Integrative Cancer Care: Rational Use of Natural Supplements

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Integrative Oncology

“It is more important to know what sort of patient has a disease than what disease a patient has.”

Moses Maimonides and Sir William Osler
What is Integrative Oncology?

The rational, evidence-based combination of conventional therapy with complementary interventions into an individualized therapeutic regimen that addresses the whole person (body, mind, spirit) with cancer

Integrative Oncology

- Provides relationship-centered care
- Integrates conventional and CAM methods of treatment and prevention
  - Aims to activate the body’s innate healing response
  - Uses natural, less invasive interventions when possible
Let your food be your medicine
And your medicine be your food
Hippocrates

Proportion of Cancer Deaths Caused by Different Avoidable Cancers

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>25-40</td>
<td>29-31</td>
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<tr>
<td>Diet</td>
<td>10-70</td>
<td>20-50</td>
</tr>
<tr>
<td>Medicines</td>
<td>0.3-1.5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infection: parasites, bacteria, viruses</td>
<td>10</td>
<td>10-20</td>
</tr>
<tr>
<td>Ionizing and UV light</td>
<td>2-4</td>
<td>5-7</td>
</tr>
<tr>
<td>Occupation</td>
<td>2-8</td>
<td>2-4</td>
</tr>
<tr>
<td>Pollution: air, water, food</td>
<td>&lt;1-5</td>
<td>1-5</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>1-2</td>
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</table>

* Doll and Peto, 1981; ** Doll, 1998
ACS Comments on Supplements

“There is strong evidence that a diet rich in vegetables, fruits and other plant-based foods may reduce the risk of cancer, but there is no evidence at this time that supplements can reduce cancer risk, and some evidence exists that indicates that high-dose supplements can increase cancer risk.”

Kushi et al, CA, 2006

Poison is in everything and no thing is without poison.

The dosage makes it either a poison or a remedy.

- Paracelsus
- 1493-1541
Nutritional Risk Reduction Strategies

Eat More:

- Phytoestrogens
- Cruciferous vegetables
- Garlic and onions
- Turmeric and ginger
- Asian mushrooms
- Green tea
- Omega 3 fatty acids
- Vitamin D

Vitamin D3 (Cholecalciferol)

- A vitamin with hormone-like action
- Controls phosphorus, calcium and bone metabolism and neuromuscular function
- The only vitamin the body can manufacture from sunlight
- Increasing percentage of population now deficient b/o indoor living, heliophobia and sunscreen use
Vitamin D3 (Cholecalciferol)

• Long recognized as involved in bone health, but now felt to be linked to:
  • Depression
  • Back pain
  • **Cancer (Breast, prostate, colon, pancreas)**
  • Insulin resistance
  • Impaired immunity
  • Macular degeneration
  • Pre-eclampsia

Vitamin D and Colon CA Risk

• European Prospective Investigation into Cancer and Nutrition (EPIC)
• 52,000 participants from Denmark, France, Greece, Germany, Italy, Spain and the UK
• 1248 incident CRC cases c/w 1248 controls
• Strong inverse association between pre-dx vitamin D levels and CRC risk
  – < 25 nmol/l associated with higher risk
  – > 100 nmol/l associated with lower risk
  – Higher consumption of dietary vitamin D not associated with a reduced risk
  – Optimal level of vitamin D supplementation unknown

Jenab et al, BMJ 2010
Vitamin D in Colon Cancer

- Retrospective study of baseline vitamin D levels in newly dx’ed Stage IV CRC
- Stored specimens collected 2005-2006
- 153 of the patients had died by April 2009
- Median vitamin D level all pts - 21.5 ng/mL
  - 83% total pts were deficient (< 30 ng/mL)
  - Only 7 pts > 40 ng/mL
- Pts with low vitamin D had survival outcomes 1.5 times worse than those with nl levels
- Unknown whether aggressive vitamin D replacement would improve outcomes

Wesa et al, ASCO 2010

Vitamin D and Breast Cancer

- 194 women treated for Stage 0-III breast cancer in Rochester who had vitamin D levels drawn within 3 mos of surgery
- Patients matched 1:1 with concurrent cancer-free controls
- Optimal > 32 ng/mL, suboptimal 20-31 ng/mL, deficient < 20 ng/mL

Skinner et al 2011
Vitamin D and Breast Cancer

- Breast CA patients mean 33 ng/mL vs 37 ng/mL; twice as likely to be deficient (OR 2.4, p < .01)
- Mean vitamin D levels lower in:
  - ER neg vs ER pos (28 ng/mL vs 33; p=.04)
  - Triple-neg vs not (26 ng/mL vs 33 ng/mL; p=.02)
  - Basal-like (triple neg) vs luminal A (ER+/PR+/her2-) phenotype (24 ng/mL vs 33 ng/mL; p=.04)

Skinner et al, 2011

Vitamin D and AI Bone Loss

- Intervention study in 156 postmenopausal nonosteoporotic women (mean age 62) receiving AI’s for adjuvant Rx in early stage breast CA
- All pts received daily oral calcium 1000 mg and vitamin D3 800 IU (additional D if < 30 ng/mL at baseline)
- Each 10 ng/mL increase in 25-OH-vitamin D at 3 mos associated with a 0.55% decrease in bone loss

Smith et al 2011
Fish as Source of Vitamin D

- Sockeye salmon 687 IU
- Albacore tuna 544 IU
- Silver salmon 430 IU
- King salmon 236 IU
- Sardines 222 IU
- Sablefish 169 IU
- Halibut 162 IU

Per 3.5 oz serving

Dietary Sources of Omega-3 Fatty Acids

### Animal Sources (DHA and EPA)
- Oily, cold water fish
  - Herring 1700 mg
  - Salmon 1600 mg
  - Mackeral 1400 mg
  - Flounder 500 mg
  - Halibut 500 mg
  - Tuna 300 mg
  - Cod 200 mg
  - Catfish 200 mg

### Vegetarian Sources (α-linolenic acid)
- Nuts (English walnuts)
- Flaxseeds
- Soy
- Vegetable oils
  - Canola
  - Flaxseed
  - Olive
**Omega 3 vs Omega 6 Fatty Acids**

![Diagram showing the metabolism of omega-6 and omega-3 fatty acids]

**Dietary Sources of Omega-3 Fatty Acids**

**Animal Sources (DHA and EPA)**
- Oily, cold water fish
  - Herring: 1700 mg/3-4 oz
  - Salmon: 1600 mg/3-4 oz
  - Mackeral: 1400 mg/3-4 oz
  - Flounder: 500 mg/3-4 oz
  - Halibut: 500 mg/3-4 oz
  - Tuna: 300 mg/3-4 oz
  - Cod: 200 mg/3-4 oz
  - Catfish: 200 mg/3-4 oz

**Vegetarian Sources (α-linolenic acid)**
- Nuts (English walnuts)
- Flaxseeds
- Soy
- Vegetable oils
  - Canola
  - Flaxseed
  - Olive
Omega-3 Fatty Acid Intake

- Dietary intake of $\Omega$-3’s decreased 80% over past century
- Intake of $\Omega$-6’s has increased
- Higher ratio of $\Omega$-6/$\Omega$-3 contributes to greater inflammation
- Inflammation now felt to be related to development of cardiac disease, cancer, Alzheimer’s and other degenerative diseases

Fats, Fatty Acids and Prostate CA

- Preclinical studies had suggested that ↓ dietary fat and ↓ n-6:n-3 lowers risk and slows progression of prostate cancer
- 48 men undergoing radical prostatectomy
- Randomized to low fat (15%) diet and 5 gm fish oil (n-6:n3 2:1) or control Western diet (40% fat, n6:n3 15:1) for 4-6 wks pre-op
- Food prepared by UCLA chefs
- Serum IGF-1 levels selected as primary endpoint
  
  Aronson et al, 2011
Fats, Fatty Acids and Prostate CA

• No effect on serum IGF-1 levels
• Low fat, high n-3 group had:
  – Lower omega-6:omega-3 ratios in blood and prostate
  – Less prostate tissue (benign and malignant)
  – Reduced cancer cell proliferation (Ki-67 index)
  – Reduced prostate cancer cell proliferation in vitro with their blood added c/w controls

  Aronson et al, 2011

Fish Oil in Lung Cancer

• Preclinical studies suggest fish oil omega 3 fatty acids (EPA and DHA) may enhance activity of a number of chemotherapeutic agents vs a variety of tumor types
• As mechanisms of actions of the agents vary, suggests fish oil modulates via diverse mechanisms
• EPA and DHA may also inhibit angiogenesis and metastasis

  Murphy et al, Cancer 2011
Fish Oil in Lung Cancer

- 46 NSCLC patients (IIIB or IV) receiving first-line platinum-based doublet palliative chemotherapy
- Participants chose to enroll in open-label trial of nutritional intervention with fish oil (2.2 gm EPA and 240-500 mg DHA) or SOC
- Baseline characteristics well matched (64 yo, 77% Stage IV, BMI 26.5, ECOG 1)
- Plasma phospholipids EPA and DHA increased significantly after supplementation

Murphy et al, Cancer 2011

<table>
<thead>
<tr>
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<th>SOC (n=31)</th>
<th>Fish Oil (n=15)</th>
<th>P</th>
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<tr>
<td>Complete Response</td>
<td>1 (3.2%)</td>
<td>1 (6.7%)</td>
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<tr>
<td>Partial Response</td>
<td>7 (22.6%)</td>
<td>9 (60%)</td>
<td></td>
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<tr>
<td>Stable Disease</td>
<td>5 (16.1%)</td>
<td>2 (13.3%)</td>
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<tr>
<td>Progressive Disease</td>
<td>18 (58.1%)</td>
<td>3 (20.0%)</td>
<td></td>
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<tr>
<td>Response Rate (CR/PR)</td>
<td>8 (25.8%)</td>
<td>9 (60.0%)</td>
<td>.008</td>
</tr>
<tr>
<td>Benefit (CR/PR/SD)</td>
<td>13 (41.9%)</td>
<td>12 (80%)</td>
<td>.02</td>
</tr>
<tr>
<td>Chemo cycles received</td>
<td>3.0 ± 1.4</td>
<td>3.9 ± 0.9</td>
<td>.02</td>
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<tr>
<td>Days on chemotherapy</td>
<td>60.3 ± 31.1</td>
<td>78.9 ± 23.5</td>
<td>.05</td>
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<tr>
<td>1-Year survival</td>
<td>38.7%</td>
<td>60.0%</td>
<td>.15</td>
</tr>
</tbody>
</table>

EPA concentration after supplementation significant predictor of response

Murphy et al, Cancer 2011
Turmeric- The Anticancer Spice

- *Curcuma longa* L, family Zingiberaceae
- Cultivated in Asia for culinary and medicinal purposes for centuries
  - In Ayurveda, used internally for digestive problems and is considered a blood purifier and antimicrobial; externally for skin problems
  - In TCM, invigorates *xue* (blood); relieves pain related to liver (*Gan*); clears heat and cools the blood; benefits the gallbladder (*Dan*)
- Commission E: symptoms of mild digestive disturbances and minor biliary dysfunction

Turmeric- The Anticancer Spice

- Purported properties
  - Antioxidant
  - Anti-inflammatory
  - Chemopreventive
  - Antimutagenic
  - Anticarcinogenic
  - Antimetastatic
  - Antiangiogenic
  - Cardioprotective
Turmeric- The Anticancer Spice

• Appears to have potential as chemopreventive agent for colon and pancreatic cancers
• Two of 21 evaluable pts in Phase II trial in pancreatic cancer showed clinical biological activity (Dhillon, Clin Cancer Res 2008)
• Safe with gemcitabine but <10% pts with objective response (Bar-Sela, Curr Med Chem 2010)
• Appears synergistic with docetaxel vs lung cancer in vitro and in vivo (Yin, Acta Biochim Biophys Sin)
Turmeric- The Anticancer Spice

- Curcuminoids (diferuloylmethanes) include curcumin and its methoxylated derivatives
- Curcumin has extremely low bioavailability
- Piperine increases bioavailability 2000%
- Weakly inhibits induction and activity of CYP450 1A1, 1A2, 2B1, 2B2, 2E1
- Pronounced inhibitory effects on P-glycoprotein noted

Turmeric-Chemo Interactions

- Bleomycin: may ↓ pulmonary toxicity
- Cisplatin: may ↓ renal and neurotoxicities
- Cyclophosphamide: may ↓ toxicity and effectiveness
- Doxorubicin: may ↓ toxicity and possible effectiveness
- Taxanes: may chemosensitize malignant cells
- Vincas: may ↓ drug resistance by inhibiting efflux mechanisms

Herb, Nutrient, and Drug Interactions by Stargrove, Treasure and McKee
Mycological Nutriceuticals

<table>
<thead>
<tr>
<th>Mushroom</th>
<th>Description</th>
<th>Price</th>
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<tbody>
<tr>
<td>Reishi</td>
<td>(reduce fatigue)</td>
<td>$18.00</td>
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<tr>
<td>Cordyceps</td>
<td>(support stamina)</td>
<td>$30.00</td>
</tr>
<tr>
<td>Coriolus</td>
<td>(immune support)</td>
<td>$25.00</td>
</tr>
<tr>
<td>Maitake</td>
<td>(immune support)</td>
<td>$25.00</td>
</tr>
<tr>
<td>Triton</td>
<td>(reduce fatigue)</td>
<td>$25.00</td>
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</tbody>
</table>
History of Medicinal Mushrooms

- Hot water decoctions from certain fungi long recognized to have health promoting effects, particularly in Eastern cultures
- ~ 300 species felt to have therapeutic potential, important in Asian cuisine and as folk medicines
- Crossover to West stimulated by:
  - Cancer epidemiology of Flammulina velutipes (enokitake) farmers
  - Isolation of specific active constituents
  - Superior organoleptic properties to dominant Agaricus
  - Multimillion $ US market for edibles and medicinals

Mechanism of Immune Action

- \( \beta \)-glucans resemble molecules on bacterial cell walls
- \( \beta \)-glucans complex with complement on macrophages, mobilizing immune response
- When ingested into macrophages, \( \beta \)-glucans stimulate cytokines active in tumor inhibition, i.e. IFN-\( \gamma \), TNF-\( \alpha \), IL-2 and IL-12
- Differently branched glucans from different species stimulate T cells, NK cells or others
Anti-Cancer Activities

- Most mushrooms work as non-specific immuno-stimulants, enhance host response
- Activity may require intact T cell function
- Activity especially beneficial when used in conjunction with chemotherapy
- Some may have direct cytotoxic effects
- Most clinical trials and licensed drugs are in Asia; more studies needed

Trials of Mushrooms in Cancer: Issues in Design and Interpretation

- Information derived from:
  - *In vitro* effects
  - Animal models
  - Human trials
  - Epidemiologic observations
- Mushroom products studied:
  - Whole mushrooms: eaten, encapsulated or extracted
  - Mycelia or fruiting bodies
  - Extracts
    - Water: hot or cold
    - Ethanol
  - Isolated fractions
**Agaricus species**

- *Agaricus blazei* most common CAM Rx in Japanese cancer patients
- *Agaricus bisporus* may have aromatase inhibitor activity
  - Significance of agaritine in raw button mushrooms unclear
  - ALL mushrooms must be cooked before eating !!!

**Lentinus edodes**

- Shiitake
- Xiang gu (Fragrant mushroom)
- LEM
  - *Lentinus edodes* mycelium
- Lentinan
  - Cell wall constituent extracted from fruiting bodies or mycelium
  - Widely used as adjuvant immunotherapy in Japan
  - High MW precludes oral administration
- Active Hexose Correlated Compound base
**Grifola frondosa**

- Maitake
- Hen of the woods
- D-fraction
  - Found in mycelia and fb
  - Standardized $\beta$-1,3 and $\beta$-1,6 glucan fraction
  - MD-fraction is a more purified extract
  - Adaptogen and immunomodulator
  - May ↓ chemo side effects

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**Hericium species**

- May stimulate brain derived nerve growth factor
  - Could be considered as a neuroprotective agent vs chemo-induced neuropathy
  - Possible use in chemo-induced cognitive impairment
  - Human studies needed!
**Trametes versicolor**

- AKA *Coriolus, Polyporus*
- Turkey tail mushroom
- Yun Zhi (Cloud fungus)
- 2 proteoglycans
  - PSK (Krestin)
  - PSP
- Widely used adjuvant Rx in Japan and China
  - 25% of cancer care cost in Japan
  - Positive RCTs in GI (esp stomach) and breast

**Ganoderma lucidum**

- Reishi
  - 10,000 year mushroom
- Ling Zhi
  - Mushroom of immortality
- Polysaccharides immune enhancing activity
- Ganoderic acid triterpenoids inhibit tumor cell growth
- Worldwide extract sales 1.5 billion annually
**Cordyceps sinensis**

- Used for vigor and stamina
- Lung and kidney tonic
- Restores immune activity with chemoRx
- Prolonged survival of mice receiving chemoRx
- May also improve anemia from chemoRx

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**Mushrooms and Green Tea**

- Case control study in SE China 2004-2005
- 1009 women with confirmed breast CA and 1009 age-matched controls
  - Compared with non-consumers
    - OR- 0.36 (95% CI 0.25, 0.51) for daily intake >10g fresh mushrooms
    - OR- 0.53 (95% CI 0.38, 0.73) for daily intake > 4 g dried mushrooms
    - ORs 0.11 and 0.18 for fresh and dried in combo with >1.05 g dried green tea leaf beverages/day
  - Effects seen in pre and post-menopausal women

Zhang et al, Int J CA, 2009
Marijuana as Medicine

- Contains over 400 chemical compounds
- Highest concentration of bioactive compounds in resin exuded from flowers of female plants
- Main psychoactive component believed to be delta-9-THC
- At least 70 other cannabinoids identified in pyrolysis products
- delta-8-THC similar in potency but only in small concentration
Non-THC Components of Marijuana

- Δ9-tetrahydrocannabinol (THC) is the primary active ingredient of cannabis
- Secondary compounds may enhance the beneficial effects of THC
- Other cannabinoid and non-cannabinoid compounds may reduce THC-induced anxiety, anticholinergic effects and immunosuppression
- Terpenoids and flavonoids may increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens and provide anti-inflammatory activity

Symptom Management Challenges Associated with Cancer and Its Treatments

Cannabis as an Anti-Cancer Agent

- Increasing body of preclinical evidence suggests cannabinoids may have activity
- Anti-oxidant and anti-inflammatory effects
- Possibility of anti-tumor activity via cannabinoid receptors inducing apoptosis and impairing tumor vascularization
- Gliomas and skin tumors seem responsive in animal models

**Other potential cannabinoid anti-tumoral actions in gliomas**

Angiogenesis

- Cannabinoids
  - Downregulation of VEGF

Differentiation

- Egfr

Invasion

- Downregulation of MMP-2

Cell cycle

- Cdk1

Guzman, Integrative Oncology
Cannabinoids and Cancer

• Cannabinoid administration to nude mice curbs growth of various tumor xenografts
  – Lung carcinoma
  – Thyroid epithelioma
  – Lymphoma
  – Skin carcinoma
  – Glioma

Velasco Neuropharmacology 04

Cannabinoids and Cancer

• In cultured glioma cells, incubation with cannabinoids induces cell death via apoptosis
• Local administration of THC or WIN-55,212-2 reduced the size of tumors generated by intracranial inoculation in rats
• In engrafted tumor cells, cannabinoids effective vs GBM cells from patients
• Ongoing Spanish trial of local administration of THC in recurrent GBM

Velasco Neuropharmacology 04
Cannabinoids and Cancer: Human Studies

• Pilot phase I study administered THC intratumorally to 9 pts with recurrent GBM
  – Dose escalation study
  – Median survival 24 wks
  – Tumor cell proliferation decreased *in vitro*
    » Guzman et al, Br J Cancer, 2006

• PK study in cancer pts receiving irinotecan (12) or docetaxel (12)
  – Cannabis administered as herbal tea x 15d
  – Exposure to and clearance of chemo not altered
    » Engels et al, Oncologist, 2007

Doc, Can I Take This?

Photo by Lawenda
Herb-Drug Interactions: CYP3A4

**Anticancer Agents**  
- Camptothecins  
- Cyclophosphamide  
- EGFR-TK inhibitors  
- Epipodophyllotoxins  
- Taxanes  
- Vinca alkaloids

**Herbal Products**  
- CYP3A induction  
  - SJW  
  - Echinacea  
  - Grape seed  
  - Kava  
  - Garlic
- CYP3A inhibition  
  - Gingko

The Great Antioxidant Debate

- Antioxidants may interfere with the mechanism of action of cytotoxic chemotherapy or radiotherapy
- Use of antioxidants causes diminished treatment effect and protection of tumor

- Oxidation supports malignant proliferation
- Oxidation may interfere with standard Rx, diminishing therapeutic benefit
- Antioxidants improve Rx efficacy and protect from toxicity of treatments
Antioxidants and Chemo: Teams

Strongly Oxidative Chemo
- Cisplatin, et al
- Alkylating agents
  - Cyclophosphamide
  - Ifosfamide
  - Melphalan
- Antitumor antibiotics
  - Doxorubicin
  - Daunorubicin
  - Bleomycin

Useful Antioxidants
- Vitamin A, C, E
- Selenium
- Melatonin
- N-acetylcysteine
- Glutathione
- C0-Q 10
- Alpha-lipoic acid

Antioxidants and Chemo: Systematic Review
- 17/19 RCTs showed either significant advantage or non-stat increase in survival or Rx response
  - All 13 reports with survival showed similar or benefit to AOs (4 stat sig)
  - 16/17 reports with overall response rate with similar or benefit to AOs (2 stat sig)
  - 15/17 reports with toxicity showed similar or reduced with AOs (3 stat sig)
- No evidence of diminished chemo effect
  Block et al, CA Treat Rev 2007
My Antioxidant Approach

• Individual advice depends on goal of Rx
  – If cure, err on side of caution
    • Delay antioxidants until end of Rx
    • Discontinue day before, of, after chemo cycle
    • Antioxidant rich foods probably ok
  – If palliation, encourage use for protection of normal tissue, optimization of QOL
• Antioxidant radio- and chemoprotectants (mesna, amifostine) do not interfere with anti-tumor effects of Rx

Integrative Oncology: Bridging the Gap
“The role of the physician is to cure sometimes, heal often, support always.”

*Ambroise Pare*