticides (and only pesticides, so far)
  - Researchers look for widespread effects in rodent bodies, including on the brain, internal organs and genitals.....but not mammary glands
Toxicity

Heavy metals

- Found in breast biopsy specimens
- 55,987 pmp females highest tertile of cadmium had 21% increase risk vs. lowest tertile Am Assn of Ca Research 3/15/2012
  - Cadmium is a xenoestrogen
  - Cadmium leaches into crops from fertilizer, rainfall and sewage sludge used to fertilize fields
  - Highest concentrations in whole grains, potatoes and other vegetables as well as shellfish
Toxicity

Statins

- 576 pmp females, 12 with breast cancer on statins and 1 with breast cancer not on statins  CARE

Antipsychotic dopamine antagonists

- Large retrospective study showed 16% increase risk of developing breast cancer
Toxicity

• DES (diethylstilbestrol)
  • Synthetic estrogen given to millions of pregnant women from 1938 to the early 1970’s to prevent miscarriage
  • Linked to vaginal cancer in the daughters of those women
  • Chance of a 55yo woman developing breast cancer is 1 in 50 and for DES daughters the risk is 1 in 25 (doubled) Dr. Robert Hoover, NCI
Toxicity

Teflon / PFOA (perfluorinated compounds)

- Non-stick pans, clothing and furniture with stain-repellant coatings, fast food packaging that repels grease, cleaning products, cosmetics
- In 95% of all Americans blood
- Never breaks down in the environment and the half life in the body is 4.4 years
- In animals, causes cancer, birth defects, immune suppression and other disorders
- Elevated exposures to PFC’s in children were associated with reduced humoral immune response to routine childhood immunizations  Grandjean,P. JAMA, Jan 25, 2012. 307(4)3917.
- Also found in amniotic fluid (reference with phthalates)
Toxicity

- Perc (perchloroethylene aka tetrachloroethylene) used in dry cleaning and textile processing classified 2/2012 as “likely human carcinogen” by EPA (last prior assessment had been in 1988)
- Nanotechnology....??risks
- PCB’s (polychlorinated biphenyls, a type of organochlorine pesticide) now banned but stay in the body and environment for decades
- Organic solvents (used in glues and cleaners)
- Indoor air quality
Toxicity

• Dioxins
  • Agent orange, incinerators, paper mills
  • Recent report 2/2012 by EPA concluded that ultra-low levels of exposure can cause potentially serious effects including cancer, disrupted hormones, reproductive damage such as low sperm counts, neurological effects, immune system changes and more. More detailed report re: cancer risks still in the works.
Toxicity

- PAH’s (polycyclic aromatic hydrocarbons) from combustion-related air pollution
  - Grilled food
  - Higher levels assoc. with women in Long Island having increased rates of breast cancer

- Prior radiation: 1 of every 3 girls treated with radiation before age 16 for Hodgkin’s disease will develop breast cancer before age 40. J Royal Society of Medicine
# Toxicity

## Sample Report

**0760 Chlorinated Pesticides - Serum**

*Methodology: Gas Chromatography/Mass Spectrometry*

<table>
<thead>
<tr>
<th>Compound Tested</th>
<th>Results</th>
<th>95th Percentile**</th>
<th>Lipid Adjusted Results</th>
<th>95th Percentile**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ppb</td>
<td>ppb</td>
<td>(ng/g Lipid)</td>
<td>(ng/g Lipid)</td>
</tr>
<tr>
<td>1. DDE</td>
<td>Detected</td>
<td>12.1</td>
<td>Detected</td>
<td>1860</td>
</tr>
<tr>
<td></td>
<td>0.88</td>
<td></td>
<td>181.27</td>
<td></td>
</tr>
<tr>
<td>2. DDT</td>
<td>Not Detected</td>
<td>0.13</td>
<td>N/A</td>
<td>19.5</td>
</tr>
<tr>
<td>3. Dieldrin</td>
<td>Not Detected</td>
<td>0.14</td>
<td>N/A</td>
<td>19.0</td>
</tr>
<tr>
<td>4. Heptachlor Epoxide</td>
<td>Not Detected</td>
<td>0.13</td>
<td>N/A</td>
<td>19.0</td>
</tr>
<tr>
<td>5. Hexachlorobenzene (HCB)</td>
<td>Not Detected</td>
<td>0.19</td>
<td>N/A</td>
<td>19.0</td>
</tr>
<tr>
<td>6. Mirex</td>
<td>Not Detected</td>
<td>0.09</td>
<td>N/A</td>
<td>13.2</td>
</tr>
<tr>
<td>7. Oxychlordane</td>
<td>Not Detected</td>
<td>0.27</td>
<td>N/A</td>
<td>37.7</td>
</tr>
<tr>
<td>8. trans-Nonachlor</td>
<td>Detected</td>
<td>0.47</td>
<td>Detected</td>
<td>68.3</td>
</tr>
<tr>
<td></td>
<td>0.05 - 0.15*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cholesterol**: 198 mg/dL, <= 200 mg/dL  
**Triglycerides**: 87 mg/dL, 35 - 160 mg/dL  
**Total Lipids (calc.)**: 5 g/L

UC* = Unable to Calculate  
* Patient value falls in this range.  
** 95th percentile values are from the NHANES Fourth National Report on Human Exposure to Environmental Chemicals, CDC, 2009.


Finding a measurable amount of one or more chlorinated pesticide in serum does not mean that there are adverse health effects. Whether the concentrations reported here are a cause for health concern is not yet known. These levels provide physicians with a reference range to determine whether or not people have been exposed to higher levels of chlorinated pesticides than found in the general population.

For interpretive information, visit [www.metametrix.com/cp](http://www.metametrix.com/cp) and select the Interpretive Guide from the downloads tab.
Toxicity

- Sample report

<table>
<thead>
<tr>
<th>Compound Tested</th>
<th>Results ppg</th>
<th>95th Percentile** ppg</th>
<th>Lipid Adjusted Results (mg/g lipid)</th>
<th>95th Percentile† (mg/g lipid)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dioxin-like Polychlorinated Biphenyls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. PCB 118</td>
<td>Not Detected</td>
<td>0.22</td>
<td>N/A</td>
<td>31.†</td>
</tr>
<tr>
<td>2. PCB 126</td>
<td>Not Detected</td>
<td>0.00048</td>
<td>N/A</td>
<td>0.06†</td>
</tr>
<tr>
<td>3. PCB 156</td>
<td>Not Detected</td>
<td>0.10</td>
<td>N/A</td>
<td>15.†</td>
</tr>
<tr>
<td>4. PCB 169</td>
<td>Not Detected</td>
<td>0.00027</td>
<td>N/A</td>
<td>0.04†</td>
</tr>
<tr>
<td><strong>Non-Dioxin-like Polychlorinated Biphenyls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. PCB 74</td>
<td>Not Detected</td>
<td>0.15</td>
<td>N/A</td>
<td>22.†</td>
</tr>
<tr>
<td>6. PCB 138</td>
<td>Not Detected</td>
<td>0.48</td>
<td>N/A</td>
<td>75.†</td>
</tr>
<tr>
<td>7. PCB 153</td>
<td>Not Detected</td>
<td>0.62</td>
<td>N/A</td>
<td>97.†</td>
</tr>
<tr>
<td>8. PCB 180</td>
<td>Not Detected</td>
<td>0.53</td>
<td>N/A</td>
<td>81.†</td>
</tr>
</tbody>
</table>

Cholesterol 198 <= 200 mg/dL
Triglycerides 87 35 - 160 mg/dL
Total Lipids (calc.†) 5 g/L

* Patient value falls in this range.
** 95th percentile values are from the NHANES Fourth National Report on Human Exposure to Environmental Chemicals, CDC, 2009.

Finding a measurable amount of one or more polychlorinated biphenyls in serum does not mean that there are adverse health effects. Whether the concentrations reported here are a cause for health concern is not yet known. These levels provide physicians with a reference range to determine whether people have been exposed to higher levels of polychlorinated biphenyls than found in the general population.

For interpretive information, visit www.metametrix.com/pcbs and select the Interpretive Guide from the downloads tab.
Toxicity

- **Sample Report**

### 0762 Volatile Solvents - Whole Blood

**Methodology:** Gas Chromatography/Mass Spectrometry

<table>
<thead>
<tr>
<th>Compound Tested</th>
<th>Results (ng/mL)</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50th</td>
<td>75th</td>
</tr>
<tr>
<td>1. Benzene</td>
<td>&lt;DL</td>
<td>0.05</td>
</tr>
<tr>
<td>2. Ethylbenzene</td>
<td>&lt;DL</td>
<td>0.05</td>
</tr>
<tr>
<td>3. Styrene</td>
<td>&lt;DL</td>
<td>0.05</td>
</tr>
<tr>
<td>4. Toluene</td>
<td>&lt;DL</td>
<td>0.43</td>
</tr>
<tr>
<td>5. m,p-Xylene</td>
<td>0.18</td>
<td>0.2</td>
</tr>
<tr>
<td>6. o-Xylene</td>
<td>0.13</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Percentile values are from the NHANES Fourth National Report on Human Exposure to Environmental Chemicals, CDC, 2009.

<table>
<thead>
<tr>
<th>Compound Tested</th>
<th>Results (ng/mL)</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Hexane</td>
<td>276</td>
<td>193</td>
</tr>
<tr>
<td>8. 2-Methylpentane</td>
<td>70</td>
<td>52</td>
</tr>
<tr>
<td>9. 3-Methylpentane</td>
<td>141</td>
<td>100</td>
</tr>
<tr>
<td>10. Iso-octane</td>
<td>7.2</td>
<td>7.6</td>
</tr>
</tbody>
</table>

No national reference ranges are established for hexane, 2- and 3- methylpentane and iso-octane. Percentile ranges are based on patient samples analyzed at Metametrix.

<DL = less than detection limit

Finding a measurable amount of one or more toxicants does not mean that adverse health effects are present, therefore no levels are flagged as abnormal. The percentiles provide reference values to determine whether or not this patient’s results fall in the upper ranges of the general population.

For interpretive information, visit [www.metametrix.com/hs](http://www.metametrix.com/hs) and select the Interpretive Guide from the downloads tab.
Alcohol

- Increases estradiol levels via increased aromatase
- Increases the transcriptional capability of ER-alpha which may influence breast tissue’s sensitivity to estrogens
- Preferentially enhances proliferation and ER-alpha content in ER-positive cell lines
- Metabolized to acetaldehyde, classified as a carcinogen
- Depletes nutrients
Alcohol

- Alcohol metabolism depletes glutathione, needed for phase II detox of a carcinogenic estrogen metabolite (i.e. reduced clearance of estrogens as well as other toxins)
- Alcohol blocks oxytocin release
- Increases angiogenesis in vitro Cancer, 2004
- Increases free iron within the ductal cell by facilitating release from ferritin
Alcohol

Clear correlation between heavy use and increased risk of cancer

Earlier studies conflicting re: low or moderate use and impact on risk of developing breast cancer
Alcohol

A recent Harvard study showed:

- 3-6 alcoholic drinks a week increases risk by 15%
- 2 drinks daily increased risk 51% vs. women who never drank
- The risks remained, regardless of the stage of life the alcohol was consumed.
- Binge drinking at any stage in life was associated with increased risk [JAMA. 2 Nov 2011-vol 306, no.17, pp 1884-1921.]
Alcohol

- Small study of 36 premenopausal women randomized to cabernet sauvignon or chardonnay daily for almost a month and then switched.

- Red wine drinkers had lowered estrogen and higher testosterone suggesting that red wine is a nutritional aromatase inhibitor. Schufelt, c. et al J Women’s Health, Dec 2011.
Chronic Inflammation

- Current dietary patterns, unprecedented levels of obesity and environmental toxins are driving our bodies into a state of chronic inflammation.
- Experts predict an enormous increase in chronic disease, including cancer, as a result.
- Arachidonic acid (from excess omega-6 ingestion) promotes tumor growth in vitro and in vivo.
  - Many foods and natural substances are COX and LOX inhibitors.
- Elevated CRP increases breast cancer risk 10%.
Chronic Inflammation

Nuclear Factor Kappa Beta

- NFKB is a transcription factor that activates the genes involved in inflammation

- NFKB activation increases production of TNF-alpha, TGF-beta and IL-1, IL-6 and IL-8 (pro-inflammatory mediators)
Chronic Inflammation

Nuclear Factor Kappa Beta

• Researchers now believe that 95% of all cancers are associated with NFKB activation

• Tobacco, stress, dietary components, obesity, alcohol, infections, radiation and environmental toxins are common triggers of NFKB activation
Chronic Inflammation

Nuclear Factor Kappa Beta is linked to:

- the survival of cancer stem cells
- preventing apoptosis
- enhanced proliferation with rapid and repeated cell divisions
- invasion of cancer
- angiogenesis
- metastatic spread of cancer

This provides a strong link between inflammation and cancer.
Chronic Inflammation

Nuclear Factor Kappa Beta

- Oncogenes (abnl genes that can initiate ca development) act partially by activating NFKB
  Oncogene 2002 Mar 27;21(13):2066-78

- Most cancers have high levels of NFKB, contributing to initiation of the tumor as well as its promotion and metastasis

- Tumor cells keep abnormally high levels of NFKB which keeps them in a state of persistent inflammation

- NFKB has been linked to the survival of cancer stem cells

- Inflammatory cascade involving NFKB is required by breast cancer cells (in mice) to proliferate and metastasize
  Cancer Res. 2010 Dec 15;70(24):10464-73
Chronic Inflammation

Nuclear Factor Kappa Beta

- Many antioxidants block NFKB including vitamins C and E, carotenoids, glutathione, alpha lipoic acid, flavonoids, polyphenols, selenium, zinc, milk thistle, coffee, black pepper, garlic, ginger, green tea, isoflavones, omega-3’s, vitamin D, ashwagandha and pomegranate. 

Chronic Inflammation

- One of the most potent inhibitors of NFκB is curcumin.

- NFκB inhibition has been shown to reduce every stage of carcinogenesis, therefore making it a powerful tool for cancer prevention.
Chronic Inflammation: Iron

- Iron plays an important role in breast cancer initiation and progression
- Iron damages the sensitive ductal tissues of the breast due to chronic local inflammation
- Higher iron levels are associated with the more malignant types of breast cancer
- Breast cancer cells have more transferrin receptors on their surface than healthy cells and more ferritin inside
Chronic Inflammation: Iron

- Rising serum levels of iron are associated with increasing rates of lipid peroxidation within the breast.
- Estrogen facilitates the release of iron from ferritin inside the cell (alcohol does the same).
- Blood iron levels in breast cancer patients were almost twice as high as the cancer-free control subjects, despite a diet that contained the same, or lower, amounts of iron; the theory is that breast cancer patients absorb more iron from their diets. Blaylock Wellness Report May 2011
Nutrition: The Basics
A Return to Food

- Organic, nutrient dense
- 100% whole grains/increase fiber(best results over 25 g/day), legumes
  - Every 10 gram per day increase in soluble fiber was associated with a 26% reduction in the risk of breast cancer Aune, D. et al. Annals of Oncol Jan 2012
- Meats should be grass-fed, pasture-raised, organic
  - slow cook, don’t burn; not cured/processed
  - 350% increase incidence of breast cancer if eat grilled meat every day
- Poultry should be free-range, organic
Avoid food additives and aspartame
  - Glutamate antagonists reduce breast carcinoma growth in cultures
  - 46% of breast cancers exhibit glutamate receptors Blaylock
  - Aspartame also metabolized to formaldehyde, shown to cause DNA breaks.
  - Sucralose is not a glutamate antagonist but is a chlorinated sugar molecule, originally developed to be a pesticide
Nutrition: The Basics

- Fish no more than twice weekly (not farmed)
- Healthy fats (no trans fat, increase omega-3’s, omega-9’s, reduce processed omega-6’s, increase MCT’s)
  - Women with the highest trans fats levels had 2x risk breast cancer
- No fried food
Nutrition: The Basics

- No genetically modified food

- **Caloric restriction/management**  Russell Blaylock MD, Natural Strategies for Cancer Patients

Nutrition: Glucose

Low glycemic, high fiber carbohydrates

- Insulin spike decreases immune system function
- Increases free estradiol
- PET scans used to look for cancer use fluorodeoxyglucose (95% of cancer cells predominantly use glucose for fuel...the Warburg Effect)
- High circulating insulin increases risk breast cancer 283%
- High GI diet increases risk of breast cancer 44% vs. low GI

J Ca 2009
Nutrition: Glucose

- Meta-analysis of 15,839 cases of breast cancer in 577,538 participants showed the RR of breast cancer in the highest GI intake group compared with the lowest was 1.08, a “significant increased risk of breast cancer” Br Cancer Res Treat 2011. April;126(2):287-94.

- 49,693 PMP women after 16 years f/u had 87% increased risk in highest vs. lowest quintile of GI Silvera et al. Int J Cancer 2005; 114:653-8.

- Metabolic Syndrome strongly related to postmenopausal breast cancer

- Diabetic women have a 37% increased risk of breast cancer CTRC-AACR, San Antonio. Dec 2011.

- In mice bred to get mammary cancer, 50% of mice got tumors at 1 year of age on a Western diet whereas a low carbohydrate diet produced no tumors HO V, et al. Cancer Res.2011Jul1;71(13):4484-93.
Nutrition: Glucose

- Breast cancer cells in culture take up glucose massively when insulin (beyond normal concentrations) is added to medium
- Breast cancer cells in vitro no longer grow or divide when insulin is removed from the growth medium
- The medium used to grow breast cancer cells is only glucose, insulin and EGF
- This is in contrast to healthy breast cells (from which the tumor cells were derived) that have no insulin receptors and can thrive without insulin
IGF and Insulin

- It is theorized that insulin and IGF are accelerants that drive the excess glucose utilization of tumor cells i.e. these hormones provide the fuel for the tumors as well as the signal for the tumor to grow.
- Tumor cells have 2-3 times the # of IGF and insulin receptors as normal cells.
- Mice bred to have 25% of the normal IGF levels have significantly slower tumor growth and metastasis when mammary tumors are transplanted into them.
IGF and Insulin

- PI3 kinase enzyme that enhances a cell's sensitivity to insulin is turned on by insulin and IGF.
- PI3 kinase is turned off by the tumor suppressor gene PTEN.
- Breast and other tumor cells often mutate this kinase so that the tumor suppressor PTEN is rendered inactive against it.
- Another theory is that IGF and insulin enhance tumor risk because they turn on anti-apoptotic signals. Science. 6 Jan 2012 Taubes 335(6064);28-32
Metformin

• Type 2 diabetics treated with metformin have 25% - 40% less breast cancer than those who receive insulin or take sulfonylurea drugs that increase insulin secretion from the pancreas  San Antonio Breast Symposium, 2010

• Observational data and no causal relationship proven
Metformin

- Possible mechanisms:
  - Activates AMP kinase in the liver, decreasing synthesis and secretion of glucose.
  - AMP kinase also slows cell growth and replication (via mTOR)
  - Stimulates LKB1, a tumor suppressor gene (exercise also does this)
  - Lowers circulating insulin levels (even in nondiabetics)
  - Inhibits aromatase
  - Increases p53
Metformin

- 3500 women with breast cancer are being randomized in a new trial to receive either usual care plus placebo or usual care plus metformin.

- Mice given metformin for 13 days prior to injection with a strong breast carcinogen had significantly delayed onset of tumor development. Bojkova B et al. Neoplasma. 2009;56(3):269-74.

Nutrition: Soy

- Contradictory research findings
- Genistein and other dietary isoflavones are phytoestrogens and have been shown to stimulate growth of estrogen-sensitive breast cancer cells in vitro
- The isoflavones have also been shown to prevent movement of NFKB into the cell nucleus
- Population-based Asian studies have shown less breast cancer with more soy consumption  Br J Cancer, 2008
Nutrition: Soy

- New study showed less breast cancer recurrence with more soy intake whether ER positive or not [JAMA, 2010]
- Care should be taken in assuming cross-cultural populations will have similar outcomes.......is timing of soy exposure important?
- Avoid processing of soy: eat in moderation
- 91% US soybean fields are genetically modified, linked to infertility in animal studies [Huffington Post April 20, 2010, Jeffrey Smith]
- Strongly stimulates aromatase activity
Hormones: Estrogen Paradox

“Angel of life or angel of death?” Zava

- Over 400 functions: critical for preservation of structure and function in a woman
- Clear (?) association of lifetime increased estradiol exposure and risk of breast cancer
- We seem to develop breast cancer when estrogen levels are at their lowest
- Yet, many breast cancers are estrogen-receptor positive and anti-estrogen drugs are used to treat breast cancer
- Breast cancer rates fell quickly in the 2 years following WHI when women quit taking equine estrogens/MPA
“HRT” and Breast Cancer

- Women’s Health Initiative, 2002, showed 26% increase in breast cancer with equine estrogens and medroxyprogesterone acetate
- The study was stopped early due to many increased risks, including breast cancer
- The equine estrogen-only leg of the study continued to completion with no increase in breast cancer
- March 13, 2012, WHI follow-up showed lower rates of breast cancer in women using “estrogen” alone (CEE)
“HRT” and Breast Cancer

- The participants in WHI were further followed for 11 years (mean) and found continued increased incidence of all subtypes of breast cancers, more of which were node-positive and also increased (nearly doubled) mortality....both from breast cancer and all-cause mortality [JAMA Oct 20, 2010]

- Headlines again read “HRT unsafe”
“HRT” and Breast Cancer

- Editorial suggests it is ethical to do studies at lower doses/shorter durations to see if that also increases cancer....... never once mentioning the alternative therapies available to women

- Are the results obtained with CEE/MPA combination therapy applicable to bioidentical hormone replacement therapy?
NEW: USPSTF HRT Recommendations

- USPSTF recommends against the use of these (CEE and progestin) regimens for the prevention of chronic conditions in women
  - Based on studies that estrogen alone decreases breast cancer risk and that the combo reduces fractures BUT is offset by increased risk in the combo CEE/MPA in breast cancer, dementia, gallbladder disease, stroke, thromboembolic events and urinary incontinence
Progestin vs. Progesterone and Breast Cancer

- 50,000 women 40% increase breast cancer if synthetic progestin (MPA) used with E2, but 10% reduction if bioidentical progesterone was used with estrogen. Fournier A, et al. Int J Cancer. 2005

- 80,000 women E2 alone 29% increase, E2 plus synthetic progestin 69% increase, E2 plus bioidentical progesterone no increase i.e. same as women who never used HRT. Fournier, Br Ca Res Treat, 2008
Progestin and Breast Cancer

Nurses Health Study

- unopposed estrogen increased risk 23%
- Addition of synthetic progestin resulted in tripling of risk (67% increase)

Possible mechanism: Synthetic progestins down regulate ER-beta receptors (ER-beta inhibits proliferation)
Acknowledged that MPA causes breast cancer and that little is known about risk of breast cancer with DMPA

1,028 women ages 20-44

Recent use for 12 months or longer was associated with a 2.2x increase risk of invasive breast cancer
Estriol (E3) and Breast Cancer

- Weak estrogen
- Derived from estradiol/estrone in phase II liver detox
- Blocks the effect of the stronger E1 and E2 at the estrogen receptor alpha (ER-alpha promotes breast cell proliferation)
- Breast cancer patients have lower E3 than normal
- Pregnant women with highest E3 have 58% less breast cancer  
  Kaiser, 2002
- Asian women have higher E3 than American women
- No large scale trials re: breast cancer and estriol
Hormones: Progesterone

- Perimenopausally, this is the first hormone to decrease, leaving a woman estrogen-dominant for years.
- In normal breast cells, progesterone inhibits the estrogen-induced mitotic effect, conferring protection against breast cancer. This only applies to bioidentical progesterone, not synthetic progestins.
- 1000 women followed for 13 to 33 years showed 5x more breast cancer in women with low progesterone.
Prior to breast surgery, women were treated with placebo, estrogen, transdermal progesterone, or estrogen and transdermal progesterone for 10-13 days. Estrogen increased cell proliferation rates by 230% but progesterone decreased proliferation rates by 400%. When given together, progesterone inhibited all estrogen-stimulated proliferation. Chang, 1995 and Foidart, Fertil Steril 1998;69(5):963-9.
Hormones: Progesterone

- Progesterone induces apoptosis in breast cancer cell lines that are stimulated by synthetic progestins and other androgenic progestins Maturitas 2003;46:55-8.

- Nearly 100,000 women in French E3N cohort study, micronized progesterone regimens were associated with significantly lower breast cancer risks when compared to synthetic progestin regimens Breast Cancer Res Treat. 2008 Jan;107(1):103-11.

- 9 year study of 3000 postmenopausal women using transdermal estradiol and progesterone found no increased risk of breast cancer Climacteric 2002;5:332-40.
Hormones: Progesterone

- Primate research showed 4.9x increased lobular and ductal proliferation in response to estradiol and MPA (medroxyprogesterone acetate)
- No increased proliferation was seen with placebo or estradiol and progesterone combination  Wood, 2007
Hormones: Progesterone

- In women with breast cancer, the balance of progesterone metabolites dramatically reverses, producing increased mitogenesis and metastasis. Wiebe, Endo-Related Cancer, 2006
- The evidence suggests that the promotion of breast cancer is related to changes in cancer-inhibiting and cancer-promoting metabolites of progesterone (regardless of ER/PR status)
- Caution advised in using progesterone in breast cancer patients
Hormones: Estrogen Paradox

- Explanation for what seems to be a paradox i.e. estrogen can clearly fuel growth of ER-positive tumor but BioHRT does not increase risk of breast cancer development
  - Breast fat cells produce their own estrogen
  - Breast duct fluid estrogen is 10-50 times that of the blood
  - High estrogen levels thought to be a “cause” of breast cancer are likely a reflection of the increased production by the breast
  - Treatments with extraneous estrogen should have no effect on ductal concentrations
  - In women with a history of breast cancer, about a dozen studies have shown no increase recurrence in treating survivors with HRT and had lower recurrences, i.e. suggesting a protective effect

Mahmud, Khalid “Keeping aBreast: Ways to Prevent Breast Cancer”
BioHRT Recommendations

- Measure deficiency and if needed, use least dose possible to start
- Never use estradiol alone, even bioidentical estradiol.
- Estriol recommended alone or in combination with E2
- Always balance estrogens with progesterone
- Never use synthetic progestins
- While no treatment can be considered 100% safe, bioidentical HRT has been proven safer than previous regimens of synthetic/nonbioidentical HRT ^Holtorf
- Always consider the multiple risks of being hormone deficient
Bioidentical vs. Nonbioidentical HRT Debate

- Ken Holtorf, MD
- Postgraduate Medicine, January 2009
- Excellent review of the literature
- Conclusions that there is an enormous volume of published literature supporting the claim that bioidentical HRT is safer and more effective than nonbioidentical HRT with regards to breast cancer as well as cardiovascular risk
Hormone Debate

- 2 studies that should begin reporting in 2012 on cardiovascular effects of early HRT in women using estradiol (ELITE) and micronized progesterone (KEEPS)
- Quote from Wulf Utian, founder and president of NAMS: “It’s actually quite safe to take hormones for 5-10 years after menopause. If you minimize a woman’s exposure to progesterone, you minimize her slight risk of breast cancer. Meanwhile, the estrogen will have a beneficial effect on her brain, her skin, her bones and her heart.” WSJ Sept 27, 2011
Estrogen Metabolism

- It is not how much estrogen you have, but what you do with it. *JAMA*
- 2 of the estrogen metabolites are in research for prevention and treatment of breast cancer.
- 1 of the estrogen metabolites is thought to be an initiator of breast cancer, causing DNA adducts and breakage.
- Healthy estrogen metabolism is critical for breast health.
- Genetic variations in estrogen detox capacity confer differing risks of breast cancer.
Estrone (E1) → Estradiol (E2)

- 2-OHE1 (CYP1A1)
- 16α-OHE1 (CYP1B1)
- 4-OHE1 (CYP3A4)
- 3,4 Quinones (CYP3A4)

- 2-MeOE1 (protective) (COMT)
- Estriol (E3) (COMT)
- 4-MeOE1 (neutralized) (COMT)
- (Neutralized mercapturate) (GST)
Phase I Estrogen Metabolism: the Protective 2-OH Estrone

- 2-OH Estrone is a weak estrogen
- Does not damage DNA
- Protective against breast cancer once methylated by COMT
- Potent antioxidant
- Increasing metabolism down this pathway reduces the formation of other undesirable estrogen metabolites
Phase I Estrogen Metabolism: the Bad(?) 16-OH Estrone

- 16-OH estrone is a stimulatory estrogen (but 5x weaker than estradiol)
- Is metabolized to estriol, a beneficial estrogen so don’t want to eliminate 16-OH estrone
- Does not damage DNA (some disagreement)
- Higher levels found in breast cancer tissue (cause or effect?)
Phase I: The 2:16 ratio

- A higher 2-OH Estrone:16-OH Estrone ratio is associated with less breast cancer.
- This effect is largely because of the beneficial shift in estrogen metabolism down the 2-OH estrone pathway, lessening the formation of the 4-OH estrone metabolites that are carcinogenic (and incidentally reducing the 16-OH estrone metabolite).
Phase I Estrogen Metabolism: the Pro-carcinogenic 4-OH Estrone

- Very potent estrogen
- 4-OH Estrone is pro-carcinogenic, able to be oxidized to a quinone compound that forms DNA adducts in breast cells, causing DNA damage, which if not repaired, can lead to tumor initiation
- Carcinogenic quinones can be neutralized via GST enzyme
- Higher 4OH:2OH estrone ratio found in breast cancer tissue
Phase II: Methylation via COMT

- Major pathway for disposal of the pro-carcinogenic 4-OH estrone
- Necessary for production of 2-methoxyestradiol, a very beneficial metabolite, currently being developed as a drug for breast cancer (2-methoxyestradiol blocks the action of the more potent estradiol and estrone)
- Requires B6, methylB12, methylfolate and magnesium (use caution with methylation in known cancer pt...can improve DNA synthesis)
Phase II: Estriol Formation

- Estriol is a very weak estrogen and exhibits anti-estrogen effects when other more potent estrogens are around (blocks their action on ER-alpha).
- Preferentially stimulates ER-beta, our tumor-suppressing receptor on breast cells (ER-alpha increases mitosis) (3:1 ER alpha:beta).
- Animal studies show it prevents carcinogen-induced and radiation-induced mammary tumors.
- Women with breast cancer produce less estriol than women without breast cancer.
Estrogen Metabolism: SNPs

- Single nucleotide polymorphisms are genetic mutations affecting up to 35% of the population
- SNPs confer differing degrees of enzyme activity and risk of poor estrogen metabolism
Estrogen Metabolism: SNPs

- 1A1: can decrease the beneficial 2-OH
- 1B1: increases dangerous 4-OH formation
- 3A4: can increase the undesirable 16-OH
- COMT: is needed for methylation of beneficial 2-MeEstradiol and disposal of carcinogenic 4-OH estrone; a double mutation reduces activity of enzyme by 4-7x
- Glutathione s-transferase: is an alternate route for disposal of 4-OH estrone/quinones; this SNP increases breast cancer risk 4-fold Helzlsouer, NCI, 1998
Effect of SNP’s on Estrogen Metabolism

Sample Report
Support of Healthy Estrogen Metabolism, Phase I

- Increase beneficial 2OH metabolite:
  DIM, cruciferous vegetables, sulphoraphane, soy isoflavones, flaxseed lignans, omega-3’s, exercise, weight control, vitamin D, rosemary, turmeric, chrysin, iodine and avoiding alcohol and cigarettes

- Decrease production of less desirable 16OH and the carcinogenic 4OH metabolite:
  Avoid obesity, treat hypothyroidism, avoid pesticides, proper omega-3:omega-6 ratio, reduce inflammatory cytokines, grapefruit, adequate DHEA level
Support of Healthy Estrogen Metabolism, Phase II

- Increase methylation via COMT: B2, B6, methylB12, methylfolate, magnesium, trimethylglycine (aka betaine), s-adenosylmethionine (SAMe), reduce stress to reduce excess catecholamines

- Increase glutathione capacity: n-acetylcysteine, whey protein, oral glutathione (NAC and resveratrol protect against 4-OH estrogen-adduct induced cancers); also need B2, B6, B12, Folate and Mg for enzyme action
Estrogen Metabolism Report
Estrogen Metabolism Report

**Enzymatic Activity**

**Estrogen Metabolism**
- 2-Hydroxyestrone/16α-Hydroxyestrone Ratio
  - 16α-OHE1: Higher Risk of Breast/Prostate Cancer (RR = 1.7 - 2.6)
  - 2-OHE1: Lower Risk of Breast/Prostate Cancer

**Methylation Activity**
- 2-Methoxyestrone/2-Hydroxyestrone Ratio
  - Less Methylation
  - More Methylation (RR >= 0.2)

**Estrogen Metabolism**
- Phase 1
  - 2-OHE1
  - 16α-OHE1
  - 4-MeOE1
- Phase 2
  - 4-OHE1
SHBG and Breast Cancer

- SHBG regulates how E2 is delivered to and acts on tissue
- Low SHBG is associated with an increased risk of breast cancer e.g. in obesity, PCOS, MetS
- Gene variants that regulate the amount of SHBG are also associated with breast cancer
- E2 in conventional signaling can signal growth of breast cancer cells but if SHBG is added, this will change/reduce the stimulus to growth
- Low SHBG is associated with excess glucose and fructose, independent of insulin (thought to be sensitive to the metabolic disruption in fatty acids caused by overload of simple sugars)

Gillson MD, PhD, George. Oct 2010 Fellowship A4M webcast. SHBG:Who Knew?
Oral Contraceptive Pills

Summary: Oral Contraceptives and the Risk of Breast Cancer:

“Even though the data indicated that young women who begin use before age 20 have higher relative risks (20% increase) of breast cancer during current use and in the 5 years after stopping, this is a time period when breast cancer is very rare; and, thus, there would be little impact on the actual number of breast cancers.”

Genetics

- BRCA1 and BRCA2 are genetic mutations that predispose the cells to accumulate genetic damage and send an indirect signal for cell growth.
- BRCA1 gene is normally responsible for repairing the PTEN gene (an important tumor suppressor gene).
- When PTEN gene repair is gone, this can allow for cell growth, cell death inhibition, cell migration, new blood vessel growth, and metastasis.
Genetics

- BRCA1 and BRCA2; suspect mutation if:
  - Family history breast cancer before the age of 50
  - Ovarian cancer at any age
  - 2 or more breast cancers in an individual or family
  - Both breast and ovarian cancer in an individual or family
  - Male breast cancer
  - Ashkenazi Jewish patients with personal or family history of breast or ovarian cancer (1:40 carrier of mutation vs. 1:500 in general population)
Genetics

With a BRCA mutation, your risk of breast cancer at age 50 is 33-50% vs. general population risk of 2%

By age 70, the risk of breast cancer is 56-87% vs. 7% in general population

Male breast cancer risk at age 70 is 6% vs. general population risk <.05%
Genetics

BRCA₁ and BRCA₂ are involved with <10% of all breast cancers

With BRCA₁/₂

- Tamoxifen can reduce risk of breast cancer up to 49%
- Mastectomy can reduce risk by 90%
Tamoxifen

- Anti-estrogen which competes with natural estrogens for binding sites aka SERM (selective estrogen receptor modulator)
- Given to pre- or post-menopausal women for adjuvant therapy of breast cancer
- Tamoxifen prevents gene transcription via the TAF-2 pathway
Tamoxifen

- Overall very poor utilization by women due to fears of endometrial cancer and blood clots (26% express interest and only 4% take)
- Treatment beyond 5 years increased risk of recurrence
- Even 5 years of treatment is associated with an increase in estrogen receptor-negative cancer in the contralateral breast  Fritz and Speroff, 2011
Tamoxifen

- CYP2D6 processing of Tamoxifen now definitively shown to play a role in breast cancer recurrence with fast metabolizers benefiting and slow and intermediate metabolizers showing higher rates of recurrence and metastasis (OR 13.14)

- “The results confirmed the findings of previous studies and support FDA recommendation to perform pre-genotyping in patients before the choice of therapy is determined in breast cancer patients” AAPS J. 2012 Mar;14(1):52-9.

- What about recommendations for prevention?
Tamoxifen

- 4 trials for prevention in high risk women with combined results indicating 48% relative risk reduction in ER+ cancers for at least 15 years after the treatment ends
- Stated another way: the absolute reduction in overall incidence of breast cancer after 5 years is estimated to be about 1.1% and after 10 years, 1.7%
- No effect on ER(-) cancer risk
- Endometrial Ca increased 2.4 fold
- Venous thromboembolism increased 1.9 fold
- Other risks include stroke, cataracts, PE
- “lingering” concern: slight increase in ER(-) cancers in the f/u period after treatment in all of the prevention trials Fritz and Speroff
Raloxifene

- Selective estrogen receptor modulator (SERM) that competes with estrogen for binding to estrogen receptors, slowing cellular proliferation
- Nearly identical cancer risk reduction as Tamoxifen STAR Trial
- Less venous thrombosis and “perhaps” no increase in uterine cancer or cataracts. Increased stroke rate the same as Tamoxifen
- After 8 years, no decrease in non-vertebral fractures vs. tamoxifen
Tamoxifen and Raloxifene

“These results lead us to recommend tamoxifen prophylaxis or raloxifene prophylaxis for those women who are diagnosed with carcinoma in situ of the breast or who have atypical hyperplasia in a breast biopsy, esp. if a positive family history of br ca is also present”

Fritz and Speroff, 2011
Aromatase Inhibitors

- Block aromatase enzyme in fat cells, breast cancer cells and stromal cells that converts androgens to estrogen
- Being actively investigated as prevention agents in women with DCIS and women who are at increased risk of developing primary invasive breast cancer
- Noted that these agents when used to treat breast cancer patients decreased second, unrelated and contralateral breast cancers in women at increased risk of disease
Aromatase Inhibitors

- Mammary Prevention 3 trial with 4,560 postmenopausal women reduced invasive cancers by 65% (relative reduction) in placebo-controlled trial (after 35 months of follow-up, 32 cancers in the placebo group vs. 11 in the exemestane group) Goss P, NEJM June 23, 2011

- The NNT to prevent 1 breast cancer would be 94 at 3 years, but projected it would drop to 26 at 5 years
Aromatase Inhibitors

- Analysis by critics point out that 9,910 women would need to be treated unnecessarily for 3 years to prevent 90 ER-positive tumors.
- A tough sell? These women have only a 2-3% individual risk of breast cancer in the next 5 years. A prevention pill that cuts that risk by 65% means their risk will be about 1% instead.
- Risks commonly experienced included bone loss (3x normal over 2 years), arthritis, hot flashes, fatigue, sweating, insomnia, vaginal dryness and myalgias.
- Expert opinion
Nutrients and Nutraceuticals: Can We Influence our Genetic (and Environmental) Destiny?
Vitamin D

- Deficiency very common, even in sunny climates

- 25-OH Vit D over 52ng/ml associated with 50% lower risk breast cancer compared with levels <12ng/ml (Garland, AACR, 2006)

- Best level of 25-OH Vit D is >50ng/ml
Vitamin D

- Direct inhibitory action on initiation and progression of various cancers
- Anti-inflammatory and turns off NFkB, IL-6 and CRP
- Inversely proportional to CRP
- Growth arrest of malignant cells
- Reduces metastasis by cell junction effects
- Induces apoptosis
- Blocks overproduction of tissue-damaging cytokines
- Improves insulin sensitivity
NEW: Vitamin K and Breast Calcifications

- Breast calcifications are common reason to suspect malignancy
- Breast arterial calcifications were less common (9% vs. 13%) in the highest quartile of K2 intake vs. lowest; this correlation was no longer apparent when corrected for smoking, age and diabetes; K1 intake had no correlations at all.
- Breast arterial calcifications can be mistaken for calcifications associated with malignancy
- Nothing found in literature re: the use of vitamin K2 and regression of breast soft tissue calcifications

Iodine

- Iodine deficiency is common due to lack of iodized salt use and increased competition from fluoride, chlorine, bromine and perchlorate. Brownstein, D. Iodine, Why You Need It, 2009
- Perchlorate blocks the thyroid glands ability to absorb and utilize dietary iodine
- Absorption of iodine into the follicular cell is dependent on TSH, so don’t over-suppress TSH
- Some research has shown increased breast cancer rates in women treated for hypothyroidism
Iodine and Breast Health

- Breast tissue concentrates iodine second only to thyroid.
- Iodine deficiency can alter the structure and function of the breast, including dysplasia and atypia (Eskin, 1975, 1977).
- Iodine-deficient breast tissue exhibits increased lipid peroxidation markers, alterations in DNA and increases in estrogen receptor proteins (Breast. 2001 Oct;10(5):379-82).
Iodine and Breast Health

- Deficiency within a cell is a promoter of cancer
- Excess estradiol suppresses absorption
- Progesterone improves absorption
- Adequate iodine turns off the ability of the body to make estradiol. Eskin, 2008
- Needed for estriol formation. Wright, Jonathan
Iodine and Breast Health

- Rats that are susceptible to breast cancer were given carcinogens along with iodine and tumor formation was blocked Kato N, et al. Suppressive effect of iodine preparations on proliferation of DMBA-induced breast cancer in rat. J Jpn soc Caner Ther 1994;29(3):582-8.


- 2/3 of women newly diagnosed with breast cancer were severely iodine deficient
Iodine loading with 50mg combined iodine/iodide tablet and collection of 24 hours of urine was previous standard, but is undergoing review; this method assumes that the dose is excreted within the 24 hours and there are differences of opinion in this.

Urinary iodine tested with an am and hs sample on filter paper has been recently made available; this method looks at adequacy of iodine intake from diet and/or supplements from the last 1-2 days.
Iodine

• How to test:

Most recent is the position that the combination of urinary iodine testing (via filter paper method) combined with thyroglobulin is more reflective of long-term iodine sufficiency.
Iodine

What is clear is that we should use caution in replacing iodine if the patient is not deficient.

We should also use caution to avoid high iodine levels.

The CDC and WHO set 1100mcg daily as upper level of tolerance whereas in Japan the Ministry of Health has set the upper limit at 3000mcg daily.

It is not yet clear if adequate levels for the thyroid are adequate or optimal for other tissues, e.g. breast.
Iodine

- Studies in humans have shown that for iodine to be protective to breast tissue, 3000-6000 mcg daily are required, more consistent with Japanese consumption (where breast cancer rates are 1/5th the US rate) Kessler, JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. Breast J 2004;10(4):328-36.

- A recent study supplementing 0-2000 mcg of iodine showed all participants (except placebo) had increased TSH after 8 weeks. Thyroid volume decreased after 4 weeks in the high-iodine intervention groups (1500-2000 mcg). Conclusion is that high doses of iodine cause subclinical hypothyroidism: 5% in the 400 mcg group; and 15-47% in the 500-2000 mcg group. Am J Clin Nutr. 2012 Feb;95(2):367-73.
Radiative iodine and breast cancer risk

- Any iodine given is taken up by iodine-dependent tissues: thyroid, breast, uterus, ovaries...anywhere that iodine binds
- I\textsubscript{131} can destroy and alter DNA in these tissues
- I\textsubscript{131} therapy is associated with increased risk of several cancers
- No published studies re: breast cancer but they are underway as this is concern in the radiologic community; results expected to take 15 years
Fish Oil


- **DHA down-regulates ER-alpha and inhibits the breast cell cycle** J Nut Biochem, June 2010
Fish Oil

- Improves insulin sensitivity
- Increases the beneficial 2-hydroxylation pathways
- In mice, corn oil promoted breast cancer while omega-3 fatty acids resulted in a significant reduction in breast cancer [Bland, Nutr Res, 1989]
- Female animals prone to breast cancer were fed omega-3’s during early development and had 87% reduction in breast cancer as adults
Fish Oil

- 35,000 postmenopausal females followed for 7 years, the VITamins And Lifestyle Cohort (VITAL) showed a 32% reduction in risk of ductal breast cancer with highest intake of fish oil. Brasky et al, July 2010, Cancer Epidemiol Biomarkers Prev.

- The same study also looked at black cohosh, dong quai, soy and St. John’s Wort and found no effect on breast cancer risk.

- High risk premenopausal women with the highest omega-3:omega-6 had a 50% reduction in their risk of developing breast cancer. J Nutr. 2003 May;133(5):1409-14.
Ground Flaxseed

- Insoluble dietary fiber found in freshly ground flaxseeds binds estrogen, interrupting its enterohepatic circulation
- Dietary fiber beneficially effects the balance of bacterial flora in the gut, reducing beta-glucuronidase activity
- Lignans have been shown to inhibit estrogen-sensitive breast cancer cell proliferation
## Powerful Phytonutrients

<table>
<thead>
<tr>
<th>Phytonutrients</th>
<th>Mode of Action</th>
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<tbody>
<tr>
<td>Sulphoraphane</td>
<td>Induce phase II detox enzymes</td>
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<tr>
<td>Resveratrol</td>
<td>Counteract NFkB</td>
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<tr>
<td>Curcumin</td>
<td>Inhibit cancer growth via numerous cellular</td>
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<tr>
<td>Quercetin</td>
<td>mechanisms</td>
</tr>
<tr>
<td>EGCG</td>
<td>Increase apoptosis</td>
</tr>
</tbody>
</table>
Sulphoraphane

- Comes from broccoli; sprouts are most concentrated
- Potent inducer of Phase II detox and antioxidant enzymes
- Provides indirect antioxidant effect for 72 hours after exposure
- Inhibits breast cancer stem cells Clin Can Res, 2010
- Stimulates NrF2
Resveratrol

- Phenolic found in red wine
- Anti-oxidant, suppresses mutations, inhibits NFkB and inhibits activation of pro-carcinogens (anti-initiation)
- Inhibits COX-2, induces apoptosis, decreases anti-apoptotic proteins and down-regulates cancer activation cellular pathways (anti-promotion)
- Inhibits growth factor signaling pathways, reduces cancer cell invasiveness and growth as well as suppresses angiogenesis (anti-progression)
Resveratrol

- Is an ER agonist and may block the formation of estrogen-DNA adducts and estrogen-induced cell transformation. Proc Nat Acad Sci 1997;94:14138-43.

- Reverses the epigenetic silencing of BRCA-1, a tumor suppressor involved in DNA repair, which is down-regulated in some types of breast cancer.

- Limited bioavailability due to significant first pass metabolism; more bioavailable is the dimethylether analog pterostilbene (4x greater bioavailability); also nano- and liposomal forms being developed for greater bioavailability.
Curcumin

- A flavonoid extracted from the spice turmeric
- Beneficial in all 3 steps of cancer: initiation, progression and promotion  
- Strongly inhibits NFKB and the resultant pro-inflammatory signaling
- Inhibits cancer cell proliferation, invasion, new blood vessel formation and metastasis  
  Cancer Lett 2008 Oct 8;269(2):199-225
- Allows for apoptosis to take place in cancer cells  
- Reduces the inflammation associated with obesity  
  Aggarwal BB  
- Stimulates NrF2
Curcumin

- Potent antioxidant against virtually all types of free radicals
- Prevents lipid peroxidation
- Inhibits mTOR, a cell signaling mechanism that plays an critical role in the transformation of normal cells into cancer cells
- 1-5 grams daily
Quercetin

- Flavanoid found in black tea, green tea, capers, apples, onion and more
- Enhances breast cancer tumor suppression
- Powerful aromatase inhibitor
- Anti-inflammatory by inhibiting LOX
- Lowers blood sugars
- 500mg-1000mgTID(max 5gm daily)
EGCG

Epigallocatechin gallate polyphenol from green tea

- 25-100x more powerful antioxidant than vitamins C or E
- Blocks signaling pathways that lead to cell proliferation
- Reduces tumor growth and suppresses metastasis in mouse mammary carcinoma
- Reduced tumor blood vessel formation in ER-negative breast cancer


Additional Liver Detox Support

- **Glutathione**
  - NAC, n-acetyl cysteine, increases glutathione, the most potent antioxidant in our liver.
  - Glutathione has a linear correlation with NK cell function.
  - Whey protein increases glutathione.
  - Newer oral forms of glutathione available.

- **Selenium**
- **Milk thistle**
- **Rosemary**
- **Lycopene**
DIM (diindolylmethane)

- Found in cruciferous vegetables
- Active metabolite of Indole-3-Carbinol (I3C) (400mg BID), formed only in the presence of adequate stomach acid
- Promotes the beneficial 2-hydroxylation pathway of estrogen metabolism
- Blocks the cancer cell cycle and its growth via cyclin D
- Enhances BRCA1, our breast cancer suppressor gene
- Represses ER-alpha (needed for growth)
CoQ10

- Many functions including immune stimulation, inhibition of inflammatory cytokines, scavenges free radicals

- Deficiency in CoQ10 increases a woman’s risk of breast cancer 800%

- Recent meta-analysis showed 33% increase in risk of breast cancer in women taking statin drugs (CARE)
Fermented Wheat Germ Extract

- Current use predominantly in treatment of cancer
- In mouse model, FWGE was stronger than any drug for inhibiting mammary cancer. Am Soc Clinical Oncology
- Unpublished study in animals predisposed to mammary cancer, usual rate in placebo group and zero mammary cancer in the FWGE group
- Study showing tamoxifen plus FWGE increases breast cancer cell apoptosis more than tamoxifen alone

Fermented Wheat Germ Extract

Affects many mechanisms of cancer cell survival:

- Selectively inhibits glucose metabolism in cancer cells
- Enhances apoptosis (inhibits PARP, a SNA repair enzyme and enhances production of caspase 3 enzyme that initiates apoptosis)
- Helps immune system identify cancer cell (cancer cells use surface molecule MHC-1 to hide from NK cells)
- Enhances macrophage function by stimulating TNF alpha production
- Normalizes TH₁/TH₂ balance
NEW: Fermented Wheat Germ Extract

- 2007 American Society of Clinical Oncology study “FWGE Inhibits Mammary Carcinoma”
- Rodents had mammary tumors transplanted and normally 100% growth is expected
- FWGE reduced expected tumor growth by 50%
- Tamoxifen by 66%
- FWGE and Tamoxifen combo 59%
- Anastrazole 70%
- FWGE and anastrazole combo 60%
- Exemestane 53%
- FWGE and exemestane 39%
Ellagic acid

- Very powerful anti-cancer plant-derived polyphenol from pomegranate and raspberries
- Inhibits aromatase activity  
  Cancer Prev Res Jan 2010
- Reduces breast cancer cell proliferation
- Induces apoptosis
- Prevents proliferation of breast cancer stem cells in mouse model  
  Oncol Rep, Oct 2010
Feverfew

- Parthenolide made from feverfew
- Regulates selectively in cancer stem cells the activity of NFkB and p53
**Gamma-tocotrienol**

- A member of the Vitamin E family
- Induces apoptosis in human breast cancer cells
- Gene analysis revealed alterations in the expression of multiple genes involved in cell growth and proliferation, cell death, cell cycle, cellular development, cellular movement and gene expression.
- Modulates NRF-2 mediated oxidative stress response and the ER (endoplasmic reticulum) stress response
- The most highly upregulated gene was Activating transcription factor 3, ATF3, essential in apoptosis

Synergism in Nutrients

- Mice prone to DMBA-induced mammary cancer treated with DMBA got 100% cancer as predicted. Mice then treated with selenium, magnesium, vitamin C or vitamin A:
  - With 1 nutrient, avg. 50% reduction in # mice w/br ca
  - With 2 nutrients, avg. 30% reduction in # mice w/br ca
  - With 3 nutrients, avg. 20% reduction in # mice w/br ca
  - With 4 nutrients, avg. 10% reduction in # mice w/br ca

In all interventions, # tumors/mouse were also decreased proportionately
Calcium d-Glucarate

- Glucuronidation is a major Phase II liver detox pathway for estrogen
- Some intestinal bacteria possess beta-glucuronidase, an enzyme that cleaves the glucuronic acid off of the estrogen, allowing estrogen to re-enter the body via the enterohepatic circulation
- Excess bacterial beta-glucuronidase activity is associated with increased breast cancer
- Ca D-Glucarate inhibits beta-glucuronidase activity and also helps phase II glucuronidation pathway
- Carotenoids and calcium d-glucarate in 1 study reduced breast cancer 70%
Probiotics

- Reduce beta-glucuronidase activity resulting in less estrogen re-circulation
- Improve digestion
- Improve transit time
- Promote healthy gut flora
- Promote healthy immune activity
Immune boosters

- Beta Glucan/Mushrooms: immunomodulators that enhance innate immunity and tumor-specific adaptive immunity
- Colostrum
- Echinacea
- Andrographis paniculata
- Tai chi
- Ensure adequate nutrients needed for immune function including zinc, selenium, iron, copper, vitamins A, C, E and B6 and folate
Adequate T3, Tri-iodothyronine

- T3 (tri-iodothyronine) has many anti-cancer effects
  - Increase NK cell activity
  - Increases interleukin-2, an important cytokine that fights cancer
  - Inhibits proliferative cancer cell proteins
  - Directly inhibits breast cancer cells in culture
  - Decreases aromatase in cancer cells
  - Increases oxytocin
  - Increases SHBG
  - Involved in DNA repair
    - Mahmud, Khalid, “Keeping aBreast: Ways to Prevent Breast Cancer”
NEW: Telomere Length and Breast Cancer

- Luminal epithelial cells undergo critical telomere shortening before they go on to develop malignancy.
- Shortened telomeres result in an unstable genome with sticky chromatin (and more aggressive tumors).
- To go from in situ cancer to invasive cancer requires reactivating telomerase.
- Telomere shortening associated with loss of tumor suppressor gene p53.
- Daughters of breast cancer pts inherit shorter telomeres than the parent and get cancer at an earlier age.
- Mice engineered with short telomeres get increased breast cancer.
  - From May 2012 Orlando A4M General Session.
Mammograms: A Risk?

- Mammograms are ionizing radiation, known to cause DNA damage.
- Each individual mammogram is low dose but the radiation damage is cumulative.
- The National Research Council Advisory Committee says that every time a premenopausal female is exposed to ionizing radiation during annual screening, her cancer risk increases 1%.
- NEJM Sept 2011 estimates 86 cancers and 11 deaths per 100,000 women screened annually due to radiation risk from mammography.
- Also, the average radiation dose to which persons in the USA have been exposed has doubled in the last 30 years, much of it from medical radiation.
- New 3-D mammograms (tomosynthesis) approved with double the radiation and increases accuracy 7%.
Mammograms: A Risk?

Average Dose (mSv) in common radiographic studies

<table>
<thead>
<tr>
<th>Radiographic Study</th>
<th>Average Dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR</td>
<td>0.34</td>
</tr>
<tr>
<td>C-spine</td>
<td>0.17</td>
</tr>
<tr>
<td>T-spine</td>
<td>0.9</td>
</tr>
<tr>
<td>L-spine</td>
<td>1.6</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0.78</td>
</tr>
<tr>
<td>Abdo/KUB</td>
<td>0.75</td>
</tr>
<tr>
<td>Hip</td>
<td>0.4</td>
</tr>
<tr>
<td>Limbs</td>
<td>0.035</td>
</tr>
<tr>
<td>Barium enema</td>
<td>8</td>
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<tr>
<td>IVP</td>
<td>4.1</td>
</tr>
<tr>
<td>Mammography</td>
<td>0.48</td>
</tr>
<tr>
<td>UGI</td>
<td>3.6</td>
</tr>
<tr>
<td>Dental</td>
<td>0.18</td>
</tr>
<tr>
<td>CT-head</td>
<td>1.9</td>
</tr>
<tr>
<td>CT-Chest</td>
<td>6</td>
</tr>
<tr>
<td>CT-Thoracic</td>
<td>10</td>
</tr>
<tr>
<td>CT-Lumbar</td>
<td>4.4</td>
</tr>
<tr>
<td>CT-Abd</td>
<td>11.8</td>
</tr>
<tr>
<td>CT-Pelvis</td>
<td>11.5</td>
</tr>
<tr>
<td>Anglo-arterial</td>
<td>7.5</td>
</tr>
<tr>
<td>Anglo-cardiac*</td>
<td>19.4</td>
</tr>
<tr>
<td>Anglo-vascular*</td>
<td>71.9</td>
</tr>
</tbody>
</table>
Mammograms: A Risk?

- The USPSTF changes mammogram recommendations in 2009, inciting backlash and controversy about the benefits of early detection (start at age 50, instead of age 40); the AAFP, ACP, NBCC and the WHO also support these recommendations.
- ACS, NCCN, ACS, ACR and ACOG recommend starting at age 40.
- 49% of women screened over a 10 year period will have a false positive, NEJM 365;11 Sep15, 2011, often leading to additional radiation and tissue trauma from biopsy.
- “In a great many cases, mammograms find slowly growing tumors that were never going to kill anyone” biostatistician Donald Berry PhD, MD Anderson Cancer Center, Houston as quoted in Readers Digest, Oct 2011.
- Statistics most often do not differentiate between LCIS, DCIS (25% of all cases) and invasive breast cancers.
Mammograms: A Risk?

- An entire JAMA edition was dedicated to this discussion about the USPSTF guidelines
- There was only 1 sentence in the entire journal about the radiation component of mammograms
- There was also no discussion on the health implications of the long term stress of the fear of breast cancer (after an abnormal mammogram or biopsy)
Mammograms: A Risk?

- Recent study in Sweden following 130,000 women for 30 years showed 30% fewer deaths from breast cancer in the screening group and the number of lives saved increases over time.

- 40-49 year olds were screened every 2 years and 50-74 year olds were screened every 3 years.

- Screening 1000 women for 10 years prevents 3 deaths.

- False positive rate much lower than previous studies, only 3% (would the rate be the same in the USA?)

- Other studies show discrepant results. Norwegian cohort, CISNET modeling, Cochrane Review, European Trend) Journal Family Practice September 2011 reviews this.
NEW: Mammograms

- 2011 Cochrane review update of a 2006 meta-analysis reviewers estimated that screening mammography results in a 15% decrease in breast cancer deaths; this corresponds to an absolute risk reduction of 0.05% in breast cancer deaths.
- Same review showed screening led to a 30% increase in overdiagnosis and treatment; this corresponds to an absolute increase in risk of 0.5%.
- BMJ July 2011 comparing nations with similar demographics and access to care found over 17 years no difference in breast cancer mortality whether mammography screening was utilized or not.
NEW: Mammograms and Lives Saved

- Not including morbidity and mortality calculations on radiation exposure and just looking at women’s risk of being diagnosed with breast cancer and then the risk of dying from it

- It is concluded that a breast cancer survivors life was saved by screening mammography is never more than 25% and typically is less than 10%
  - Archives Internal Medicine 2011
NEW: Mammograms

- Legislation being introduced to require women to be informed of their breast density when they receive their mammogram results and that those with denser breasts be advised that they could benefit from additional screening.
- Similar laws exist in Connecticut and Texas
- Significantly drives up cost due to follow-up ultrasounds and MRI’s
Future Considerations

- MRI superiority to mammograms...a new standard for screening?
  - In Connecticut in 2009 a new law was enacted that required x-ray facilities to tell women with dense breast tissue that reduces the accuracy of the mammogram reading and that they would benefit from additional screening
- Thermography...a very helpful adjunct
- Breast cancer vaccine
- Identification of 200 mutated genes found in breast cancers. Marked heterogeneity found in tumors and so far not been helpful
- Estriol “drug” development
- 2-methoxy estradiol “drug” development
Breast Cancer Risk Reduction

How do I implement this voluminous information into the office setting?
Breast Health Plan

LIFESTYLE

- Ideal Body Weight______________________________
- Exercise________________________
- Organic, Healthy Carb, Healthy Fat Diet________________
- Sleep________________________
- Alcohol________________________
- Stress________________________
- Proper Elimination________________
- Avoiding Toxicity________________
- Pregnancy and Lactation
Breast Health Plan

SPECIFIC NUTRITIONAL FACTORS

- Multivitamin w/minerals
- Fish oil
- MethylB12/Methylfolate (B-vitamins)
- Vitamin D
- Iodine
- Ground Flaxseed
- Grapefruit
- Green tea
## Breast Health Plan

### SUPPLEMENTS
- DIM____________________
- Sulphoraphane__________
- Curcumin_______________
- EGCG(green tea)_________
- Quercetin_______________
- Resveratrol_______________
- Alpha Lipoic Acid________
- Fermented Wheat Germ Extract_________________
- Liver Detox Support_______
- Calcium D-Glucarate______
- Probiotics_________________
- CoQ10__________________

### Other Supplements
- Immune Support__________
- Melatonin________________
- Other________________________
Breast Health Plan

SEX HORMONE MEASUREMENTS
- Baseline
- Treatment levels
- Estrogen metabolism

BREAST IMAGING
- Digital mammogram
- Ultrasound
- MRI
- Thermogram
Breast Health Plan

ADDITIONAL RECOMMENDATIONS

- Melatonin levels
- Cortisol levels
- Vitamin D level
- Ferritin level
- CRP
- Omega-3 index
- Nutritional Analysis
- Fasting insulin/glucose
- Metformin
Breast Health Plan

- Telomere Testing
- Genetics (BRCA1,2/detox)
- Iodine Testing
- MTHFR/homocysteine
- Toxicity testing
- Heavy Metal testing
Breast Cancer: Is Prevention Possible?

• Use care with the term prevention
• There is no question that we are able to reduce risk for all
• By minimizing endogenous and exogenous toxicities, optimizing hormonal and nutritional factors, and optimizing the immune system we can markedly reduce the initiation, progression and promotion of many breast cancers
THANK YOU!