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Breast cancer risk and 2/16 hydroxyestrone ratio

BACKGROUND

The effect of prolonged exposure to estrogen is an established risk factor for the development of breast cancer.¹ The estrogen metabolite ratio (2/16 hydroxyestrone) is becoming recognized as a risk factor for breast and prostate cancers.^{2,3} Part of the explanation for this increased risk resides in the nature of estrogen’s metabolism which primarily proceeds down one of two metabolic pathways (see page 3). Each pathway exerts a different biological effect on the estrogen receptor thereby affecting risk.⁴ Multiple dietary, lifestyle and environmental variables can influence this metabolism and provide a framework to influence risk reduction.

In 2006 a large, case-controlled study found that the ratio of estrogen metabolites in the urine was associated with a risk for developing invasive breast cancer, especially among premenopausal women.⁵ One metabolite, 2-hydroxyestrone (2-OHE1), is a weak estrogenic agonist that likely has anti-estrogenic properties as well. In contrast the 16[alpha]-hydroxyestrone (16-OHE1) metabolite, forms strong, covalent bonds with the estrogen receptor, is genotoxic, and has been shown to promote the growth of estrogen dependent breast cancer cells in vitro.^{6,7} The ratio of these metabolites, the 2/16 hydroxyestrone ratio, has been identified as a marker for breast cancer risk. A low ratio (low = 2-OHE1; high = 16-OHE1) suggests a high risk. The therapeutic goal is to raise this ratio.

INCREASING THE 2/16 RATIO

Exercise and Movement

Dietary and lifestyle modifications can change the 2/16 ratio to one that has less estrogenic stimulatory effects. One study of 77 eumenorrheic women found that those with increased amounts of daily activity had higher 2/16 ratios, independent of their BMI, suggesting that exercise may shift estrogen metabolism towards more 2-hydroxyestrone (2-OHE1) production.⁸ A recent, small, prospective study of 24 women found that four months of moderate exercise, in conjunction with calorie restriction, increased the 2/16 ratio in those with a low ratio at baseline.⁹ However, the 2/16 ratio of women whose ratio was higher at baseline did not change, suggesting that the initial 2/16 profile may be a predictor of those likely to respond to this type of intervention.

Maintaining Appropriate Weight

Obesity has been strongly linked to breast cancer, and each one-point gain in BMI increases the risk for developing postmenopausal breast cancer by 3%.¹ Women who are obese have 130% higher levels of estradiol concentrations as well as increased levels of insulin-like growth factor that promote inflammatory changes that stimulate epithelial cell growth and the risk of carcinogenesis. Finally, when diagnosed, obese women with breast cancer have a poorer prognosis.¹⁰

Flaxseed

Estrogen metabolism is affected by dietary habits as well. Ground flaxseed is a rich source of lignans and alpha-linoleic acid, both of which have estrogenic lowering properties.¹ One study found that flaxseed consumption increased the urinary 2/16 ratio in a dose dependent fashion.¹¹ Supplementing with 25 grams of ground

flaxseed daily had a more positive effect on the 2/16 ratio than equal amounts of soy supplementation.¹²

Cruciferous Vegetables

Cruciferous vegetable consumption (broccoli, cabbage, brussels sprouts, kale, cauliflower) has been shown to increase the 2/16 ratio among healthy postmenopausal women when their intake was increased for 4 weeks.¹³ Giving an extra 500 g/day of broccoli for 12 days increased the 2/16 ratio by 29.5% in a small study of 16 human subjects.¹⁴

Supplementation with indole-3-carbinol (I3C), a phytochemical in cruciferous vegetables, also increases the 2/16 ratio, with one study finding that both obese and non-obese women responded.^{15,16} In addition to the effects on shifting estrogen metabolism, the cruciferous vegetables are metabolized into products that promote the creation of detoxifying enzymes. Furthermore, these foods contain many chemoprotective phytonutrients such as folate, carotenoids, fiber and chlorophyll.¹⁷ At this time, the degree to which eating these foods reduces breast cancer risk has yet to be fully elucidated, yet increasing one's consumption can have beneficial health implications overall. Due to the likely synergy of multiple chemicals found within the whole plant, it is likely more beneficial to eat the whole food versus one isolated chemical (i.e., I3C).

Xenobiotic Influences

A xenobiotic is a foreign body that is not of the biological world. They are often resistant to biodegradation and may have hormonal influences. Pesticides and other environmental toxins are ubiquitous with potentially significant effects on breast carcinogenesis. Organochlorine pesticides have been shown to significantly reduce the 2/16 ratio in vitro with the greatest effects from the chemicals DDT, o,p-DDE, kepone, and atrazine.¹⁸ Although research is limited in regards to giving definitive

guidance as to which chemicals are cancer causing in humans, a recent study identified 216 chemicals as being mammary gland carcinogens in animals. Several chemicals, including polycyclic aromatic hydrocarbons (found in diesel exhaust), chlorinated solvents, benzene, and perhaps ethylene oxide have been identified in epidemiological studies as having some association with breast cancer.¹⁹ While research is still needed in these areas, the precautionary principle is a reasonable approach to consider by encouraging patients to reduce exposures to these chemicals in a manner that is sustainable to them. For more information regarding this issue, the following website is available: www.silentspring.org/sciencereview

NEED FOR TESTING 2/16 HYDROXYESTRONE RATIO?

It is important to note limitations and suggested guidelines to determine whether to test or not:

- 1) The test for the 2/16 ratio is often an "out-of-pocket expense" for patients and screening guidelines have not been established or justified.
- 2) The test may be appropriate for women with increased risk for developing breast cancer.
- 3) The test may help identify those who may benefit most from diet and lifestyle modification.

Laboratories that offer this test include:

Metamatrix: urine testing
www.metamatrix.com

Genova Diagnostics: a serum assay
www.gdx.net/home/

Rocky Mountain Analytical (Canada)
www.rmalab.com

Estramet™: an immunoassay urine test kit for lab use
www.immunacare.com/Kit.htm

Increasing the 2/16 ratio to reduce breast cancer risk

- Engage in regular exercise and movement
- Maintain appropriate weight
- Eat cruciferous vegetables
- Ingest ground flaxseed (one tbspc twice daily)
- Reduce xenobiotic exposure (See table below)
- Consider supplementing with Indole-3-Carbinol 300 mg daily
- Consume soy protein
- Drink green tea
- Increase consumption of omega-3 fatty acids
- Reduce simple sugars/sweets (low glycemic index/load diet)

Reducing exposure to estrogen disruptors (xenobiotics)

- Limit fat intake from meat and dairy since animals store these chemicals in their fat
- Eat organic, unprocessed foods when available
- Drink filtered water
- Avoid petroleum-base cosmetics
- Store and heat products in glass containers to reduce PCB exposure found in plastics
- Grow plants in the home (spider plants, Boston ferns) to reduce levels of air pollutants
- Buy a car with an air filter to reduce exposure to diesel exhaust

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– SH, DR

Facts about breast cancer risk

Well-confirmed factors that INCREASE breast cancer risk*

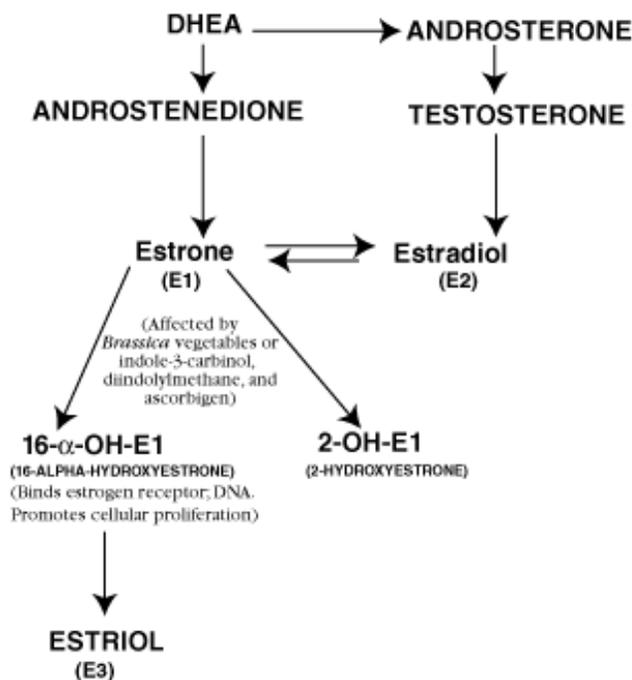
- Increasing age
 - Geographical location (Western world)
 - Family history of breast cancer
 - Mutations in BRCA1 and BRCA2 genes
 - Ionizing radiation exposure in childhood
 - History of benign breast disease
 - Late menopause (>54 years)
 - Early age of menarche (<12 years)
 - Nulliparity/older age at first birth
 - Hormone replacement therapy
 - Recent oral contraceptive use
 - Obesity in postmenopausal women
 - Tall stature
 - Alcohol consumption (>1 drink/day)
 - High insulin-like growth factor 1 (IGF-1) levels
- Probable factors that increase breast cancer risk:**
- High saturated fat diet
 - High socioeconomic status

Well-confirmed factors that DECREASE breast cancer risk*

- Geographical location (Asia and Africa)
- Early age of first full-term pregnancy
- Higher parity
- Breast feeding (longer duration)
- Fruits and vegetables consumption
- Physical activity
- Pharmaceutical chemo preventive agents
- Nonsteroidal anti-inflammatory drugs

*Adapted from Boyce, J. Breast Cancer. In Integrative Medicine, Editor D. Rakel, Saunders 2007, p. 822.

Metabolism of Selected Estrogens



<http://www.tahoma-clinic.com/images/pic1.gif>

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Into the dark: melatonin and breast cancer

Research exploring the relationship between melatonin and cancer has increased ever since a meta-analysis published in 2005 showed a higher incidence of breast cancer in night shift workers.¹ Melatonin levels appear to be lower in women with breast cancer^{2,3,4} and melatonin has a number of mechanisms that appear to benefit breast cancer, particularly in those cases that are hormone-receptor positive.

Melatonin properties that may benefit breast cancer⁵:

- Free radical scavenger
- Broad-spectrum anti-oxidant
- Cytoprotective, reducing adverse toxicities of chemotherapy and radiation therapy.
- Binds to immunomodulators and up-regulates the production

of interferon gamma and interleukins.^{1,2,6}

- Inhibits tumor angiogenesis, tumor proliferation and metastasis.
- Stimulates programmed cell death (apoptosis)
- Acts as a selective estrogen receptor modulator (SERM)⁶
- Reduces estrogen synthesis.⁶

When used therapeutically for breast cancer, melatonin appears to have promising effects. When combined with tamoxifen, high doses (20-40 mg) appear to boost survival and even double one year survival rates in limited, small studies.^{7,8}

Several options are available to enhance melatonin levels that may have an overall positive influence. Until more is known, however, high therapeutic doses are not

recommended due to the limited evidence of benefit and the potential negative effects on quality of life (fatigue).

Take home advice:

- Practice what nature teaches. The rhythmic polarity of night and day is important to our health.
- During the day, get outside in direct sunlight to stimulate Vitamin D production and exercise to maintain appropriate weight.
- Enjoy meals rich in multi-colored whole foods with people you love and care about.
- Enjoy a restful night's sleep in a dark environment.
- Repeat!

– DR
> References

Boosting melatonin levels ~ Invest in a healthy sleep-wake cycle

Ensure 7-8 hrs of complete darkness while you sleep	Light stimulates photoreceptors in the eye that reduce melatonin production in the pineal gland. Darkness stimulates production.
Remove electromagnetic fields (EMF) from around the head while sleeping (radios, active cell phones, multiple electrical plugs)	Magnetic fields are perceived by the eye as "light" and reduce melatonin levels. ⁵
Maintain ideal weight	Elevated weight has been inversely correlated with melatonin levels. ⁶
Avoid medications that can lower melatonin	Beta-blockers, Calcium Channel Blockers and psychotropics (anti-depressants, anti-psychotics and anti-convulsants) ⁶
Consume foods rich in melatonin	Tomato, rice, orange, apple, banana, cherries, cucumber, cabbage, almonds, walnuts and seeds (sunflower, mustard, fennel) ⁶
Consider checking serum Zinc levels and supplement if low.	Zinc supplementation can increase melatonin in animals (rats) ⁹
Consider a B-vitamin	Folic Acid and vitamin B6 raise melatonin in animals (rats) ⁶

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Fighting cancer with food and nutrition

Nutritionists are often asked if a diet, a food or a supplement will help cure cancer or prevent it from recurring. To answer, we need to understand what we know about fighting cancer with food and nutrition.

- The food you eat can increase your body's ability to fight cancer and survive.
- The food you eat can decrease your risk of developing some cancers.
- It makes sense that what you eat to prevent cancer may help in decreasing risk of cancer recurrences.

However, there is no evidence that any special diets or that any single food will cure cancer or prevent it from recurring. In fact, diets that exclude or limit some food groups may be harmful.

Nutrition research on preventing and treating cancer is continually changing as scientists develop studies and report findings. Information on the health benefits or health dangers of a specific food is often interesting and exciting to hear, but is frequently based on preliminary data. To prevent becoming a victim of the "food of the week" syndrome, it is important to wait for collaborating studies and scientific consensus.

Everyday dietary patterns and general eating habits are key in preventing and treating cancer.

- Choose a variety of colorful fruits and vegetables. Although there are many controversies in the area of food and nutrition, there is total agreement that fruits and vegetables are the number one cancer fighters. Choose the most colorful for the highest amounts of cancer fighting phytonutrients, including antioxidants, vitamins

and minerals. Among the highest in antioxidant power are:

- Blueberries, blackberries, strawberries, oranges, cranberries, grapes, cherries, apples and melons;
- Broccoli, spinach, asparagus, peppers, peas, beets, tomatoes, carrots, squash, pumpkin, sweet potatoes, cabbage, onions and garlic.
- Increase fiber and select whole grains. Hundreds of studies have shown strong associations between high fiber diets and reduced cancer risk. Check the label of food for fiber content. A good goal is 25 – 30 grams of fiber per day. Fruits and vegetables provide some fiber, other high fiber foods include:
 - Breads and cereals made with whole grains, nuts and seeds;
 - Beans and legumes (red, white, black and kidney beans).
- Drink a lot of fluids. Any liquid counts as part of your fluid intake—water, juices, tea, even coffee. Studies show that tea has special characteristics that decrease the risks of some cancers and possibly slow some cancer cell growth. Green, white and red teas are best, either caffeinated or decaffeinated.

- Choose good protein foods at every meal. Eat more fish. Poultry, eggs, low fat dairy products, nuts, beans, soybeans and legumes are also good proteins. Limit high fat animal products and other saturated and trans fats. Recent studies found decreased risk of breast cancer and prostate cancer recurrences when a low fat diet was followed.
- Find ways to increase essential omega-3 fats in your diet. These

fatty acids are abundant in oily fish, especially salmon. Other choices are olive oil, canola oil, walnuts, flax seed, flax oil and fish oil supplements.

- Multivitamins and mineral supplements with close to 100% DV of most nutrients are usually recommended, but large amounts of single vitamins are not. Calcium and Vitamin D supplements are important for those who do not eat dairy products regularly. Check with your physician or nutritionist on any herbal supplements.
- Exercise regularly. Regular exercise decreases cancer risks and may decrease risk of some cancers recurring. Choose an exercise program that works for you. Remember that any exercise is better than no exercise.
- A healthy weight is the goal. Studies show excess weight increases risk of many cancers. The good news is that there is every reason to assume that reaching and maintaining a healthy weight will decrease the risk of cancer.
- And the best news—dark chocolate is a good source of antioxidants. Choose a chocolate treat that does not run around with bad friends (a lot of sugar and fat).

– DW

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Foodways of the spice/silk routes:

Recipe: Sichuan Toasted Sesame and Cabbage Salad

Ingredients:

- 1 head Chinese cabbage (Napa is a looser leaf head of cabbage, about 2 lbs), washed, pat dried, and shredded
- 1 long seedless cucumber or 4 pickling cucumbers, peeled and thinly sliced
- 1 large carrot (about ¼ lb), peeled and shredded
- ½ cup chopped fresh parsley or scallions

Salad Dressing:

- 2 cloves garlic, peeled and crushed
- 1 teaspoon salt
- 1 teaspoon toasted ground red pepper (Sichuan or a milder Arbol pepper)
- 1 tablespoon sugar
- 4 tablespoons rice vinegar
- 1 tablespoon olive oil
- 2 tablespoons toasted sesame oil

Garnish:

- ½ cup toasted sesame seeds

Directions:

1. Place the cabbage, cucumber, carrots and parsley in a salad bowl and set aside
2. To make the salad dressing. Thoroughly mix all the salad dressing ingredients and adjust seasoning to taste.
3. Pour the dressing and toasted sesame seeds over the salad and toss well.
4. Serve with plain rice, pasta, bulgur or bread.

Serves 6; Preparation: 20 minutes; Cooking time: none

From Batmanglij, Najmieh. *A Silk Road Cooking: A Vegetarian Journey*. Marg Publishers, Washington DC, 2002, p. 70. (www.najmiehskitchen.com)

BREAST CANCER RISK AND 2/16 HYDROXYESTRONE RATIO

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INTO THE DARK: MELATONIN AND BREAST CANCER

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