Integrative Cancer Care

Donald I. Abrams, M.D.
Oncology, Zuckerberg San Francisco General
Integrative Oncology
UCSF Osher Center for Integrative Medicine
Professor of Clinical Medicine
University of California San Francisco
Donald Abrams Disclosures

• Scientific Advisor
  – AXIM
  – Insys Therapeutics
  – Intec Pharma
  – VIVO Cannabis
  – Maui Wellness
  – Scripyx
  – Tikun Olam

• I did go to college in the ‘60’s

• And I will be discussing off-label use
  – Of an illegal substance
Integrative Cancer Care

“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 Cancer Care?

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
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
Integrative Oncology Patient Subsets

• Seeking alternatives to conventional cancer therapy

• Seeking complementary therapies while undergoing conventional therapy
  – To mitigate symptoms of cancer or treatment
  – To prolong remission

• Seeking any possible salvage therapy

• Seeking integrative end-of-life care

• Seeking optimal survivorship care
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-hypnnosis
- Connect with family and friends
- Engage spirituality and religion
Three Closing Questions

• What brings you joy?
• What are your hopes?
• Where does your strength come from?
Let your food be your medicine
And your medicine be your food

Hippocrates
Figure 3. Number of Deaths and Percentage of Disability-Adjusted Life-Years Related to the 17 Leading Risk Factors in the United States in 2010 for Both Sexes Combined.

- Risk factors and related deaths
- Diseases and injuries:
  - Intentional injuries
  - Unintentional injuries
  - Transport injuries
  - Other noncommunicable
  - Musculoskeletal disorders
  - Diabetes/urogenital/blood/endocrine
  - Mental and behavioral disorders
  - Neurological disorders
  - Digestive diseases
  - Cirrhosis
  - Chronic respiratory diseases
  - Cardiovascular and circulatory diseases
  - Cancer
  - Other communicable
  - Nutritional deficiencies
  - Neonatal disorders
  - Maternal disorders
  - Neglected tropical diseases and malaria
14 Components of Dietary Risk

- **Diets low in:**
  - Fruits
  - Vegetables
  - Whole grains
  - Nuts and seeds
  - Milk
  - Fiber
  - Calcium
  - Seafood omega 3s
  - PUFA’s

- **Diets high in:**
  - Red meat
  - Processed meat
  - Sugar-sweetened beverages
  - Trans fatty acids
  - Sodium

Lim et al, Lancet 2012
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
WEIGHT GUIDELINES

• Maintain a healthy weight throughout life
• Balance caloric intake with physical activity
• Avoid excessive weight gain throughout the life cycle
• Achieve & maintain a healthy weight if currently overweight or obese

Be as lean as possible without becoming underweight
But why are our health care costs higher than other countries?

...Who said that?
Obesity-Associated Malignancies

AICR report estimates that obesity-related excesses of these 7 cancers account for approx 115,000 preventable deaths a year in the US

Estimated Percentages of Annual US Cancers Caused by Excess Body Fat

- Breast: 17%, 33,000 cases
- Esophagus: 35%, 5,800 cases
- Pancreas: 28%, 11,900 cases
- Gallbladder: 21%, 2,000 cases
- Colorectal: 9%, 13,200 cases
- Endometrial: 49%, 20,700 cases
- Kidney: 24%, 13,900 cases

Source: AICR/WCRF "Policy and Action for Cancer Prevention” report, 2009
Body Fat Increases CA Risk

- Fat increases estrogen production
- Body fat secretes cytokines that promote inflammation
- Increase in body fat may impair immunity
- Too much body fat triggers insulin resistance, raising levels of insulin and growth factors that promote cancer
WCRF/AICR Recommendations to Reduce Cancer Risk 2007

1. Be as lean as possible without becoming underweight
2. Be physically active for at least 30 minutes every day
Exercise in Cancer Survivors

• Meta-analysis of 16 breast and 7 CRC studies with ~50,000 survivors
  – The most active breast CA survivors had lower rates of death from breast CA (RR, 0.72; (0.60-0.85) and other causes (RR, 0.52; 0.42-0.64)
  – The most active CRC survivors had lower rates of death from CRC (RR, 0.61; (0.40-0.92) and other causes (RR, 0.58; 0.48-0.70)
  – Survivors reporting an increase in activity after diagnosis had lower risk of death (RR, 0.61; 0.46-0.80) than those who did not

Schmid & Leitzmann, Ann Oncol 2014
The Role of The Oncologist

- Majority of non-small cell lung cancer survivors desired advice re: PA with 80% preferring face-to-face rec from an MD; 92% preferring under CA Center auspices
  
  » Philip et al, Support Care Cancer, 2014

- Survey of Canadian oncologists showed 62% agreed that PA was safe and beneficial, but only 42% ever recommended it and only 26% within past month

  » Jones et al, Support Care Cancer, 2005

- Oncologist recommending PA resulted in increase of 60 min vigorous walking/week

  » Jones et al, Ann Behav Med 2004
WCRF/AICR Recommendations to Reduce Cancer Risk 2007

1. Be as lean as possible without becoming underweight

2. Be physically active for at least 30 minutes every day

3. **Avoid sugary drinks**
   
   Limit consumption of energy dense foods
   Particularly processed foods high in added sugar, low in fiber or high in fat
Insulin and IGF-1 and Cancer

Gallagher and LeRoith, Trends in Endo and Metab, 2010
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 199 cancer clinical trials

Chong and Chabner, *The Oncologist* 2009
WCRF/AICR Recommendations to Reduce Cancer Risk 2007

4. Eat more of a variety of vegetables, fruits, whole grains and legumes

- Phytoestrogens
  - Soy foods
  - Flaxseed
- Cruciferous vegetables
- Garlic and onions
- Turmeric and ginger
- Green tea
- Omega 3 fatty acids
LACE Study of Soy in Breast CA

• 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 0.48, 0.21-0.79, p=0.008)
    – Does not appear to negate the effects of tamoxifen

• Shanghai Breast Cancer Survival Study confirmed 30% ↓ in recurrence and mortality; WHEL analysis also confirmed benefit of soy

Guha, Breast CA Res and Treat, 2009; Shu, JAMA, 2009; Caan, CA Epi Biomark; Messina, Oncology 2013
WCRF/AICR Dietary Recommendations to Reduce Cancer Risk 2007

5. Limit consumption of red meats (beef, pork and lamb) and avoid processed meats
Dietary Fats & Inflammation

**OMEGA-6 FATS**
Commercially-raised meat, poultry, dairy and eggs (yolk).
Also nuts, seeds, vegetable oils (corn, safflower, soy, etc.)

**OMEGA-3 FATS**
Cold-water fish, flax, hempseed oil, grass-fed meat, poultry, dairy & eggs. Small amounts in canola oil, black walnuts, and leafy greens

**PRO-INFLAMMATORY**
Compounds
foster tumor growth & progression, promote angiogenesis, suppress immune function

**ANTI-INFLAMMATORY**
Compounds
inhibit tumor growth, complement RT+chemo, anti-angiogenesis
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
I'LL HAVE THE HALF-POUND DOUBLE-DELUXE BACON STEERBURGER, PLEASE...

YOU WANT CHEMOTHERAPY WITH THAT?
Does It Really Matter After A Cancer Diagnosis?
6. Please describe your typical diet:
   Breakfast: Buttered, toasted bagel; orange juice; coffee
   Lunch: Rarely
   Dinner: Restaurants/burgers/fries/frozen dinners
   Snacks: Occasional ice cream

7. Do you change your eating habits when you are upset, worried, or sad?  [ ] Yes  [x] No

8. Do you eat when you are rushed?  [x] Yes  [ ] No

9. Do you skip meals?  [x] Yes  [ ] No
   - Breakfast  [ ] Lunch  [x] Dinner

10. How many glasses of fluids (water, juice) do you drink a day?  five to eight

11. How many cups/cans of caffeinated drinks (coffee, tea, soda) do you drink/day?  six to eight
Dietary Patterns in Colon CA

- Prospective observational study of 1009 pts with Stage III colon cancer enrolled in CALGB 89803 between 4/99-5/01
  - Pts reported on dietary intake using a ffq during and 6 months after the trial
  - Two major dietary patterns recognized
- Two major dietary patterns identified
  - Western pattern characterized by high intakes of meat, fat, refined grains, and dessert
  - Prudent pattern characterized by high intakes of fruits and vegetables, poultry and fish
  - Every patient scored along the spectrum of both
- Patients were followed up for cancer recurrence or death

Meyerhardt et al JAMA 2007
CALGB Prospective Observational Study: Western Dietary Pattern and Cancer Outcomes

• F/U 5.3 years, 324 patients recurred, 223 died with recurrence and 28 died without CA.
Dietary Patterns in Colon CA

- Highest quintile in Western diet had daily median
  - 1 serving of red meat
  - 5 servings of refined grains
  - 2 sugar desserts
- Lowest quintile in Western diet had daily median
  - 0.3 serving red meat (2 per week)
  - 2 servings refined grain
  - 0.5 sugar desserts (3 per week)
- “So the recommendation is more of an avoidance than an increase in diet components”

Meyerhardt Personal Communication
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
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
Recommended Supplements

- Vitamin D3 (depending on 25OHD level)
- Calcium/Magnesium
- Omega 3’s
- Medicinal Mushrooms
- Turmeric
- Probiotic
Recommended Supplements

- Vitamin D3 (depending on 25OHD level)
- Calcium/Magnesium
- Omega 3’s
- Medicinal Mushrooms
- Turmeric
- Probiotic
- Cannabis
Symptom Management Challenges Associated with Cancer and Its Treatments

Cannabis sativa
Cannabis 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 100 other cannabinoids identified in pyrolysis products
• delta-8-THC similar in potency but only in small concentration
• Cannabidiol (CBD) is non-psychoactive but analgesic, anti-inflammatory and anticonvulsant
Therapeutics

- In adults with chemotherapy induced nausea and vomiting, oral cannabinoids are effective antiemetics.
- In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms.
- In adults with multiple sclerosis (MS) related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.
- For these conditions the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess their effects.
Approved in 1986 for N&V from chemoRx; AIDS anorexia in 1992
Cannabis as an Anti-Cancer Agent

• In 1975 NIH investigators reported that delta-9-THC, delta-8-THC and CBD inhibited Lewis lung adenocarcinoma cell growth in vitro and in mice.

• Increasing body of preclinical evidence suggests cannabinoids may have anti-cancer activity.

• Anti-oxidant and anti-inflammatory effects may contribute as well.

• Possibility of anti-tumor activity via cannabinoid receptors inducing apoptosis and impairing tumor vascularization.
Cannabinoids and Cancer

- Cannabinoids induce apoptosis in mouse gliomas
- Cannabinoids administration in mouse models differentiates tumor vascular hyperplasia
  - Associated with reduced expression of VEGF and VEGF receptors (inhibition of tumor angiogenesis)
- Cannabinoids decrease the activity of matrix metalloproteinase-2; hence may also modify glioma invasiveness (inhibition of metastasis)
- Despite above, normal glial cells unaffected

Velasco et al, Neuropharmacology 2004
Cannabinoids and Cancer

- Multiple tumor cell lines inhibited *in vitro*
- Cannabinoid administration to nude mice curbs growth of various tumor xenografts
  - Lung, breast, colorectal and pancreas carcinoma
  - Skin carcinoma
  - Melanoma
  - Thyroid epithelioma
  - Lymphoma
  - Glioma

» Velasco et al, Neuropharmacology 2004
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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

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

• Effective for cancer-related fatigue in breast cancer
  » Molassiotis et al, JCO 2012

• Decreases chronic xerostomia symptoms
  » Simcock et al, Annals of Oncology 2013

• Safe in children with cancer Rx related thrombocytopenia
  » Ladas et al, Support Care Cancer 2010
Bridging the Gap
“The role of the physician is to cure sometimes, heal often, support always.”

Ambroise Pare