

# Rational Use of Natural Supplements In Integrative Oncology

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## Integrative Oncology

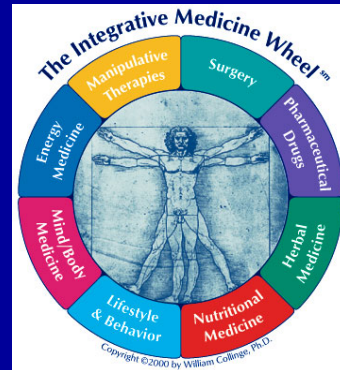
“It is more important to know  
what sort of patient has a disease  
than what disease a patient has.”

Moses Maimonides and  
Sir William Osler



## What is Integrative Oncology?

The rational, evidence-informed 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

- Research suggests that our presence as medical or mental health clinicians, the way we bring ourselves fully into connection with those for whom we care, is one of the most crucial factors supporting how people heal- how they respond to our therapeutic efforts.

» Daniel Siegel *The Mindful Therapist* 2010

## Integrative Oncology

- Provides relationship-centered care
- Integrates conventional and complementary methods of treatment and prevention
  - Aims to activate the body's innate healing response
  - Uses natural, less invasive interventions when possible

## Integrative Oncology

- Engages mind, body, spirit and community
- Encourages providers to model healthy lifestyles for their patients
- Focuses attention on lifestyle choices for prevention & maintenance of health
- **Maintains that healing is always possible even when curing is not**

## Where Does CAM Fit In? NCCAM: The Tools for Healing: 5 Categories of CAM

- **Mind/Body Medicine**
- **Manual therapy**
- **Energy Therapies**
- **Pharmacological & Biological Therapies**
- **Culturally-Based Healing Traditions**



## Oncologists and CAM

- Most oncologists admit to (very) limited knowledge about CAM
- In direct observations of oncology visits MD/Pt communication re: CAM is suboptimal
- CAM/cancer patients identified 3 barriers
  - Physician's indifference or opposition
  - Physician's emphasis on scientific evidence
  - Patients' anticipation of a negative response from their physician
- Just asking a directed question about CAM during history-taking increased disclosure from 7 to 43%

## Men's Choices of CAM in Prostate CA

- Survey of 34 men using CAM in the UK
- Choice of particular therapies was based on forms of "evidence" that were personally meaningful
  1. Personal stories of people helped by CAM
  2. Long history and enduring popularity of the Rx
  3. The plausibility of the mechanism of action
  4. A belief or trust in individual therapies or their providers
  5. Scientific evidence
- Must acknowledge the different standards of evidence used by patients and clinicians to evaluate the benefits or not of CAM therapies

Evans et al 2007

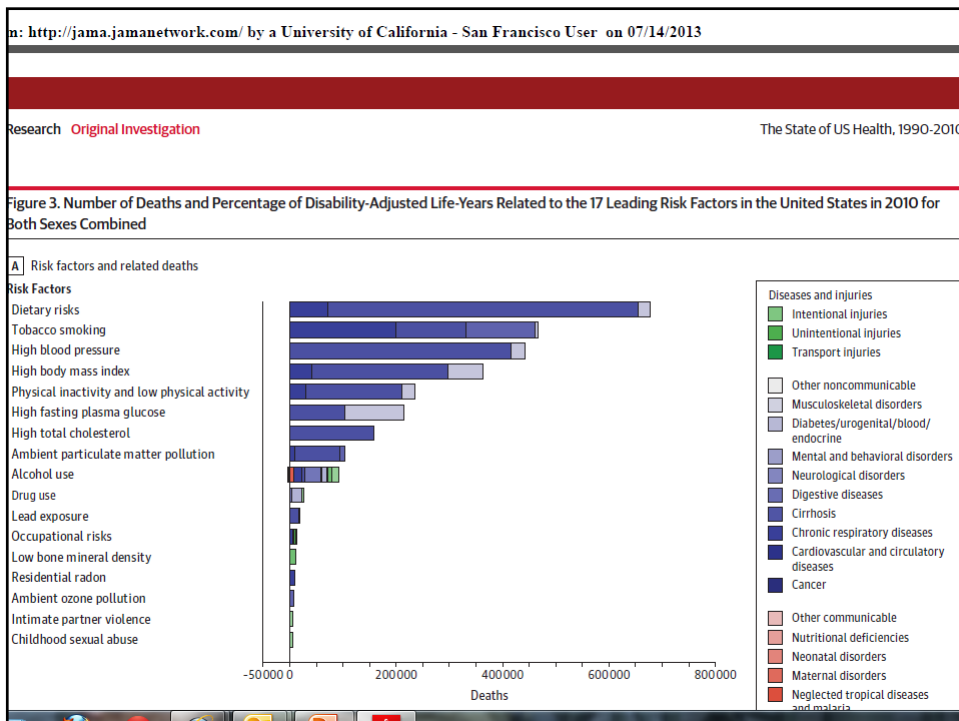
## Goals of Integrative Oncology

- Increase patient's sense of control
- Decrease ongoing inflammation
- Increase body's innate immunity in fight against cancer
- Decrease stress
- Increase hope

## Increasing Sense of Control

- Control weight
- Alter diet
- Increase physical activity
- Use appropriate supplements
- Become aware of breathing
- Consider guided imagery or self-hypnosis
- Connect with family and friends
- Engage spirituality and religion

Let your food be your medicine  
 And your medicine be your food  
 Hippocrates



## 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
- Vitamin D
- Omega 3 fatty acids



## 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 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

## 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

## Plasma Fatty Acids and Prostate CA

- 3 of 4 prior studies showed high blood [long-chain omega-3 PUFA] associated with increased risk CaP
- In SELECT subjects, men in highest quartile had  $\uparrow$  risk for low-grade (HR 1.44, 1.09-1.88), high-grade (HR 1.71, 1.00-2.94) and total (HR 1.43, 1.09-1.88) prostate cancer

	No Cancer N=1364	Total CA N=834	Low Grade N=648	High Grade N=156
EPA+DPA+DHA	4.48	4.66 (.002)	4.66 (.002)	4.71 (.03)
EPA	0.61	0.65 (.03)	0.66 (.02)	0.65 (.40)
DHA	2.91	3.01 (.006)	3.01 (.02)	3.09 (.009)
TFA 16:1	0.21	0.22 (.002)	0.22 (<.001)	0.22 (.02)

Braskv et al. JNCI. 2013

- Moreover, historians of science since [Thomas Kuhn](#) have pointed out that legitimate science rarely abandons a theory the moment falsifying observations come in, preferring instead (sometimes for decades) to chalk up counter evidence to experimental error. Asma, NYTimes, 9/28/13

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The screenshot shows a web browser window displaying a Bloomberg news article. The article title is "Eating Fish Among Habits to Cut Prostate-Cancer Risk" by Simon Bennett, dated Sep 29, 2013. The article text states: "A set of six healthy habits, including eating more tomatoes and less processed red meat, helped men reduce their risk of dying from prostate cancer, a study found." Below the text, it mentions that researchers analyzed information from almost 46,000 men for 25 years and found that those who adopted five or six of the habits had a 39 percent lower risk of developing lethal prostate cancer. The browser interface includes a menu bar (File, Edit, View, Favorites, Tools, Help), a toolbar with various icons, and a sidebar with recommended articles such as "First U.S. Shutdown in 17 Years at Midnight Seen Probable", "Arnault Pits Son Versus Daughter in LVMH Succession Test", and "Republicans' Shutdown Fight Exposes Simmering Civil War".

## 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

## Fish Oil in Lung Cancer

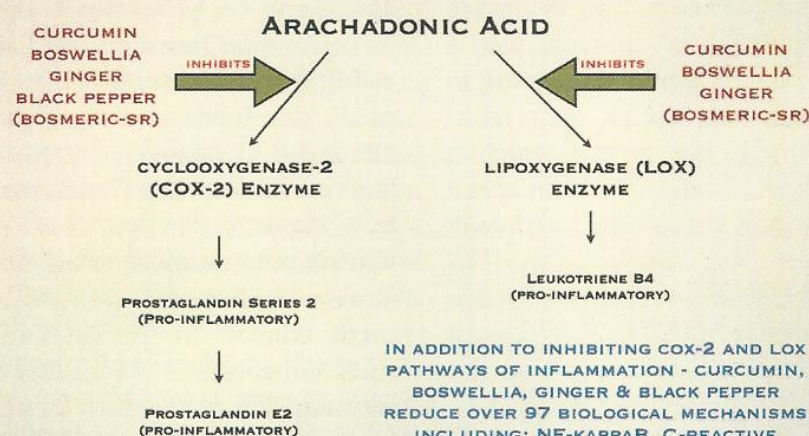
	SOC (n=31)	Fish Oil (n=15)	P
Complete Response	1 (3.2%)	1 (6.7%)	
Partial Response	7 (22.6%)	9 (60%)	
Stable Disease	5 (16.1%)	2 (13.3%)	
Progressive Disease	18 (58.1%)	3 (20.0%)	
Response Rate (CR/PR)	8 (25.8%)	9 (60.0%)	.008
Benefit (CR/PR/SD)	13 (41.9%)	12 (80%)	.02
Chemo cycles received	3.0 ± 1.4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

EPA concentration after supplementation significant predictor of response

Murphy et al, Cancer 2011

### Omega-3 Pathway and Natural Anti-Inflammatories

#### ANCIENT WISDOM - MODERN SCIENCE



IN ADDITION TO INHIBITING COX-2 AND LOX PATHWAYS OF INFLAMMATION - CURCUMIN, BOSWELLIA, GINGER & BLACK PEPPER REDUCE OVER 97 BIOLOGICAL MECHANISMS INCLUDING: NF-KAPPA B, C-REACTIVE PROTEIN, IL-1BETA, IL-6, IL-12, TNF-ALPHA, IFN-GAMMA, AP-1, MACROPHAGE INFLAMMATORY PROTEIN, MATRIX METALLOPROTEINASE, HUMAN LEUKOCYTE ELASTASE (HLE), ETC.

Pai, CA Strategies 2014



## Turmeric- The Anticancer Spice

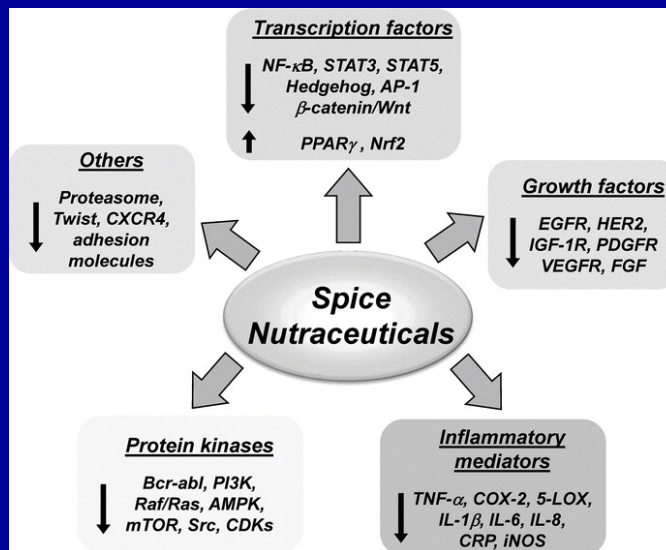
- *Curcuma longa* L, family Zingiberaceae
- Cultivated in Asia for culinary and medicinal purposes for centuries
  - In Ayurveda, used internally for digestive problems and is considered a blood purifier and antimicrobial; externally for skin problems
  - In TCM, invigorates *xue* (blood); relieves pain 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



Sung et al. Nutrition and Cancer 2011

## 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		
Reishi	(reduce fatigue)	\$18.00
Cordyceps	(support stamina)	\$30.00
Coriolus	(immune support)	\$25.00
Maitake	(immune support)	\$25.00
Triton	(reduce fatigue)	\$25.00

## History of Medicinal Mushrooms

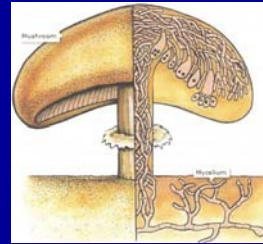
- Hot water decoctions from certain fungi long recognized to have health promoting effects, particularly in Eastern cultures
- ~ 300 species felt to have therapeutic potential, important in Asian cuisine and as folk medicines
- Crossover to West stimulated by:
  - Cancer epidemiology of *Flammulina velutipes*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

## 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  $\downarrow$  chemo side effects

## *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*



Fungi Perfecti Photo

- 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*



Fungi Perfecti Photo

- 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*



Fig. 1. The habitat of Cordyceps in China. (A) a prairie at an elevation of 3500-5000 m, mainly in the provinces of Qinghai, Tibet, Sichuan, Yunnan and Gansu; (B and C) the parasitic complex of the fungus and the caterpillar it feeds in the soil; (D) freshly collected Cordyceps sinensis in (B and C) indicate the Cordyceps.

- 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

## 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

## 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

## Stress and Cancer

- Not much evidence that stress directly causes cancer; neither necessary nor sufficient to initiate carcinogenesis
- Stress hormones can accelerate growth of established tumors
- Catecholamines released from stressed mice stimulated angiogenesis, increased number and caused metastases in injected ovarian cancer cells

Sood Nature Medicine 2006

## Stress and Cancer

- Women with ovarian cancer interviewed pre-op
- In women who lacked social support and had higher levels of distress, tumor had higher levels of VEGF
- First association between a psychological factor and a cytokine involved in tumor angiogenesis

Cole Nature Reviews Cancer 2006

## VEGF, Stress and H&N CA

- 37 newly diagnosed head & neck pts with squamous cell CA surveyed
- Higher levels of perceived stress and depressive sx were significantly associated with greater VEGF expression
  - “Intense” VEGF expression had mean PSS 47% higher than pts with “weak” expression
  - Associations strongest for early stage pts
  - High VEGF more than 2.5 times more likely to die

Fang et al 2011

# Mind-Body Interventions

- Support Groups
- Journaling
- Disclosure
- Guided Imagery
- Hypnosis
- Breathwork
- Therapy



## Hypnosis Before Breast Cancer Surgery

- 200 women scheduled for breast biopsy or lumpectomy randomly assigned to hypnosis or control group
  - Scripted 15 minute hypnosis session within one hour of surgery by trained psychologist
  - Control group spent 15 minutes with psychologist talking and receiving emotional support
- Anesthesiologists, surgeons and research assistants blinded to patient group

Montgomery et al, JNCI 2007

## Hypnosis Before Breast Cancer Surgery

- Women in the hypnosis group
  - Required less anesthesia; same post-op pain meds
  - Reported less pain intensity, unpleasantness, nausea, fatigue, discomfort and emotional upset
  - Spent 10.5 minutes less in surgery, saving \$770

JNCI 2007

## Acupuncture in Cancer



- Antiemetic during chemotherapy
- Pain control, including neuropathy
- Anxiety/Depression
- Breathlessness
- Xerostomia after radiation therapy
- Hot flashes secondary to hormonal therapy
- Chronic post-chemotherapy fatigue
- Constipation/diarrhea
- Sleep disturbance
- Immune enhancement



## Acupuncture for AI Arthralgias

- Aromatase inhibitor induced arthralgias and muscle stiffness in 5-50% pts
- 51 participants randomized to true or sham AP (sham= superficial needle insertion at locations not recognized as true acupoints)
- 38 pts evaluable (58 yrs, 55% Hispanic, 70% anastrozole)
- At 6 wks, pain reduced 50% in TA from baseline with no change in SA group

Crew et al, JCO 2010

## Benefits of Acupuncture

- Equal to venlafaxine in relief of hot flashes
  - » Walker et al, JCO 2010
- Effective in hot flashes in men undergoing ADT for prostate cancer
  - » Beer et al, Urology 2010
- Safe in children with cancer Rx related thrombocytopenia
  - » Ladas et al, Support Care Cancer 2010
- Effective for cancer-related fatigue in breast cancer
  - » Molassiotis et al, JCO 2012
- Decreases chronic xerostomia symptoms
  - » Simcock et al, Annals of Oncology 2013

## Integrative Oncology: Bridging the Gap



**“The role of the  
physician is to  
cure sometimes,  
heal often,  
support always.”**  
*Ambroise Pare*

