"Efficacy of Dried Cruciferous Powder for Raising the 2/16 Hydroxyestrogen Ratios"

When "less" is "more"
Outline

1. Look at how the 2 / 16 hydroxyestrogen metabolites are important risk markers for development of cancer in estrogen sensitive tissues (breast, uterus, prostate) including a few confirming studies.

2. Take a few minutes to review how the body processes / metabolizes estrogen

3. Review how these markers are typically modified using isolates or fractions of cruciferous vegetables and why we think that approach is not necessary.

4. Look at the study that we did and the amazing results we achieved!

5. Review how to incorporate this into your wellness practice
Efficacy of Dried Cruciferous Powder for Raising the 2/16 Hydroxyestrogen Ratio

Metametrix Institute

Jerry Morrison, ND; Dennis Mutell, DC, Terry A. Pollock, MS, Elizabeth Redmond, PhD, J. Alexander Bralley, PhD, and Richard S. Lord, PhD*

Abstract

Urinary 2-hydroxyestrogens, 16-α-hydroxyestrone, and the 2/16 hydroxyestrogen ratio were determined in 13 premenopausal women before and after the addition of dietary supplements containing 3.6 g of powdered organic Brussels sprouts and organic kale for 90 days. Twelve of the subjects had an initial 2/16 hydroxyestrogen ratio that was below the cutoff of 2.0. Lower 2/16 hydroxyestrogen ratios have been associated with increased risk for cancers of estrogen-sensitive tissues. 11 of the 13 subjects showed positive increases of their ratios, and the three subjects with the lowest initial ratios had an average increase of 500%. The results demonstrate that dehydrated whole brassicae supplementation can significantly raise the 2/16 hydroxyestrogen ratio in premenopausal women.

Introduction

Incidence of breast cancer increases with total estrogen exposure, and urinary concentrations of estrogen decreases the flux of estrogens through the alternative 16-α-hydroxylation pathway in liver and extrabhepatic tissues, raising the 2/16 ratio.
Subject Background

Since the late 1970’s researchers have studied the known correlation between women who regularly consume brassica vegetables and the reduced risk of developing breast cancer. Over 150 studies. 1,9,10,11,14,23,24,26,27

The emphasis here is on “populations of women who consume brassica vegetables” and not “women who consume fractions or portions of those vegetables”
The study of Luo et al, {21} and Ho et al, {24} was a case-control study of 101 Chinese women, comprising 65 breast cancer patients, and 36 controls. These investigators found that the profile of urinary estrogen metabolites was distinctly altered in breast cancer patients. Multiple linear regression analysis showed that the odds ratio of breast cancer for women with higher 2/16 (>0.9) was 0.1, or one-tenth that of those with 2/16<0.9. This significant difference was seen for both pre- and postmenopausal women. Controls were
The study of Luo et al. and Ho et al. was a case-control study of 101 Chinese women, comprising 65 breast cancer patients, and 36 controls. These investigators found that the profile of urinary estrogen metabolites was distinctly altered in breast cancer patients. Multiple linear regression analysis showed that the odds ratio of breast cancer for women with higher 2/16 (>0.9) was 0.1, or one-tenth that of those with 2/16 < 0.9. This significant difference was seen for both pre- and postmenopausal women. Controls were randomly selected from women who were confirmed to have benign breast disease by histology of breast biopsies.
In a case-control study, Kabat et al. {23} found that postmenopausal women with a 2/16 ratio below 1.38 had a multivariate adjusted odds ratio of 33 for breast cancer risk, whereas those with a 2/16 ratio between 1.38-1.90 had an odds ratio for breast cancer of 10. Analyses of the individual metabolites indicated that urinary 16α-hydroxyestrone was also a strong risk factor.

A THREEFOLD RISK INCREASE !!
“In every experimental model in which 2-hydroxylation was increased, protection against tumors was achieved. Correspondingly, when 2-hydroxylation was decreased, an increase in cancer risk was observed.”

Bradlow HL et al. 2-Hydroxyestrone: the 'good' estrogen. J of Endocrinol 1996, 130:S259-S265

Copyright 2008: Jerry Morrison ND

Copyright 2002, 2008: Jerry Morrison ND
Estrogen metabolites

Improper COMT function and GSH levels have been shown to increase breast cancer risk in Caucasian women 300 to 400 % !!!
Functions of estrogen metabolites

2-hydroxyestrone (2-OHE1), tends to inhibit cancer growth and confers a protective effect to estrogen sensitive tissues.

16-a-hydroxyestrone (16-a-OHE1), actually encourages cellular growth (tumor development).

A woman’s (or Man’s) "biochemical individuality" determines which of these metabolites predominates. Studies have shown that measuring the ratio of these two metabolites provides an important indication of risk for future development of estrogen-sensitive cancers.
Measuring E2 / E16 ratios

The Estronex™ 2/16 Test from Metametrix Clinical Laboratory measures the ratio of these two critical estrogen metabolites from a single urine specimen. Estronex 2/16 ratios less than 2.0 indicate increasing long-term risk for breast, cervical, and other estrogen-sensitive cancers. Importantly, nutritional interventions can help raise Estronex 2/16 ratios and decrease long-term risk.

For $113 (practitioner cost)/ $139 patient pre-pay this is a no brainer test and an invaluable screening tool for any wellness oriented practice.
Estronex Test

◆ Q: Does this take the place of mamograms or thermography?
  – NO

◆ The Estronex test is to help screen for risk factors which increase the likelihood of developing breast cancer years or decades before it occurs.
Estronex Test

- Thermography and mammograms only confirm a detectable pathology that has already developed but do NOTHING to help reduce a woman's risk.
**0142 Estronex™ - 2/16 OH Estrogen Ratio in Urine**

Methodology: Enzyme Immunoassay, Colormetric Assay

<table>
<thead>
<tr>
<th>Result</th>
<th>Reference Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:16 Ratio</td>
<td>2.00 - 8.00</td>
</tr>
<tr>
<td>2.00</td>
<td>1.78</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Result</th>
<th>Pre-Menopausal</th>
<th>Post-Menopausal without hormone therapy</th>
<th>Post-Menopausal with hormone therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Hydroxyestrogens (2OHE)</td>
<td>20.8</td>
<td>3 - 40</td>
<td>10 - 75</td>
</tr>
<tr>
<td>16-Hydroxyestrone (16OHE1)</td>
<td>11.7</td>
<td>2 - 8</td>
<td>5 - 25</td>
</tr>
</tbody>
</table>

**Creatinine = 100 mg/dl**

The ideal value for the 2/16 ratio is above 2.0. The following have been shown to raise the ratio:
- Cruciferous vegetables (e.g. broccoli, bruss sprouts, cabbage, cauliflower)
- Supplementation of indole-3-carbinol (I-3-C) or diindolylmethane (DIM)
- Soy isoflavones
- Flax seeds (not oil)
- Omega-3-fatty acids (DHA & EPA) found in fish (e.g. mackerel, lake trout, herring, sardines, salmon) and marine algae also may help to lower cancer risk. Assure antioxidant adequacy when adding polyunsaturated oils.

---

* These guidelines are intended as a starting point for the clinician who requested the test and are based only on the laboratory results included in this report. Final recommendations should be implemented by the clinician with consideration of medical history and current clinical observations.
* These tests are not intended for the diagnosis of specific disorders.
Vitanox (tumeric, catechins) - 1 to 2 per day
Protefood (methionine) - 1 bid w/meals
Soy bean lecithin or Choline - 1 to 2 per day w/meals
a few Brazil nuts per week (methionine)
a few servings of lentils a week (methionine, choline)

Elevated Beta Glucaronidase cleaves glucaronide bound estrogens which re-enter circulation

oranges and brassicas > calcium D gluucarate
Metabolism of Selected Estrogens

DHEA → ANDROSTERONE

ANDROSTENEDIONE → TESTOSTERONE

(Aromatase; inhibited by chrysin)

 Estrone (E1) → Estradiol (E2)

(Affected by Brassica vegetables or indole-3-carbinol, diindolylmethane, and ascorbigen)

16-α-OH-E1 (16-ALPHA-HYDROXYESTRONE) → 2-OH-E1 (2-HYDROXYESTRONE)

(Possibly increased by iodine)

ESTRIOL (E3)

(Binds estrogen receptor; DNA. Promotes cellular proliferation)
Figure 1. Catabolism of Estradiol

Separate cytochrome P450 enzymes carry out 2- and 16α-hydroxylation. A portion of the 2- and 4-hydroxy derivatives is converted to methoxyforms (-MeOE), depending on individual methyl donor and cofactor status.
Active Estrogen

Estradiol

DIM Action

Estrone

Estrogens

Intracellular Cytochrome Enzymes

2-OH Estradiol

Protective

2-Methoxy-Estradiol

Anti-Proliferative

2-OH Estrone

Protective

16α OH Estrone

Carcinogen & Active Estrogen

2-Methoxy-Estrone

Protective

4-OH Estrone

Carcinogen & Active Estrogen

Estriol

Active Estrogen

Estrogen Metabolites
Reductionistic Dilemma

- Naturally, researchers want to attribute these protective effects to isolated components of brassica vegetables (I3C and DIM) as opposed to recognizing the synergistic effects of the hundreds of chemical compounds identified in brassica vegetables.
Reductionistic Dilemma

There are over 90 chemical compounds typically found in Kale and Brussels sprouts, many of which have known anti-carcinogenic properties. How foolish it is to think we can take just one of those components and elicit the same physiological benefits as consuming the whole food.

Dr. Dukes Phytochemical and ethnobotanical databases - http://www.ars-grin.gov/duke/index.html
Meanwhile back at the ranch!

- Proponents and opponents of both I3C and DIM have been attacking each other during the last several years claiming that their compound is better and safer than the other. Dr. Leon Bradlow who was one of the original discoverers of the cruciferous connection and breast health, was originally one of the biggest promoters of I3C. He now has switched sides and supports DIM.
The Big Question

Can a whole food supplement with less than 1/100th of the identified “active ingredient” that is currently being used by most manufacturers possibly have the same or greater effectiveness as the “high strength” supplements?
YES !!!
Power of synergy

In a study by Dr. Elizabeth Jefferies it was shown that consuming Brussels Sprouts powder increased GSH and Intracellular Glutathione by 900% as well as large increases in COMT function.

Also, bioflavonoids, curcuminoids from Turmeric and Catechins from Green Tea have all been shown to be strong potentiatiors of the COMT enzyme pathway.
Holly
Brassica Protection Products LLC was founded in 1997 to develop and market to the public scientifically-proven, highly-effective, cancer-protective foods, functional foods, nutriceuticals, and pharmaceuticals. The company is commercializing technology developed by Paul Talalay, M.D. and Jed W. Fahey M.S., Sc.D., researchers in the Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine.

In September 1997, Dr. Talalay and Dr. Fahey, in collaboration with other Johns Hopkins scientists, published a paper in the Proceedings of National Academy of Sciences, USA explaining that broccoli sprouts-three-day old broccoli plants-are an exceptionally rich source of sulforaphane. Broccoli sprouts contain levels of sulforaphane 20-50 times more concentrated than mature broccoli and are more consistent in composition.
Talk is cheap...... Can you prove it?
The estronex / Cruciferous
Complete project
60 pre and post menopausal women were initially selected (screened) to participate in the study. Due to stipulations from co-sponsoring company we were not able to exclude the following groups. The data was sorted after the study was completed.

- age range was from 21 to 65
- both cycling and non cycling
  - Initial exclusions
  - HRT users
  - Certain medication users, H2 agonist and PP inhibitor users
  - Those with a history of liver disease
Purpose of study?

- Prove that small amounts of organic whole food concentrates (CRUCIFEROUS COMPLETE) can have the same or greater effect of higher dose isolated compounds DIM (diindolylmethane), I3C (indole-3-carbinol) currently being used to alter 2/16 ratios.
◆ Is it a perfect study?
   No

◆ Is there an absolute correlation between 2/16 metabolism and breast cancer development?
   Nothing is absolute.

◆ Does this at least show that we can achieve clinically significant outcomes by using "low dose" whole food supplements?
   ABSOLUTLEY!
Gilsbar Estronex - Organic Kale / Brussels sprout Study

❖ Study criteria
  – Participants were expected to participate in pre and post testing in a timely manner.
  – Participants agreed to complete a post study interview.
  – Participants were not asked to make any significant to their diets or exercise patterns.
  – Participants were asked not to begin or discontinue any current supplements or medications unless deemed medically necessary by their PCP.
Highlights from official white paper

Eleven of the 12 subjects showed positive increases of their ratios, and the three subjects with the lowest initial ratios had an average increase of 497%. The results demonstrate that dehydrated whole brassicaca supplementation can be effective for helping women who need to raise their 2/16 hydroxyestrogen ratio to lower their risk of cancers of breast and other estrogen-sensitive tissues.
Highlights from official white paper

A number of recent studies and meta analyses have shown that the beneficial physiological effects of whole fruit and vegetables, including the crucifers, cannot be attributed to only one component in the food.¹⁴-²⁰ Such effects include detoxification and cancer protection.
Highlights from official white paper

◆ Such single compound extracts may lose effectiveness through the lack of potential benefits from the entire range of natural compounds found in whole crucifers. In addition, relatively large doses of I3C may fail to undergo complete conversion to the active metabolite, DIM, especially in individuals with low stomach acid output.24 While the protective, anti-cancer effect of high fruit and vegetable intake has been demonstrated repeatedly, single nutrient supplementation has generated conflicting results.25
Highlights from official white paper

- Such results that exceed those found for concentrated I3C extracts are suspected to be due to synergistic effects of multiple phytonutrients in the whole foods on hepatic cytochrome P450 stimulation.

- Use of dietary supplements containing 3.6 g of dehydrated Brussels sprouts and kale is effective for lowering risk of cancer in estrogen-sensitive tissues for premenopausal women with low ratios of 2-hydroxyestrogens to 16-hydroxyestrone. Individuals with the lowest ratios have the most dramatic increases.
The power of a “whole food” based supplement

Figure 1. Shifts from initial to final 2/16 hydroxyestrogen ratios produced by cruciferous powder dietary supplements. Each line represents the initial and final 2/16 hydroxyestrogen values for one subject. The strong trend to move from lower to higher values is apparent, though 2 subjects showed final values less than their initial levels.
Caveats and things to remember

- Certain medications have a negative effect on CYP450 activity which may outweigh the positive effects of using “CC”.
  - fluvoxamine ciprofloxacin cimetidine amiodarone fluoroquinolones furafylline1 interferon methoxsalen mibefradil - inhibitors
  - amitriptyline caffeine clomipramine clozapine cyclobenzaprine estradiol fluvoxamine haloperidol imipramine N-DeMe mexiletine naproxen olanzapine ondansetron phenacetin1 acetaminophen propranolol riluzole ropivacaine tacrine theophylline tizanidine verapamil warfarin zileuton zolmitripta - substrates
Caveats and things to remember

- Individuals with hypochlorhydria, whether naturally occurring or induced (prilosec, nexium, pepcid), may result in less than optimal breakdown of the various phtochemical compounds in dietary brassica consumption and not see satisfactory results.
Common sense

◆ Does raising 2/16 estrogen ratios guarantee a patient won’t develop Breast Cancer?
  – No
◆ Will Cruciferous Complete always fix 2/16 estrogen ratios?
  – No
◆ Are 2/16 Estrogen ratios the most important risk factor?
  ◆ ???
Breast Cancer risk reduction plan

- To increase 2/16 ratio of hydroxyestrogens
  - *Cruciferous Complete - 2 to 3 bid w/meals*
  - *(if hypochlorhydria is suspected consider Zypan after meals)*
Breast Cancer risk reduction plan

- To support phase 2 methylation of estrogens (methionine, choline, and COMT function
  - Vitanox (tumeric, catechins) - 1 to 2 per day
  - Protefood (methionine) - 1 bid w/meals
  - Soy bean lecithin or Choline - 1 to 2 per day w/meals
  - Spanish Blck Radish - 2 to 4 per day
    - especially if woman is experiencing cyclical breast tenderness.
  - a few Brazil nuts per week (methionine)
  - a few servings of lentils a week (methionine, choline)
Breast Cancer risk reduction plan

– To aid in clearance of methylated estrogens from the body
  – a TBSP or 2 of fresh ground flax at least 3 or 4 times a week
  – Supply natural levels of Calcium D Glucarate
    ◆ Oranges
    ◆ Cruciferous Complete
  – Evaluate and address gut ecology
    ◆ GIFX panel
A final thing to consider

For men with prostate problems - BPH or prostate cancer remember that the prostate has as many or more estrogen receptors as testosterone receptors!
Questions
Resources

Metametrix - 1 (800) 221-4640

Dukes Phytotherapy Database