Dealing with the side effects of Breast Cancer Treatment Panel

Naturopathic tools
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Education
- Kim Furtado received her Doctor of Naturopathic Medicine (N.D.) degree from Bastyr University in Kenmore, Washington.
- She also holds a Bachelor of Science Cum Laude in Biology from George Washington University in Washington, D.C.

What is Naturopathic Medicine?
- Naturopathic medicine is a system of medicine founded on the most time tested medical principle, vis medicatrix naturae, the healing power of nature.
- Under this system, the goal is to restore the natural functioning of the body-mind-spirit through the use of substances and treatments that enhance the body's innate healing abilities.
Vis Medicatrix Naturae

- The Healing Power of Nature

“The work of the naturopathic physician is to elicit healing by helping patients to create or recreate conditions for health to exist within them. **Health will occur where the conditions for health exist.** Disease is the product of conditions which allow for it.”

- Dr. Jared Zeff, N.D.
Naturopathic Tools: Clinical Spotlights and Review of Literature

Radiation Therapy
- Reducing toxicity
- Improving efficacy

Chemotherapy
- Reducing toxicity
- Improving efficacy

Nutrition and Mind Body Medicine
- Fatigue
- Pain/neuropathy
- Sleep
- Depression/anxiety
- Hot flashes
- Key Take Home Points
Big Picture about Antioxidants

- Largely in need of more research
- Labriola and Livingston article in Oncology 1999

Researchers suggestions for busy oncologists:

1. Develop a plan based on pharmacology of both conventional and nonconventional substances. “a knowledgeable consultant can be asked to develop the non-conventional plan”

2. Instruct a patient to avoid all non-conventional therapies during the period when conventional agents are most vulnerable to interactions, based on standard pharmacokinetics

3. Instruct a patient to discontinue all non conventional nutritional supplementation during course of anti-cancer treatment
### Vulnerability of Chemotherapy agents to Interactions with Antioxidants

**Drug/drug class** | **Comment**
--- | ---
**Agents with actions dependent on reactive oxygen species**<br>• Classical Alkylating agents<br>• Anthracyclines (eg doxorubicin, daunorubicin, epirubicin)<br>• Mitomycin<br>• Bleomycin<br>• Podophyllum agents | Vulnerable to interaction with Antioxidants; avoid concurrent administration

**Agents with unestablished molecular pharmacology**<br>• Plicamycin | Treat as though interaction is possible

**Agents with actions not highly dependent on reactive oxygen species**<br>• Hormones<br>• Biological Agents<br>• Antimetabolites<br>• Vinca alkaloids<br>• Taxanes | Probably not vulnerable to Interactions; avoid high levels of Antioxidants until long term Studies done
Impact of antioxidant supplementation on chemotherapeutic toxicity: A systematic review of the evidence from randomized controlled trials


This systematic review provides preliminary evidence, limited by quality and sample size of the reviewed studies, suggesting that certain antioxidant supplements may reduce adverse reactions including neurotoxicity, asthenia, stomatitis/mucositis, and weight loss.

Significant reductions in toxicity may alleviate dose-limiting toxicities so that more patients are able to successfully complete prescribed chemotherapy regimens, suggesting an improved therapeutic index.
Big picture about antioxidants

- Tumor response rates were not the focus of this review, however it is noteworthy that all but one of the antioxidant supplemented groups in studies reporting tumor response experienced the same or better response than the control group.

- No studies reported significantly worse survival or response in the antioxidant supplement group, as reported in our previous publication, which reviewed studies that reported tumor response or survival.
Big picture about antioxidants

- In conclusion, it was difficult to determine whether antioxidants may have an impact on treatment outcomes or whether they may ameliorate adverse effects of chemotherapy and radiotherapy.
- Discussion of antioxidant use has sometimes distinguished palliative versus curative regimens.
- For curative regimens, it is important not to inhibit therapy in any way, and patients are usually in better overall condition to tolerate side effects.
- In palliative or recurrent settings, however, patients are less able to tolerate side effects, and cytotoxic efficacy may be less of a concern than maintaining the patient in treatment.
Big picture about antioxidants


- Basically, stable disease is acceptable in this situation if side effects can be managed. Thus, it is important that clinicians make an integrated decision, taking into account the following: (1) the antioxidant dosage and types, (2) the background and state of the patient, and (3) type of cancer and antitumor therapy.
Big picture about antioxidants


- It is desirable to **use an evidence-based method to select supplements** best suited to cancer patients. Although there are many opinions about the risks or benefits of antioxidant supplementation, the only **supportable conclusions** based on the present research are that it is difficult to demonstrate **definitively that antioxidants ameliorate therapeutic toxicities** and that there is no evidence of antioxidant supplementation causing harm alongside cancer therapy, except for smokers undergoing radiotherapy.
My Clinical Context

- General premise: that when clients seek Naturopathic consult with desire to achieve recommendation 1, we individualize and focus on her regimen.
- There are MANY options for this work that are NOT antioxidants.
- This is our main focus today.
Radiation

- Do antioxidants interfere with radiation therapy for cancer?
- *Integr Cancer Ther.* 2007; 6(3):281-92
- With few exceptions, most of the studies draw positive conclusions about the interaction of antioxidants and radiotherapy. Although further studies are needed, the preponderance of evidence supports a provisional conclusion that dietary antioxidants do not conflict with the use of radiotherapy in the treatment of a wide variety of cancers and may significantly mitigate the adverse effects of that treatment.
Radiation and Breast Cancer

- Topical Vitamin E to radiation site
- Topical Aloe Vera gel to radiation site
- Multi-nutrient and protein powder medical food (Ultrainflamx (metagenics)) - 2 scoops per day; avoid use for 24 hours before and after treatment
Chemotherapy: Reduce Toxicity

- Neuropathy
- Cardiotoxicity
- Myelosuppression
- Gastrointestinal distress
- Mucositis/ mouth sores
Neuropathy


- The following databases PubMed, the Cochrane Library, Science Direct, Scopus, EMBASE, MEDLINE, CINAHL, CNKI, and Google Scholar were searched for relevant article retrieval.

**Table 3**
- Nutraceuticals agents trialed for CIPN8.
## Neuropathy

<table>
<thead>
<tr>
<th>Chemotherapy agent</th>
<th>Nutraceutical trialled</th>
<th>Level of evidence</th>
<th>Total number of participants from trials</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Vitamin E&lt;sup&gt;[84,86,93]&lt;/sup&gt;</td>
<td>Level II</td>
<td>190</td>
<td>Recommended as an adjunct during treatment to prevent CIPN. Dose 400 mg/day</td>
</tr>
<tr>
<td></td>
<td>Glutamine&lt;sup&gt;[94]&lt;/sup&gt;</td>
<td>Level III</td>
<td>26</td>
<td>Possible recommendation as it may reduce severity of CIPN. Dose: 2days consequently with cisplatin</td>
</tr>
<tr>
<td></td>
<td>Alpha-Lipoic acid&lt;sup&gt;[95]&lt;/sup&gt;</td>
<td>Level II, Level IIIa</td>
<td>243</td>
<td>Not recommended as no protection noted</td>
</tr>
<tr>
<td></td>
<td>Glutathione&lt;sup&gt;[96,97,98]&lt;/sup&gt;</td>
<td>Level II</td>
<td>244</td>
<td>Trend toward protection. Dose: 1.5-2.5 g daily</td>
</tr>
<tr>
<td></td>
<td>Vitamin B6&lt;sup&gt;[89]&lt;/sup&gt;</td>
<td>Level IIIb</td>
<td>248</td>
<td>Prevented CIPN but adversely affected response duration. Dose: 300mg daily</td>
</tr>
</tbody>
</table>
## Neuropathy

<table>
<thead>
<tr>
<th>Chemotherapy agent</th>
<th>Nutraceutical trialled</th>
<th>Level of evidence</th>
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<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>Magnesium/calcium infusions[94,99, 100,101,102,103,104]</td>
<td>Level II</td>
<td>418</td>
<td>Conflicting results but is not recommended to use in conjunction with treatment</td>
</tr>
<tr>
<td>Vitamin E[105]</td>
<td></td>
<td>Level II</td>
<td>34</td>
<td>Not recommended as no differences noted. Dose: 400 mg/day</td>
</tr>
<tr>
<td>Alpha-lipoic acid[95,106]</td>
<td></td>
<td>Level III</td>
<td>15</td>
<td>Reduced severity of severe CIPN. Dose: 800 mg daily</td>
</tr>
<tr>
<td>N-acetyl cysteine[107]</td>
<td></td>
<td>Level IIIa</td>
<td>14</td>
<td>Not recommended as no differences noted. Dose: 1200 mg daily</td>
</tr>
<tr>
<td>Glutathione[8 7,89]</td>
<td></td>
<td>Level II, Level IIIb</td>
<td>79</td>
<td>Possible protection as one trial had a significant protective effect. Dose: 1500 mg</td>
</tr>
<tr>
<td>Glutamine[10 8]</td>
<td></td>
<td>Level IIIa</td>
<td>88</td>
<td>Possible recommendation as it may reduce severity of CIPN. Dose: 15 g twice a day, or IV 20 g for 2 days consequently with oxaliplatin</td>
</tr>
<tr>
<td>Vitamin B6[109]</td>
<td></td>
<td>Level II</td>
<td>23</td>
<td>Recommended, as it may prevent CIPN</td>
</tr>
</tbody>
</table>
## Neuropathy

<table>
<thead>
<tr>
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<th>Level of evidence</th>
<th>Total number of participants from trials</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Taxanes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamine[110,111]</td>
<td>Level IIIa</td>
<td>47</td>
<td>Not recommended as it was not statistically significant. Dose: 10 g t.i.d for 4 days after chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Acetyl-L-carnitine [112]</td>
<td>Level IIIa</td>
<td>409</td>
<td>Not recommended as worsened CIPN in patients taking ALC. Dose: 3000 mg daily</td>
<td></td>
</tr>
<tr>
<td><strong>Omega 3 fatty acids</strong>[91]</td>
<td>Level IIIa</td>
<td>69</td>
<td>Recommended as it showed statistical significance. Dose: 640 mg t.i.d</td>
<td></td>
</tr>
<tr>
<td>Vitamin B12[113]</td>
<td>Level IIb</td>
<td>1</td>
<td>Recommended as possible protection. A case study from a trial of 71 people. Dose: 1000 mcg daily</td>
<td></td>
</tr>
</tbody>
</table>
## Neuropathy

<table>
<thead>
<tr>
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<th>Total number of participants from trials</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/taxol</td>
<td>Vitamin E [99,114]</td>
<td>Level II</td>
<td>247</td>
<td>Not recommended but may have possible protection in some patients. Dose: 400 mg/day</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Acetyl-L-carnitine [115]</td>
<td>Level II</td>
<td>19</td>
<td>Not recommended to be given prophylactically</td>
</tr>
<tr>
<td>CIPN treatment</td>
<td>Acetyl-L-carnitine [92,93]</td>
<td>Level IV</td>
<td>51</td>
<td>May provide improvement of symptoms if administered after chemotherapy cessation. Dose: 1 g t.i.d</td>
</tr>
<tr>
<td></td>
<td>Alpha-lipoic acid [116]</td>
<td>Level III</td>
<td>14</td>
<td>Improved neurological symptoms. Dose 600 mg IV weekly over 3-5 weeks</td>
</tr>
</tbody>
</table>
Neuropathy

For neutraceuticals, Vitamin E shows potential for prevention of cisplatin-induced ototoxicity, intravenous glutathione for oxaliplatin administration, Vitamin B6 for both oxaliplatin and cisplatin and omega 3 fatty acids for paclitaxel administration.

Acetyl-L-carnitine may provide some relief as a treatment option for CIPN after chemotherapy cessation but should not be used as a preventative agent during chemotherapy.

Acupuncture may be of benefit for some patients and GJG may be of benefit for protection of oxaliplatin-IPN for patients in Japan.

A number of Asian herbs have been found to have possible benefits for treatment and may provide some relief for patients experiencing neuropathic pain from chemotherapy.
Neuropathy


**METHODS:**

- Twenty-two consecutive patients beginning chemotherapy for breast cancer with paclitaxel, or docetaxel were enrolled. Patients received melatonin 21 mg daily at bedtime. Incidence and severity of neuropathy were assessed using neurological examinations, toxicity assessment per NCI-CTC 3.0 scale and FACT-Taxane quality of life questionnaire.
Melatonin

- **CONCLUSION:**
  - Patients receiving melatonin during taxane chemotherapy had a reduced incidence of neuropathy.
  - Melatonin may be useful in the prevention or reduction of taxane-induced neuropathy and in maintaining quality of life. **Larger trials are warranted** to further explore the role of melatonin in neuropathy treatment and prevention.
Cardiotoxicity

- Anthracycline cardiotoxicity
- Clinical studies review show small evidence of cardio protection with use of CoQ 10 from 60-200 mg daily in both adult and pediatric populations
- L-Carnitine for reducing doxorubicin toxicity
- Hawthorn solid extract - empirical use
Myelosuppression

- Cyclophosphamide (Cytoxin)
- Dose limiting toxicity is myelosuppressive which can result in fatigue, secondary infections and slow wound healing

**Strategies**
- High dose **melatonin**- 20 mg at bedtime
- Medicinal mushrooms- maitake, reishi, cordyceps
- Astragulus
Mushrooms as immunomodulators: *Trametes versicolor* or *Coriolus versicolor*

**Background**

Polysaccharide peptides extracted from the medicinal mushroom *Trametes versicolor* (PSK Krestin™) have been shown to improve disease free survival in 31 randomized clinical trials conducted in Japan, Korea, and China.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>RCTs</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach cancer</td>
<td>16</td>
<td>6462</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>8</td>
<td>1374</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>4</td>
<td>279</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>3</td>
<td>1517</td>
</tr>
</tbody>
</table>

PSK (Krestin™) was approved in 1977 as a cancer therapy by the Japanese National Health Registry and represents 25% of the total national costs of cancer care in Japan.

Melatonin

- Preclinical and clinical data demonstrate that melatonin reduces myelosuppression in combination with:
  - Cyclophosphamide (Cytoxan)
  - Doxorubicin (Adriamycin)
  - Cisplatin
  - Epirubicin
  - Bleomycin
  - Cytarabine
Gastrointestinal Distress

GI toxicities caused by chemotherapy can negatively affect patients’ nutritional status by decreasing food intake and can result in a delay or discontinuation of chemotherapy, thereby negatively affecting tumor response to treatment. Oral mucositis, one of the most common GI toxicities, results in

- increased pain,
- difficulty in swallowing,
- nutritional compromise, and
- an increased risk of infection.
Gastrointestinal Distress

Naturopathic Nutritional therapies

- Herbs - demulcients and carminatives
- Pureed Soups
- Physicians Elemental Diet
- Medical foods
Physicians Elemental Diet

- Physicians’ Elemental Diet is intended for use under medical supervision for the dietary management of patients who have limited or impaired capacity to digest, absorb, or metabolize ordinary foods or certain nutrients.
- Physicians’ Elemental Diet contains a balanced blend of macronutrients fortified with essential vitamins, minerals, and electrolytes to assure comprehensive support as a sole source of nutritional intake for limited periods.

It has been:
- Specifically formulated to contain free amino acids, partially hydrolyzed carbohydrate and medium chain triglycerides to aid in their absorption from the GI lumen.
- Designed to maintain nutritional sustenance as a sole source of nutrition for up to four weeks.
- Produced as a strictly hypoallergenic formula, free from intact protein, polypeptides, corn, gluten, wheat, soy, and dairy.
- Formulated with a well-tolerated flavor for improved patient adherence.
Mucositis/ Mouth Sores


- These model studies have indicated potential new preventive and ameliorating interventions, including supplementation with
  - **natural bioactive diets** (e.g., milk fractions, colostrum, and plant extracts),
  - **nutrients** (e.g., polyunsaturated fatty acids, short-chain fatty acids, and glutamine),
  - and **growth factor peptides** (e.g., transforming growth factor and glucagon-like peptide-2),
  - as well as **manipulations of the gut microbiota** (e.g., prebiotics, probiotics, and antibiotics).
Mucositis/ Mouth sores

Dr Kim’s Favorites:

- Aloe Vera Gelcaps
- Glutamine
- Slippery Elm powder
- Restore/test microbiome before starting treatment and treat accordingly
Diet: WHEL study

- The Women’s Healthy Eating and Living (WHEL) Randomized Trial: Multi-institutional randomized controlled trial of dietary change in 3088 women previously treated for early stage breast cancer who were 18 to 70 years old at diagnosis.

- The intervention group (n=1537) was randomly assigned to receive a telephone counseling program supplemented with cooking classes and newsletters that promoted daily targets of:
  - 5 vegetable servings plus 16 oz of vegetable juice
  - 3 fruit servings
  - 30 g of fiber
  - Limit energy intake from fat to 15% to 20%

- The comparison group (n=1551) was provided with print materials describing the “5-A-Day” dietary guidelines.

Leading Controllable Dietary Factors Associated with Cancer Risk

**Increased Cancer Risk**
- Excessive Meat and Dairy product consumption
- Animal/saturated fats
- Grilling/charcoal
- Salting meats

**Decreased Cancer Risk**
- Vegetable consumption
- Fruit consumption
- Carotenoids
- Vitamin C
- Fiber
- Whole Grains
Other treatment related side effects

- Fatigue
- Sleep disruption
- Depression/Anxiety
- Hot flashes
Fatigue

Treat underlying possible root causes, beyond the cancer pathology

- Myelosuppression
- Poor nutrition/absorption
- Protein or essential fatty acid deficiencies
- Adrenal fatigue
- Subclinical hypothyroidism
Sleep

Powerful means for you to impact your health in a positive way during treatment is to **restore healthy sleep**

- Various herbs available
- Amino Acid formulas
- Guided Imagery
- Acupuncture
- Massage
- Yoga and Meditation
- Adrenal healing/ balance your cortisol and catecholamines
- melatonin
Sleep and Breast cancer

• In a prospective study of 23,995 Japanese women, short sleep duration was associated with higher risk of breast cancer (143 cases).

• Women who slept $\leq 6$ hr per day had a 62% increased risk of developing breast cancer compared to women who slept 7 hr per day (multivariate hazard ratio 1.62 (95% confidence interval: 1.05-2.50; $P$ for trend=0.03)

• A duration of 30+ years of working the night shift is associated with a 2-fold increased risk of breast cancer.

Sleep and immune function

- Reduction of sleep time triggers a stress response, leading to augmented levels of glucocorticoids and adrenaline.
- These hormones regulate components of the innate immune system such as natural killer (NK) and NKT cells.
There are specific types of immune cells, namely cytotoxic natural killer cells and CTL, floating around in your body that peak in number during the day. They fight off foreign antigens and repair damaged tissue during the day when tissue damage is most likely to occur.
Sleep and immune function

- At night, during the early stages of sleep and particularly during slow wave sleep (SWS),
- different types of immune cells peak in concentration (T helper cells and antigen presenting cells),
- prolactin and growth hormone peak, and cortisol and catecholamine productions drops.
- All of these changes make for an environment that supports inflammation.
Sleep and Cortisol

- Chronic sleep deprivation dysregulates cortisol secretion.
- In studies on individuals who were sleep deprived (four hours of sleep per night), evening cortisol levels were elevated and the levels decreased six times slower when compared to control subjects. These elevations in cortisol further increase the likelihood of developing diabetes and obesity.
Sleep and Inflammation Control

- Whenever you chronically skimp on sleep, the inflammatory state is unbalanced. Blood levels of C-reactive protein, go up when sleep is too short for a prolonged period of time.
- This inflammatory state resulting from a lack of sleep has been shown to do nothing to support the immune system, only to impede it’s function, and put the body at risk for infection, chronic diseases, and cancer.
Sleep and Inflammation Control

- When we get adequate amounts of sleep this inflammatory state supports the immune system by enhancing the body’s ability to form an initial immune response to invading "bugs." It also enhances long-term immune function. Basically, the body remembers the invaders over a long period of time. This inflammatory system, when you’re getting enough sleep, is balanced by the anti-inflammatory hormone, cortisol.
Melatonin

- Neuropathy
- Myelosuppression
- Sleep
- General anti-cancer properties / Cytotoxic effects
- Decreases estrogen production
Melatonin

- Endogenous hormone
- Also present in fruits, vegetables and botanical extracts
- Melatonin is an indoleamine (N-acetyl-5-methoxytryptamine)
  - Derived from tryptophan → serotonin → melatonin
- Bioavailability varies from 10%-56% (variation due to hepatic first pass)
- Normal peak nocturnal concentrations in humans are 60-80 pg/mL; average nocturnal concentration = 18-40 pg/mL; ½ life is 30-47 minutes
- This same concentration can be achieved with the ingestion of 300 mcg of exogenous melatonin

Melatonin: physiological functions

- Circadian rhythm monitor
- Free radical scavenger and antioxidant
- Cytoprotective (via free radical scavenging and regulation of GABA \(\rightarrow\) decreased neuroexcitation)
- Immunomodulator (increases T cell activity and interferon gamma, IL-1, 2, 6, 12 production)
- Decreases estrogen production
- Oncostatic (decreases linoleic acid uptake, inhibits telomerase, decreases angiogenic endothelin-1, increases p53 expression)
- Thermoregulator

Melatonin

- At nocturnal levels, melatonin inhibits cell proliferation by delaying cells in G1 phase of cell division
- At pharmacological levels, melatonin:
  - Exerts cytotoxic effects on cancer cells by stimulating apoptosis
  - Alters adhesion molecule expression thus reducing invasiveness
  - Regulates ER expression
  - Influences kinase pathways

Melatonin

- Over 1534 scientific publications on melatonin and cancer
- Over 88 human clinical trials on melatonin in cancer
- 41 Randomized Clinical Trials
- In a meta analysis of 8 RCT’s in solid tumor cancers (n=761), 20mg of melatonin po nightly in conjunction with chemo or radiation.
- Melatonin significantly improved the complete and partial remission (16.5% vs. 32.6%; RR = 1.95, 95% CI, 1.49-2.54; P < 0.00001)
- Melatonin improved 1-year survival rate over control (52.2% vs. 28.4%; RR = 1.90; 95% CI, 1.28-2.83; P = 0.001)
- Melatonin significantly decreased radiochemotherapy-related side effects including:
  - thrombocytopenia (19.7 vs. 2.2%; RR = 0.13; 95% CI, 0.06-0.28; P < 0.00001)
  - neurotoxicity (15.2 vs. 2.5%; RR = 0.19; 95% CI, 0.09-0.40; P < 0.0001)
  - fatigue (49.1 vs. 17.2%; RR = 0.37; 95% CI, 0.28-0.48; P < 0.00001).
- Effects were consistent across different types of cancer. No severe adverse events were reported.

Melatonin and Breast Cancer

14 patients with metastatic breast cancer:
- 3 were non-responders to TMX
- 11 progressed after initial disease stabilization with TMX

Patients received TMX 20mg/d + MLT 20mg QHS [mean duration of treatment = 8 mo.]

Partial response in 4/14 patients (28.5%)

IGF-1 decreased in responders

Melatonin and ER+ tumors

- Melatonin inhibits cyp19 Aromatase and NADPH-cyp reductase which catalyze androgens to estrogens
- Aromatase activity is higher in breast tumor tissue than in healthy breast tissue
- Melatonin demonstrates significant aromatase inhibition in MCF-7 human breast cancer cells
  - Melatonin inhibits aromatase mRNA expression
- Inhibition was observed using 1nM of melatonin – equivalent to nocturnal levels of melatonin

1. Downregulates gonadal estrogen synthesis.
2. Decreases ERα expression and inhibits E₂-ER complex binding to ERE in DNA = SERM.
3. SEEM (selective estrogen enzyme modulator): decreases aromatase activity.
Melatonin (MLT) and cytokines

- Exogenous MLT
  - CD4
    - IL-2
    - IL-12
  - Th1
    - IFNγ
    - MLT
  - NK cell
  - T cell
  - Tumor destruction

- Th2
  - IL-2

People with cancer have a Th2:Th1 ratio.

TNFα → Cachexia

Depression/Anxiety

- Related to Sleep and Cortisol
- Related to Liver Function and Adrenal Function
- Related to life circumstances and challenges
Stress and Breast Cancer

- A twofold increase in breast cancer risk is evident after disruption of marriage owing to divorce, separation or death of a spouse.
- Cancer risk has been shown to be increased after chronic depression that has lasted for at least 6 years.
- The combination of extreme stress and low social support was related to a 9-fold increase in breast cancer incidence.
- However, findings have been inconsistent. In general, stronger relationships have been observed between psychosocial factors and cancer progression than between psychosocial factors and cancer incidence.

Social isolation, stressed fat and breast cancer

- Based on rodent models of TN breast cancer, social isolation causes a heightened stress response which, in turn, increases expression of genes in adipocytes that increase glucose metabolism, lipid synthesis and leptin secretion.
- These metabolic changes increased the conversion of mammary carcinoma in situ to invasive carcinoma.

- Mammary fat has heightened sensitivity to stress hormones over visceral fat, making breast tissue esp. vulnerable to stress

Mindfulness based stress reduction

- A meta-analysis of 10 studies showed a significant improvement in psychological and physical quality of life.
- MBSR has been shown to reduce depression and fear of recurrence in women diagnosed with breast cancer.
- MBSR lowers cortisol, reduces IL-6, lowers systolic blood pressure and improves NK cell activity.

Meditation and Relaxation Practice

- Take care of self vs take care of others
- Investment in Self: 10% investment in self is 9 hours of relaxation practice per week
- Energy medicine
- Yoga
- Acupuncture
- Tai Chi
- Massage
- Guided Imagery
Meditation and Relaxation Practice
http://www.amfoundation.org/relaxation.htm

Relaxation Practices
- Biofeedback
- Breathing Exercises
- EFT/Tapping
- Guided Imagery
- Hypnotherapy
- Mindfulness Based Stress Reduction

Meditation Practices
- Buddhist tradition
- Chakra meditation
- Christian Tradition
- Labyrinth Meditation
- Native American Healing
- QiGong
- Tai Chi
- Transcendental Meditation
- Yoga
<table>
<thead>
<tr>
<th>HIGH CORTISOL LEVEL SYMPTOMS</th>
<th>LOW CORTISOL LEVEL SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High blood pressure</td>
<td>• Sugar &amp; salt craving</td>
</tr>
<tr>
<td>• Fatigue</td>
<td>• Decreased sex drive</td>
</tr>
<tr>
<td>• Erectile dysfunction</td>
<td>• Anxiety</td>
</tr>
<tr>
<td>• Reduced sex drive</td>
<td>• Irritability</td>
</tr>
<tr>
<td>• Weakened immune response</td>
<td>• Bone &amp; muscle loss</td>
</tr>
<tr>
<td>• Weight Gain</td>
<td>• Weight gain</td>
</tr>
<tr>
<td>• Hyperglycemia</td>
<td>• Depressed Mood</td>
</tr>
<tr>
<td>• Insomnia</td>
<td>• Insomnia</td>
</tr>
<tr>
<td>• Poor concentration/memory</td>
<td>• Fatigue</td>
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Cortisol-Reducing Foods

Wild Salmon for Omega 3 Fatty Acid

Omega 3 is known to have a calming effect on the nervous system. The fatty acids EPA and DHA found in Omega 3 is believed to reduce mental stress. Omega 3 is known to reduce inflammation & oxidative stress in the body.

Citrus Fruits for Vitamin C

Vitamin C provides a subtle cortisol-lowering effect. Increase your intake of oranges, bell peppers and dark green leafy vegetables to boost your Vitamin C level and reduce cortisol.

Green Tea for L-Theanine

This essential nutrient is almost exclusively found in green tea. Theanine can cross blood-brain barrier and cause relaxation without feeling drowsy. While green tea contains caffeine, researchers believe that its theanine content is so effective that it can override the effect of caffeine and end up reducing cortisol levels.

Cheese for Glutamine

Glutamine is the most common amino acid in muscle cells and help preserve the muscles by managing cortisol levels. Also, it provides other benefits such as increase in protein synthesis and enhanced immune function.

Soybeans for Phosphatidylserine

PS is a known cortisol blocker, removing toxins from cells and driving nutrients into.
Hot Flashes

- Sage tea
- Adrenal support is very clinically relevant
- NO Phytoestrogens like black cohosh? But wait...
Black Cohosh
*(Cimicifuga racemose)* CR

- A pharmacoepidemiological cohort study demonstrated a **4.5-year longer recurrence-free survival after breast cancer for CR users** (2007, Germany).

- In 2010, the Herbal Medicinal Product Committee (HMPC) of the European Medicinal Agency monograph attested the well-established use of drugs containing CR extract based on previously published studies on menopausal symptoms.

- According to the HMPC, there is no limit on the length of use, but after 6 months of therapy, a medical professional should be consulted. **Breast cancer patients are not excluded from treatment of MPS with CR as long as a medical professional is consulted.**
Actea racemosa (Black cohosh) formerly Cimicifuga racemosa

- Blk cohosh extracts induce cell cycle arrest at G1.
- Cyclin D1 promotes transition from G1 to S and is overexpressed in 50%-60% of primary human breast carcinomas.
- Blk. cohosh, actein in particular, decreases cyclin D1.
- This growth inhibition was demonstrated with alcoholic extract of Blk. cohosh for both ER+ and ER- cells.
- Effect in humans and required dose is unknown.

Black cohosh: safety in breast cancer patients

- Meta-analysis
- Ability of black cohosh to relieve menopausal symptoms is inconclusive
- Antiproliferative action demonstrated, particularly in breast and prostate cancers.
  - This is not, however, due to a phytoestrogenic effect as black cohosh lacks estrogenic activity
  - Due, instead to pro-apoptotic mechanisms
- Safety profile is good
  - Isolated reports of liver toxicity are likely due to Chinese sourced Actaea products; products also potentially contaminated with trace pharmaceuticals or pesticides
- Conclusion: black cohosh is safe in women with breast cancer and, in fact, exerts protective and anti-proliferative effects through non-hormonal mechanisms.
Black cohosh: clinical data

- Population based control study with 949 breast cancer patients and 1524 controls from Philadelphia metropolitan area
- Assessed use of Hormone Related supplements and association with breast cancer
- Use of black cohosh has a significant cancer protective effect (adjusted odds ratio 0.39, 95% CI 0.22-0.70).

Black cohosh: clinical data

- Investigation of the effect of isopropanolic extract on disease free survival (including ER+) after a diagnosis of breast cancer
- Observational retrospective cohort study
- 18,861 subjects observed for an average of 3.6 years
- After two years from diagnosis, 14% of control group developed recurrence
- The black cohosh group took 6.5 years to reach 14% recurrence
- After controlling for age, tamoxifen use and other confounders, black cohosh use demonstrated a protective effect on the rate of recurrence (hazard ratio 0.83, 95% CI 0.69-.099)
Secondary analysis of WHEL study

- Self-report of hot flashes (HFs) after treatment for early-stage breast cancer has been associated with an approximately 25% to 30% decreased risk for additional breast cancer events, independent of the type of antiestrogen therapy.
  - The HF are due, in part, to lowered levels of circulating estrogen.

- Hypothesis: the protective dietary effect might be limited to the subgroup of patients with potentially higher circulating estradiol levels and worse prognosis (ie, women without HF at baseline).

Dietary influences on estrogen levels

- Changes in dietary patterns to either decrease energy from fat or increase fiber intake can alter the enterohepatic recirculation of estrogens, leading to lower circulating estrogen concentrations.
- Reduction in fat consumption has been shown to result in 18%-27% reductions in circulating estrogen levels.
- Binding of fiber to unconjugated estrogens in the gut impedes reabsorption of estrogen, resulting in up to 20% difference in circulating estrogen levels in high fiber diets vs. low fiber diets.
Conclusions

- This dietary intervention was associated with reduced risk of second breast cancer events among women who reported no HFIs at baseline.
  - These women had a 31% lower event rate than HF-negative women in the comparison group over 7.3 years of follow-up.
  - Among HF-negative postmenopausal women, the intervention effect was even stronger, with a 47% reduction in risk compared with HF- women assigned to the comparison group.

I'M STILL HOT, IT JUST COMES IN FLASHES NOW
Why do we need liver protection?

Daily life overloads the liver leading to poor health and disease

- Coffee & energy drinks
- Alcohol Intake
- Excessive Workload
- Smoking
- Prescription & OTC Medicines
- Infection/ Illness [Acute or Chronic]
- NZ Soils Deficient in Key Detox Minerals
- Allergies/ Food Intolerances
- Environmental Toxins [Heavy Metals, Pesticides]
- Processed Foods [Sugar and White Flour products]
- Stress [Psychological/ Emotional]
Naturopathic Lab Assessments

- Review of important biomarkers
- Summary of important tests to ask for
- Salivary Hormones tests vs serum tests
Alschuler’s Bucket List Top 5 Priorities

- Chronic Inflammation
- Immunity
- Hormonal imbalance
- Insulin resistance
- Detoxification

Remember, your lab results helps you prioritize this bucket list
- Resources/ references listed in end of presentation or on slide

- [https://www.gdx.net/clinicians/medical-education/previous-webinars/integrative-strategies-for-supporting-patients-diagnosed-with-breast-cancer-1](https://www.gdx.net/clinicians/medical-education/previous-webinars/integrative-strategies-for-supporting-patients-diagnosed-with-breast-cancer-1)

**Lise Alschuler, N.D., F.A.B.N.O.**

Lise Alschuler is a naturopathic doctor with board certification in naturopathic oncology and has been practicing since 1994. Dr. Alschuler works as an independent consultant in the area of practitioner and consumer health education.

- She maintains a naturopathic oncology part-time practice out of Naturopathic Specialists, based in Scottsdale AZ. Dr. Alschuler is the co-author of *The Definitive Guide to Cancer: An Integrative Approach to Prevention, Treatment and Healing* and *The Definitive Guide to Thriving After Cancer: A Five-Step Integrative Plan to Reduce the Risk of Recurrence and Build Lifelong Health*.

- She co-created [http://www.FiveToThrivePlan.com](http://www.FiveToThrivePlan.com), and co-hosts a radio show, *Five To Thrive Live!*, on the Cancer Support Network about living more healthfully in the face of cancer. Learn more at [http://www.drlise.net](http://www.drlise.net).
Chronic Inflammation
- Stool Analysis, bacterial & fungal cultures
- Homocysteine*
- hsCRP*
- Ferritin*
- Fibrinogen*

Immunity
- Galactin 3*
- IL-6 and IL-8*
- IGF-1*
- Vitamin D*

Hormonal Imbalance
- Salivary Hormone Panel (E1, E2, E3, Progesterone, DHEA, Testosterone)
- Salivary Melatonin circadian
- Thyroid Function * & (BBT)
- Cortisol (circadian)

Insulin resistance
- C peptide (insulin)*
- Hemoglobin A1C and fasting glucose*

Detoxification
- 23andme.com (COMT and MTHFR) estrogen metabolism pathways
- Toxic metals profile, urine (provoked DMSA)

Summary of tests
* Indicates your PCP should be able to order the blood tests

- The others are salivary or other functional medicine tests ordered by naturopathic doctors
Inflammation biomarker ‘panel’

- **Homocysteine**: elevated homocysteine is associated with increased risk of breast cancer
  - <8.0 mol/L is optimal
- **hsCRP**: marker of acute inflammatory stress
  - <1.0mg/L is ideal
- **Ferritin**: elevated ferritin can occur with iron overload, but can also be the result of liver disease, cancer and inflammation
  - <150ng/mL is optimal
- **Fibrinogen**: clotting factor that increases with inflammation, IR, malignancy. Fibrinogen is the precursor for fibrin which coats cancer cells creating immune camouflage and which facilitates angiogenesis
  - Fibrinogen Ag <400mg/dL is optimal
- **IL-6**: secreted by tumor cells and associated fat and stromal cells; correlates with increased invasiveness and angiogenesis
  - < 7pg/mL is optimal
- **IL-8**: associated with angiogenesis and invasiveness
  - < 11 pg/ml is optimal
Prognostic biomarkers: vitamin D

- Serum 25-hydroxyvitamin D3 at diagnosis: (n=1800 women with early breast cancer)
  - Low 25-OHD (<20 ng/mL) is correlated with larger tumor size at diagnosis, but not with lymph node invasion, receptor status or tumor grade.
  - High 25-OHD (>30 ng/mL) at diagnosis is significantly correlated with improved Overall Survival (p=0.0101) and DFS (0.0192) up to 3 years from diagnosis.
    - Inverse correlation between low vit. D and risk of death; HR = 0.79.
  - Relapse rate at median follow-up of 4.7y = 7.8% for low Vit. D vs. 5.6% for high Vit. D – difference was noted in postmenopausal women only.
  - Risk of distance metastasis in postmenopausal women decreased by 66% in women with 25OHD >30ng/mL vs. less than 30ng/mL.

a.m. cortisol and 4-point cortisol

- Elevated cortisol and flattened diurnal variation are associated with decreased immunity and increased breast cancer progression
  - Some breast cancer cells express corticoid receptors, the activation of which increases transcription of genes involved in proliferation and invasiveness
- Morning (6a – 8a) is the most sensitive single draw to assess overall cortisol influence.
  - Normal: 6-23 mcg/dL
- Diurnal cortisol x 4 with DHEA-sulfate x 1 (salivary) provides a more sensitive measurement of overall cortisol along with stress patterns.

Sephton S, et al. JNCI. 2000;92(12):994-1000
Thyroid function

- Low thyroid function is associated with decreased cell repair and increased breast cancer risk
- There is an increased prevalence of autoimmune thyroid disease in patients with breast cancer
- Normal ranges:
  - TSH: 0.4 - 4.0 mIU/L
  - Free T4: 0.9 and 1.8 ng/dL
  - total T3: 100 - 200 ng/dL.
- If abnormal, run TPO antibodies

Self Care routine

- Self exam
- Lymphatic massage/ counter the bra effects
- **Topical St Johns Wort Oil** (herb pharm) + liquid vitamin D
- **Breast Care Balm with Tulsi & Palmarosa** (banyan botanicals) 4 oz.
- Daily breast massage stimulates the lymphatic system, promotes circulation and supports gentle detoxification. Breast Care Balm is an organic moisturizing formula that adds a soothing and comforting element to this healthy practice.
- **DIRECTIONS**: Apply liberally to breast area and massage gently into the skin using circular motion.
Additional Resources

- The Definitive Guide to Thriving After Cancer: A Five-Step Integrative Plan to Reduce the Risk of Recurrence and Build Lifelong Health by Lise Alschuler, ND, FABNO
- The Journey Through Cancer: Healing and Transforming the Whole Person, by Jeremy Geffen, M.D.
Breast cancer can be a door to greater health, and life affirming well-being
Quakertown Wellness Modalities

Quakertown Wellness is committed to providing you with the very best in integrative services. With the focus centered on your health and healing, we are proud to offer several different healing modalities.

- Acupuncture & Chinese Medicine
- Naturopathic Medicine
- Massage Therapy
- Bio-Energetic Medicine
- Intuitive Counseling & Healing

Quakertown Wellness Center

Contact each practitioner directly or call 644-0130
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