Integrating Complementary and Conventional Therapies in Cancer Care

6/25/13

Donald I. Abrams, M.D.

BIOGRAPHY:

Donald I. Abrams, M.D. is chief of the Hematology-Oncology Division at San Francisco General Hospital, an integrative oncologist at the UCSF Osher Center for Integrative Medicine and Professor of Clinical Medicine at the University of California San Francisco. He graduated from Brown University in 1972 and from the Stanford University School of Medicine in 1977. After completing an Internal Medicine residency at the Kaiser Foundation Hospital in San Francisco, he became a fellow in Hematology-Oncology at the UCSF Cancer Research Institute in 1980. During his fellowship, Dr. Abrams spent eight months working in the retrovirology laboratory of Harold Varmus, M.D. during the time that the first cases of AIDS were being diagnosed. He subsequently returned to the clinical arena where he was one of the original clinician/investigators to recognize many of the early AIDS-related conditions. He conducted numerous clinical trials investigating conventional as well as complementary therapies in patients with HIV including therapeutic touch, Traditional Chinese Medicine interventions, medicinal mushrooms, medical marijuana and distant healing. His interest in botanical therapies led him to pursue a two-year Fellowship in the Program in Integrative Medicine at the University of Arizona which he completed in December 2004. His particular passion in the field involves nutrition and cancer. Since completing his Fellowship, Dr. Abrams has been providing Integrative Medicine consultation to people living with and beyond cancer at the UCSF Osher Center for Integrative Medicine where he served as Director of Clinical Programs from 2006-2008. His integrative oncology research interests are in medicinal mushrooms, Traditional Chinese Medicine interventions and nutrition. He co-edited the Oxford University Press textbook *Integrative Oncology* with Andrew Weil, M.D.. He is a member of the NCI PDQ CAM Editorial Board. Dr. Abrams was President of the Society for Integrative Oncology in 2010.

BIBLIOGRAPHY:


Alschuler LN and Gazella KA. *Five to Thrive: Your Cutting Edge Cancer Prevention Plan*. Active Interest Media; 2011.


Lipsenthal L. *Enjoy Every Sandwich: Living Each Day as If It Were Your Last*. Harmony. 2011.


Integral Oncology: Challenges and Controversies

Donald I. Abrams, M.D.
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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

"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

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

**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

• 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
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

Integrative Oncology: 3 Domains of Care

- For reducing risk of cancer
- For cancer treatment
- For symptom management and palliation of cancer

Integrative Cancer Risk Reduction

- Focus mainly on lifestyle issues
  – Maintenance of healthy body mass index
  – Regular aerobic and resistance exercise
  – Dietary guidelines
- CAM therapies may be useful interventions in smoking cessation
  – Hypnosis/Guided imagery
  – Acupuncture
- Judicious use of supplements may have value in decreasing inflammation, boosting innate immunity
CAM for Cancer Treatment

- CAM for *treatment* of cancer is far from compelling
- Advise your cancer patients:
  - Do NOT use unproven CAM therapies in place of proven traditional therapies, or delay your treatment while seeing if an alternative therapy will work
  - Alternative therapies, even vitamins, can interact with your chemotherapy and radiation treatment, so always tell your doctors what you are taking

Role of CAM therapies in Symptom Management and Palliative Care

- Relieve or prevent treatment side effects
  - Reduce side-effects of chemoradiotherapy
  - Enhance tolerance of conventional therapy
  - Promote relaxation
  - Reduce stress
  - Relieve pain
  - Improve sleep
  - Enhance quality of life
- Improve immune function
- Alter disease progression
  - Prevent recurrence or metastasis
  - Prolong survival

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
- Use appropriate supplements
- Increase physical activity
- 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

Proportion of Cancer Deaths Caused by Different Avoidable Cancers

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<td>Tobacco</td>
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* Doll and Peto, 1981; ** Doll, 1998

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AICR 2009

94%
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### Cancer Is a Preventable Disease That Requires Major Changes in Life Style

<table>
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<tr>
<th>Cancer Incidence (%)</th>
<th>Tobacco</th>
<th>Diet</th>
<th>Obesity</th>
<th>Infections</th>
<th>Pollution &amp; Radiation</th>
<th>Genetic</th>
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<tbody>
<tr>
<td>Percentage</td>
<td>10</td>
<td>35</td>
<td>14.2</td>
<td>16</td>
<td>7</td>
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AICR 2009

* Doll and Peto, 1981; ** Doll, 1998
Diet and Cancer

- Probably involved in 30-35% of all cancers
- Certainty about diet less firm than tobacco
  - Contradictory study results i.e. fiber
  - Hard to define what the diet actually is
    - Diets are very complex
    - Diets vary over time
- Is it what we ate in the past? Or perhaps what our mothers ate? Or theirs?

ACS and WCRF/AICR Guidelines

WCRF/AICR Recommendations to Reduce Cancer Risk 2007

- Be as lean as possible without becoming underweight
- Be physically active for at least 30 minutes every day
Obesity Trends® Among U.S. Adults
BRFSS, 1990, 2000, 2010
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

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<th>Year</th>
<th>No Data</th>
<th>&lt;10%</th>
<th>10%–14%</th>
<th>15%–19%</th>
<th>20%–24%</th>
<th>25%–29%</th>
<th>≥30%</th>
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Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity-Associated Malignancies

- Breast (post-menopausal)
- Endometrium
- Prostate
- Kidney
- Colon
- Esophagus
- Pancreas
- Gallbladder

AICR report estimates that obesity-related excesses of these 7 cancers account for approx 105,000 preventable deaths a year in the US.

Obesity and Cancer

- Multiple myeloma
- Renal cancer
- Non-Hodgkin’s lymphoma
- Cervical cancer
- Pancreatic cancer
- Rectal cancer
- Uterine cancer
- Endometrial cancer
- Breast cancer
- Colon cancer
- Gastric cancer
- Gallbladder cancer

Body Fat Increases CA Risk

- Body fat secretes cytokines that promote inflammation
- Fat increases estrogen production
- Increase in body fat may impair immunity
- Too much body fat triggers insulin resistance, raising levels of insulin and growth factors that promote cancer

Physical Activity and Colon CA

- Women’s Health Initiative cohort studied for relationship between BMI, recreational activity and survival in post-menopausal women with colorectal cancer
- 2093 women of the 161,808 enrolled developed CRC with 1339 eligible for analysis
- Grouped into categories of physical activity: 0 metabolic equivalents (MET) hrs/wk; 0-2.9; 3-8.9; 9-17.9; >18 (9 MET = 3 hrs/wk moderate activity

Physical Activity and Colon CA

- In multivariate analysis, women with prediagnostic physical activity level of 18 or more MET hrs/wk compared with 0 MET group
  - 32% reduction in CRC-specific mortality
  - 37% reduction in all-cause mortality
  - Benefit more prominent with BMI 18.5-24.9 kg/m²
  - 9-17.9 MET group had >20 reductions but NS
- 606 women eligible for postdiagnostic activity
  - Greater than 18 MET hrs/wk had 71% ↓ CRC mortality and 59% ↓ risk all-cause mortality
- BMI not associated with mortality either analysis

WCRF/AICR Recommendations to Reduce Cancer Risk 2007

- Be as lean as possible without becoming underweight
- Be physically active for at least 30 minutes every day
- Avoid sugary drinks
  - Limit consumption of energy dense foods
  - Particularly processed foods high in added sugar, low in fiber or high in fat
How can anyone consume that much sugar???

Cancers Increased in Diabetics

- Liver
- Colorectal
- Pancreatic
- Breast
- Endometrial
- Renal
- Multiple myeloma

Vigneri et al., Endocr. Relat. Cancer, 2009
Mortality in CA with Diabetes

- Explanations for observed association
  - Increased proliferation and metastases with hyperinsulinemia, hyperglycemia and ↑ ROS
  - Less aggressive CA treatment offered DM pts
  - DM pts may have poorer response to CA Rx
  - Pts with DM may present with later stage dz b/o suboptimal screening
  - Dx and Rx of CA may distract from glycemia mx
  - Excess mortality may be independent of CA & Rx

Barone et al, JAMA, 2008

Insulin and IGF-1 and Cancer

- Label ingredients of a nutritional supplement include:
  - WATER, CORN MALTODEXTRIN, SUGAR (SUCROSE), CORN SYRUP, MILK PROTEIN CONCENTRATE, COCOA POWDER (PROCESSED WITH ALKALI), SOY OIL, SHORT-CHAIN FRUCTOOLIGOSACCHARIDES, SOY PROTEIN ISOLATE, CANOLA OIL

- Is this a healthy supplement to recommend to cancer patients?
  - 1) Yes
  - 2) No
But What About Metformin?

• Relative of isoamylene guanidine, active ingredient in French lilac (*Galega officinalis*) used for polyuria in diabetics
• Epidemiologic studies show decreased cancer risk in patients on metformin
• Exerts *in vitro* inhibition of prostate, ovarian and breast CA cells
• Selectively kills cancer stem cells
• Currently in cancer clinical trials

Chong and Chabner, The Oncologist 2009

Metformin Mechanism of Action

• Directly on the tumor or indirectly on the host by lowering insulin levels
• In the liver, MET inhibits transcription of key gluconeogenesis genes and ↑s glucose uptake in skeletal muscles
  - ↓ levels circulating glucose
  - ↑ insulin sensitivity
  - ↓ insulin resistance-associated hyperinsulinemia

Dowling et al, BMC Medicine 2011
WCRF/AICR Recommendations to Reduce Cancer Risk 2007

• Be as lean as possible without becoming underweight
• Be physically active for at least 30 minutes every day
• Avoid sugary drinks
  – Limit consumption of energy dense foods
  – Particularly processed foods high in added sugar, low in fiber or high in fat
• Eat more of a variety of vegetables, fruits, whole grains and legumes

U.S. Diets Fall Short on F&Vs

• CDC reports only 14% of adults eat recommended number of servings/day
  – 33% eat 2 or more servings of fruit a day
  – 27% eat 3 or more servings of vegetables
• DC 20.1%, VT, ME, HI, MA top 5
• WV, SD, AL, OK/SC, MS 8.8% rank last
• Only 9.5% of high school students meet recommendations (32% fruit, 13% veg)
• Healthy People 2010 objective was to have 75% meet fruit and 50% vegetable
  
Centers for Disease Control 2009

Nutritional Risk Reduction Strategies

Eat More:
• Phytoestrogens
  – Soy foods
  – Flaxseed
• Cruciferous vegetables
• Garlic and onions
• Turmeric and ginger
• Green tea
• Omega 3 fatty acids
• Vitamin D
Sulforaphane in Prostate Cancer

- Sulforaphane is a constituent of cruciferous vegetables such as broccoli
- CVs strongly associated with lower CaP
- Preclinical studies suggest sulforaphane inhibited histone deacetylase (HDAC) function and suppresses androgen receptor signalling
- GSTM1 gene contributes to sulforaphane metabolism

Sulforaphane in Prostate Cancer

- 20 men with CaP and PSA recurrence despite surgery or radiation
- Treated with sulforaphane 200 umol/day
- 16 patients completed 20 weeks
  - 1 had a PSA decline >50%
  - 7 had PSA declines 3-20%
  - 3 had final PSA less than baseline
- PSA doubling time went ↑ed 6 to 9.4 mos

Soy and Breast Cancer

- Numerous nutritional benefits
  - Isoflavones
    - Daidzein (40%), genistein (50%) and glyceitin (10%)
  - Essential amino acids
  - Fibers
  - Poly-unsaturated fatty acids
  - Vitamins and minerals
- Isoflavones acts as selective estrogen receptor modifiers
- ? Safety of soy products in ER+ women

“‘The compound we used is limited by not having several species toxicity, which will be necessary prior to dose escalation.’”
“Groups are working on developing a synthetic version with druglike properties.”
“There are also OTC preparations, but I am not familiar with their quality control.”

– Joshi J. Alumkal, MD, OHSU, Portland, OR June 2013

www.cancernetwork.com
LACE Study

- Life After Cancer Epidemiology Study followed 1954 breast CA survivors dx 97-00 for 6.3 yrs
  - 282 breast CA recurrences ascertained
  - Isoflavone intake assessed
- Soy intake at levels comparable to those consumed in Asian population
  - May reduce the risk of recurrence in women who have been treated with tamoxifen
  - In postmenopausal women (HR 0.45, 0.21-0.79, p=0.008)
  - Does not appear to negate the effects of tamoxifen
- Further confirmation required before recs issued

Guha et al, Breast CA Res and Treat, 2009

Turmeric- The Anticancer Spice

- Purported properties
  - Antioxidant
  - Anti-inflammatory
  - Chemopreventive
  - Antimitogenic
  - Anticancerogenic
  - Antiangiogenic
  - Cardioprotective

Sun 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-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

WCRF/AICR Dietary Recommendations to Reduce Cancer Risk 2007

- Limit consumption of red meats (beef, pork and lamb) and avoid processed meats
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
Meat and Colorectal Cancer

- Total iron intake and dietary iron both inversely associated, although the more bioavailable heme iron was positively associated
- Nitrate intake from processed meat positively associated; nitrite not (p=0.055)
- Heterocyclic amine intake (MeIQx and DiMeIQx) positively associated but only associated with colon, not rectal CA

Cross et al. Cancer Res 2010

WCRF/AICR Dietary Recommendations to Reduce Cancer Risk 2007

- Limit consumption of red meats (beef, pork and lamb) and avoid processed meats
- If consumed at all, limit consumption of alcoholic drinks to 2 for men and 1 for women a day

Alcohol and Breast Cancer

- Relative risk for developing ER+/PR+ breast cancer based on alcohol consumption

Lew et al. HemOnc Today 2008
ADDITIONAL AICR GUIDELINES

- If consumed at all, limit consumption of alcoholic beverages to two a day for men, one a day for women (one a week for women with ↑ed breast cancer risk)
- Don’t use supplements to protect against cancer
- After Rx, cancer survivors should follow the recommendations for cancer prevention

SELECT Study Meds Stopped

- 35,000 men > 50 enrolled 2001-2003
- Randomized to one of 4 arms
  - Two placebo pills n=8696
  - Selenium and placebo n=8752
  - Vitamin E and placebo n=8737
  - Selenium and vitamin E n=8702
- DSMC asked participants to d/c Rx in 9/08
  - Not likely to see 25% reduction risk of CaP
  - Trends towards ↑ CaP in vit E, ↑ AODM in Se (NS)

NCI Cancer Bulletin Nov 4, 2008; Results in Lippman et al JAMA, 2009

Poison is in everything and nothing is without poison.
The dosage makes it either a poison or a remedy.
- Paracelsus
  - 1493-1541
SELECT Follow-Up 2011
• Report includes additional 54,464 person-years of follow-up and 521 additional cases of prostate CA since 2009
• DSMB recommended reporting new data
  – 529 in placebo group developed CaP
  – 620 in vitamin E (HR 1.17; 1.004-1.36, P=.008)
  – 575 in selenium (HR 1.09; 0.93-1.27, P=.18)
  – 555 in Se plus E (HR 1.05; 0.89-1.22, P=.46)
• Vitamin E supplementation significantly increased the risk of CaP in healthy men

Klein et al, JAMA 2011

Folic Acid & B₁₂ in Norway
• 6837 people with ischemic heart disease treated with B vitamins or placebo 98-05
  – FA 800 mcg + B₁₂ 400 mcg + B₆ 40 mg (1708)
  – FA 800 mcg + B₁₂ 400 mcg (1703)
  – B₆ 40 mg (1705)
  – Placebo (1721)
• Results obtained after a median 39 mos treatment and 38 mos follow-up

Ebbing et al, JAMA 2009

Vitamin B₁₂ and Folate

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
Vitamin D3 (Cholecalciferol)

- Estimate that 1 billion people worldwide may be Vitamin D deficient
- Dark skin, obesity, heredity may hinder production
- Older adults need to ingest more because of decreased skin and renal synthesis
- 25(OH)-Vitamin D is good blood test
  - < 30 ng/mL insufficient
  - ~ 45 ng/mL adequate
  - > 80 ng/mL optimal

Vitamin D

- Cancer cells exposed to calcitriol undergo differentiation, cell cycle arrest and apoptosis depending on model and dose
- Vit D may be an important factor in angiogenesis with high dose D inhibiting tumor growth via disruption of angiogenesis
- Calcitriol potentiates anti-tumor activity of taxanes, anthracyclines, alkylating agents and antimetabolites in vitro and in vivo

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
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

Wess et al, ASCO 2010

Doc, Can I Take This?

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

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

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

Herb-Drug Interactions: CYP3A4

Photo by Lawenda
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
- Co-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

With all that we know about how stress aggravates cardiovascular disease, promotes viral infections, exacerbates metabolic diseases, halts reproduction, and regulates the normal function of virtually every cell in the body, why would cancer cells somehow be exempt?

Cole NCI Cancer Bulletin 2006
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
• Cathecholamines 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 stongest 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

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% anastrazole)
- At 6 wks, pain reduced 50% in TA from baseline with no change in SA group
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
- Remission of persistent hiccoughs in cancer patients
  » Ge et al, J Alt and Compl Med 2010
- Safe in children with cancer Rx related thrombocytopenia
  » Ladas et al, Support Care Cancer 2010

Integrative Oncology: Bridging the Gap

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