

Clinical Considerations of Herbal Product Utilization within the Oncology Patient Population

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No Disclosures

- No financial relationship exists between speaker and any natural health products, supplements, medical foods or websites in this presentation

Learning Objectives

- Describe Integrative Oncology and how it pertains to the judicious, evidence-based use of foods during cancer treatment
- Understand the importance of communication between patient and provider to fully disclose use of herbs and supplements
- Describe the aspects of herbal product quality with regard to purity, potency, and authenticity
- Discuss future directions of herbal product usage during survivorship

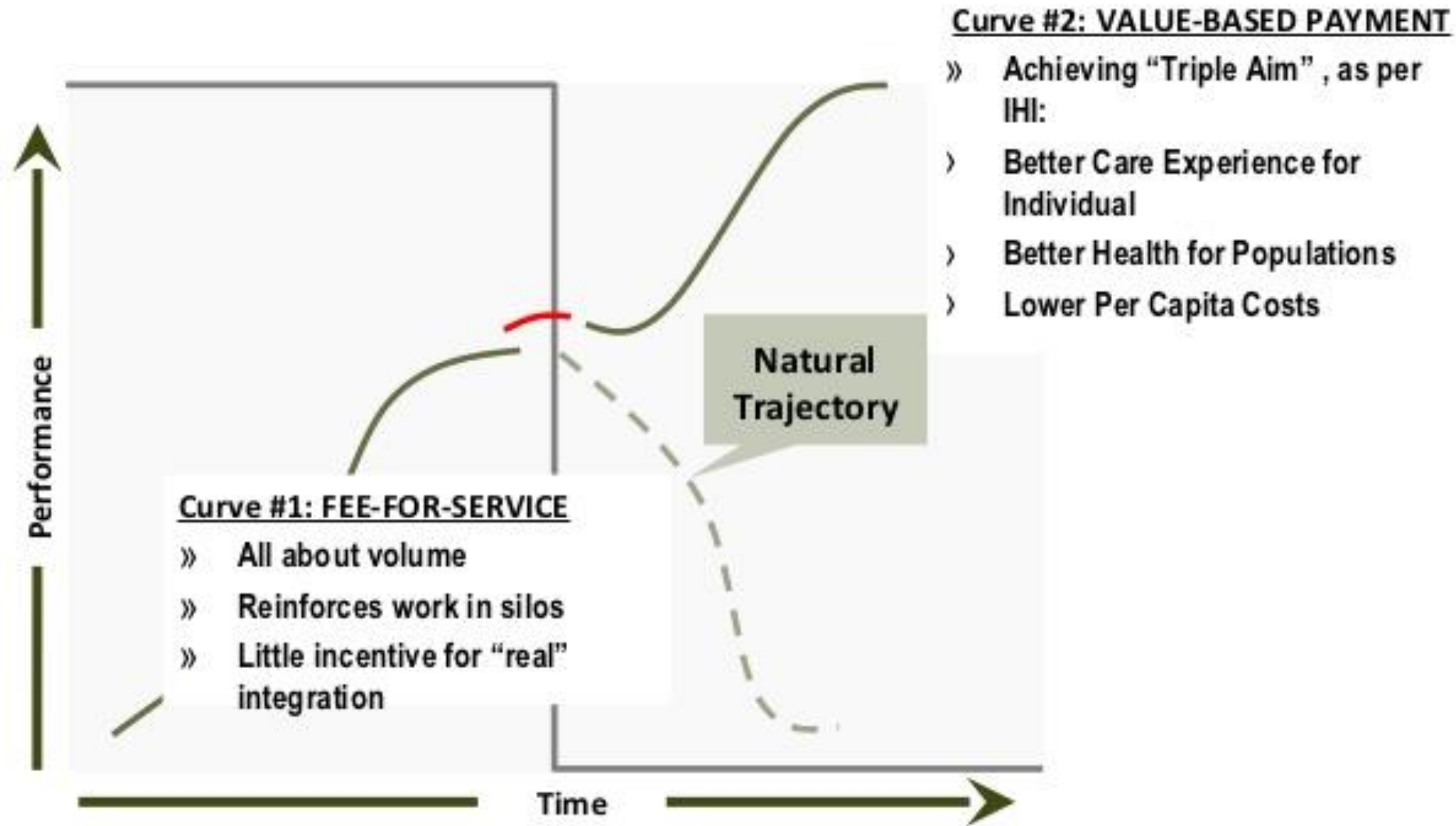


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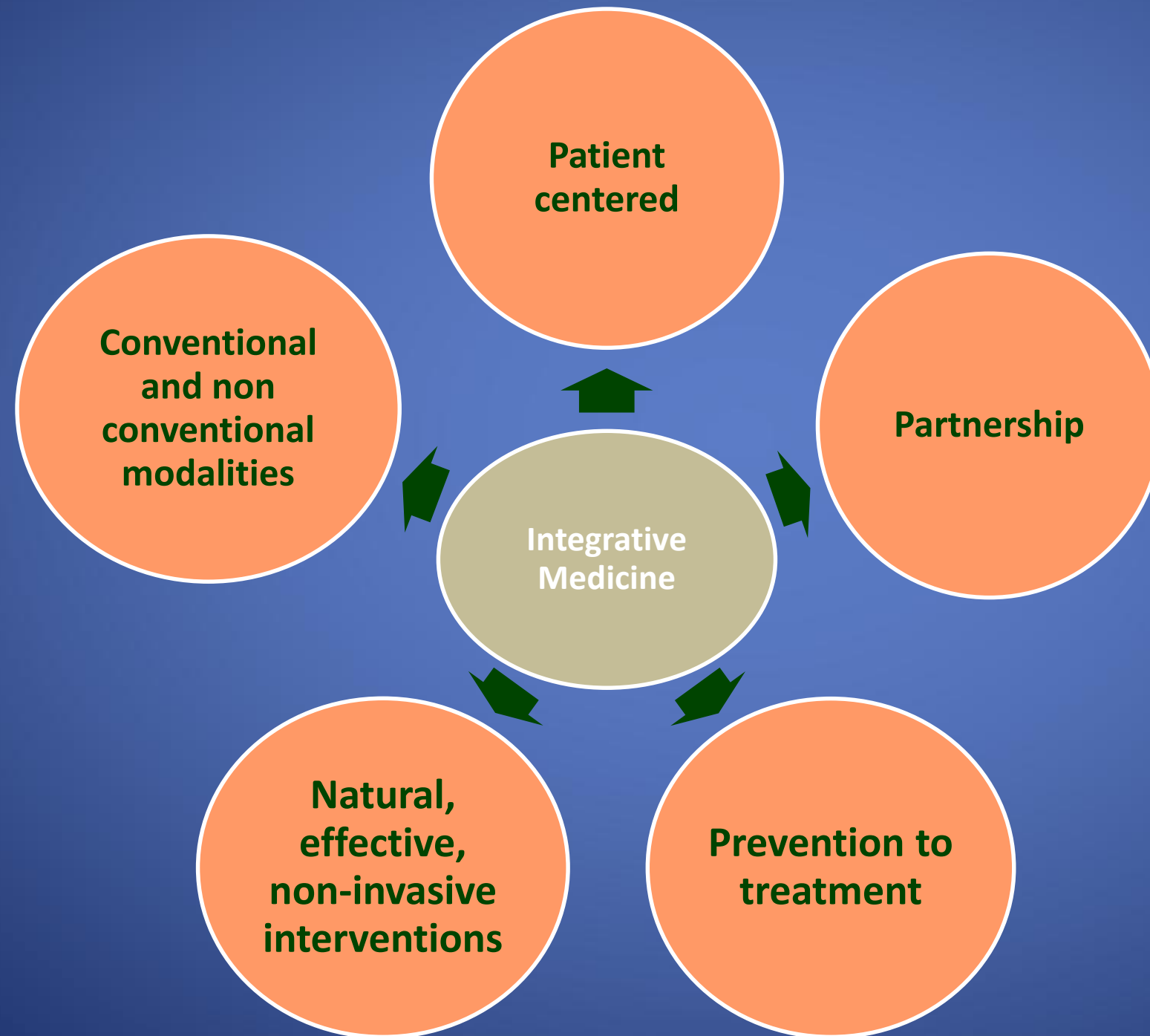
With My
Medical Degree **a**

Health Delivery Systems All Confront The Need To *Jump To The Second Curve*



Courtesy of Navigant. Source: Institute for Health Improvement, Ian Morrison and NCI analysis .

Integrative Medicine - Attributes



High Tech and High Touch



“When you are treating thousands of patients, little differences save lives.”

- Dr Clifford Hudis FLASCO Fall 2017

Prevalence of Integrative Medicine - Driver

- Many Americans, nearly 40 percent, use health care approaches developed outside of mainstream Western, or conventional, medicine for specific conditions or overall well-being.



Integrative Medicine – Driven by Consumers

- According to a recent survey by the American Hospital Association and the Samueli Institute, a nonprofit research group focusing on complementary medicine, 42 percent of the 714 hospitals that responded offered at least one such therapy in 2010, a significant jump over just five years earlier, when 27 percent of hospitals offered such treatments.

Andrews, Michelle; *Hospitals Offering Complementary Medical Therapies*. Kaiser Health News, Nov 15 2011.

Complementary and Alternative Medicine Use in Minority and Medically Underserved Oncology Patients: Assessment and Implications.

Jones D¹, Cohen L¹, Rieber AG¹, Urbauer D¹, Fellman B¹, Fisch MJ², Nazario A¹.

RESULTS:

- Patients (n = 165) reported a high awareness and use of CAM therapies. CAM use was highest for prayer (85%), relaxation (54%), special diet (29%), meditation (19%), and massage (18%). Patients' interest in using CAM was high for nearly all therapies. Lack of adequate knowledge and cost of use were reported as deterrents to use. Female patients reported higher use of aromatherapy relative to males (37.1% vs 19.4%, $P = .02$); those with higher education reported greater use of relaxation (60.8% vs 28.6%, $P = .02$); non-Hispanics reported higher use of relaxation relative to Hispanics (63.5% vs 44.2%, $P = .03$), and African American patients reported higher use of relaxation relative to White patients (69.2% vs 50%, $P = .03$).

Patient-physician communication about complementary and alternative medicine in a radiation oncology setting.

Ge J¹, Fishman J, Vapiwala N, Li SQ, Desai K, Xie SX, Mao JJ.

- RESULTS:
- Among the 305 participants, 133 (43.6%) reported using CAM, and only 37 (12.1%) reported discussing CAM therapies with their radiation oncologists.
- In multivariate analyses, female patients (adjusted odds ratio [AOR] 0.45, 95% confidence interval [CI] 0.21-0.98) and patients with full-time employment (AOR 0.32, 95% CI 0.12-0.81) were less likely to discuss CAM with their radiation oncologists. CAM users (AOR 4.28, 95% CI 1.93-9.53) were more likely to discuss CAM with their radiation oncologists than were non-CAM users.

Huang Di “The Yellow Emperor”



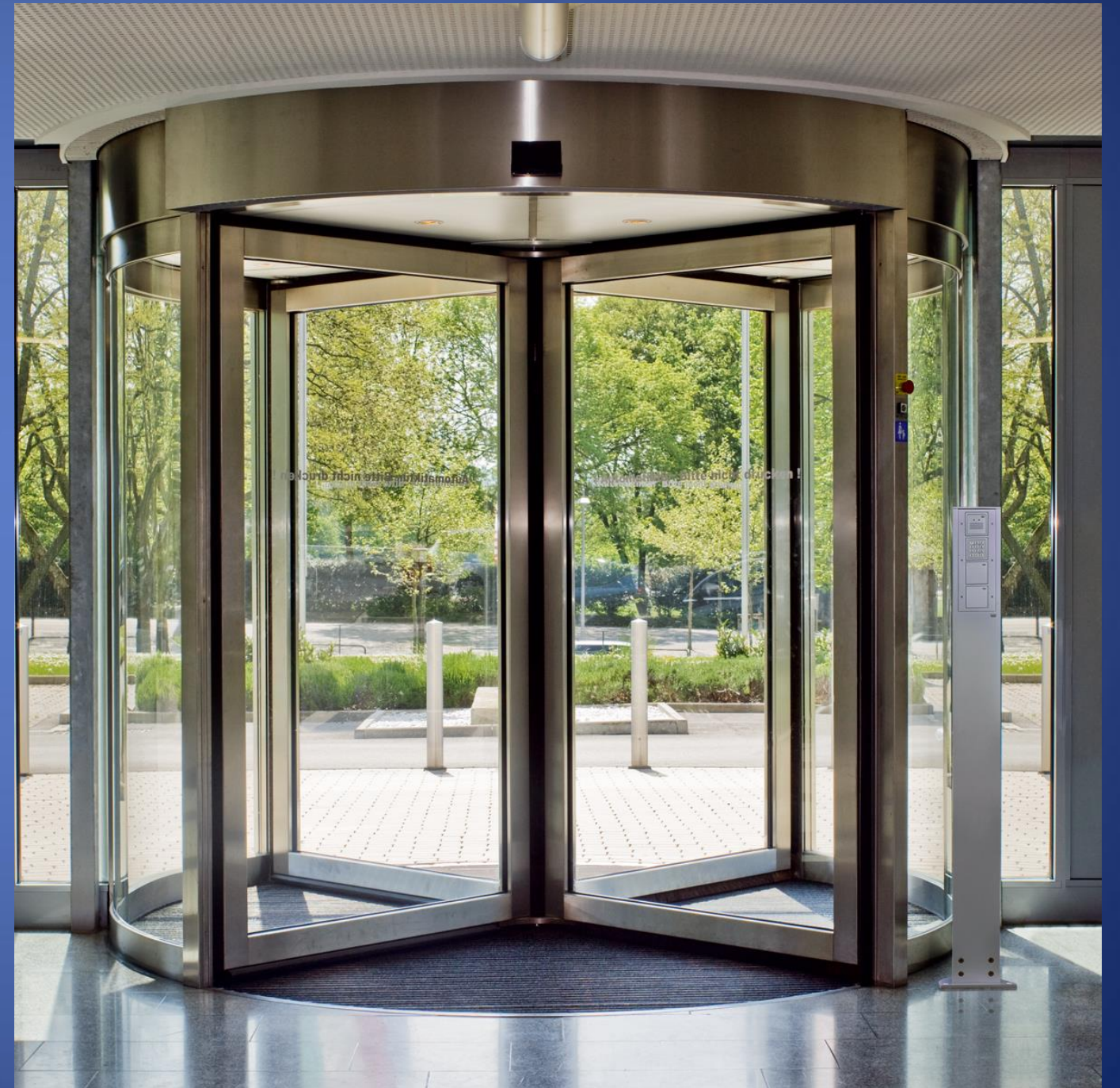
The Canon of Chinese Medicine 2,600 B.C.

Symptom Clusters During Cancer Treatment

- Fatigue
- Weight loss/gain
- Poor sleep quality
- Depression
- Anxiety
- Neuropathy
- Cognitive slowing
- Pain
- Physical deconditioning

Integrative Medicine at Memorial

- Physician consultation
- Nutrition
- Exercise
- Acupuncture
- Massage
- Yoga
- Mindfulness
- Music/Art Therapy
- Group Programs



AICR Recommendations to Reduce Cancer Risk

- Be as lean as possible without becoming underweight
- Be physically active for at least 30 minutes every day

Obesity-Associated Malignancies

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

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

Body Fat Increases CA Risk

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

AICR Recommendations to Reduce Cancer Risk

- Avoid sugary drinks
- Limit consumption of energy dense foods
- Particularly processed foods high in added sugar, low in fiber or high in fat

AICR Recommendations to Reduce Cancer Risk

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

Let your food be your medicine -

Hippocrates



Nutritional Risk Reduction Strategies

- Cruciferous vegetables – Indole 3 Carbinol
- Asian Mushrooms - AHCC
- Turmeric and ginger - Curcuminoids
- Green tea - EGCG
- Vitamin D

Benefits of a Plant-based diet

- A double-blind, placebo-controlled randomized trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer.
- Thomas R, et al. Prostate Cancer Prostatic Dis. 2014 Jun;17(2):180-6. doi: 10.1038/pcan.2014.6. Epub 2014 Mar 11.

Baseline characteristics

	<i>FSG (134)</i>	<i>PG (65)</i>
Age (mean years)	71.8	76.4 ^a
PSA (mean $\mu\text{g l}^{-1}$)	6.5	6.5
Gleason grade ≤ 7	127 (95%)	57 (88%)
Gleason grade > 7	7 (5%)	8 (12%)
Gleason grade mean ($\mu\text{g l}^{-1}$)	6.5	6.2
BMI (mean kg m^{-2})	28.1	28.3
Cholesterol (mean mmol l^{-1})	4.87	4.72
BP (mean systolic/diastolic mm Hg)	146/83	150/82
Serum glucose (mean mmol l^{-1})	5.15	5.30
C-reactive protein (mean mg l^{-1})	1.51	1.74

Table 1

Summary of baseline characteristic in the randomly assigned groups

Enrollment
Allocation
Follow-up
Analysis

Assessed for eligibility (n = 288)

Excluded (n = 5)
Not meeting inclusion criteria (n = 1)
Refused to participate (n = 4)
Other reasons (n = 0)

Randomized (n = 283)

Allocated to intervention (n = 136)
Received intervention (n = 134)
Did not receive intervention (n = 2)

Allocated to intervention (n = 67)
Received intervention (n = 65)
Did not receive intervention (n = 2)

Lost to follow-up (n = 0)
Discontinued intervention (n = 0)

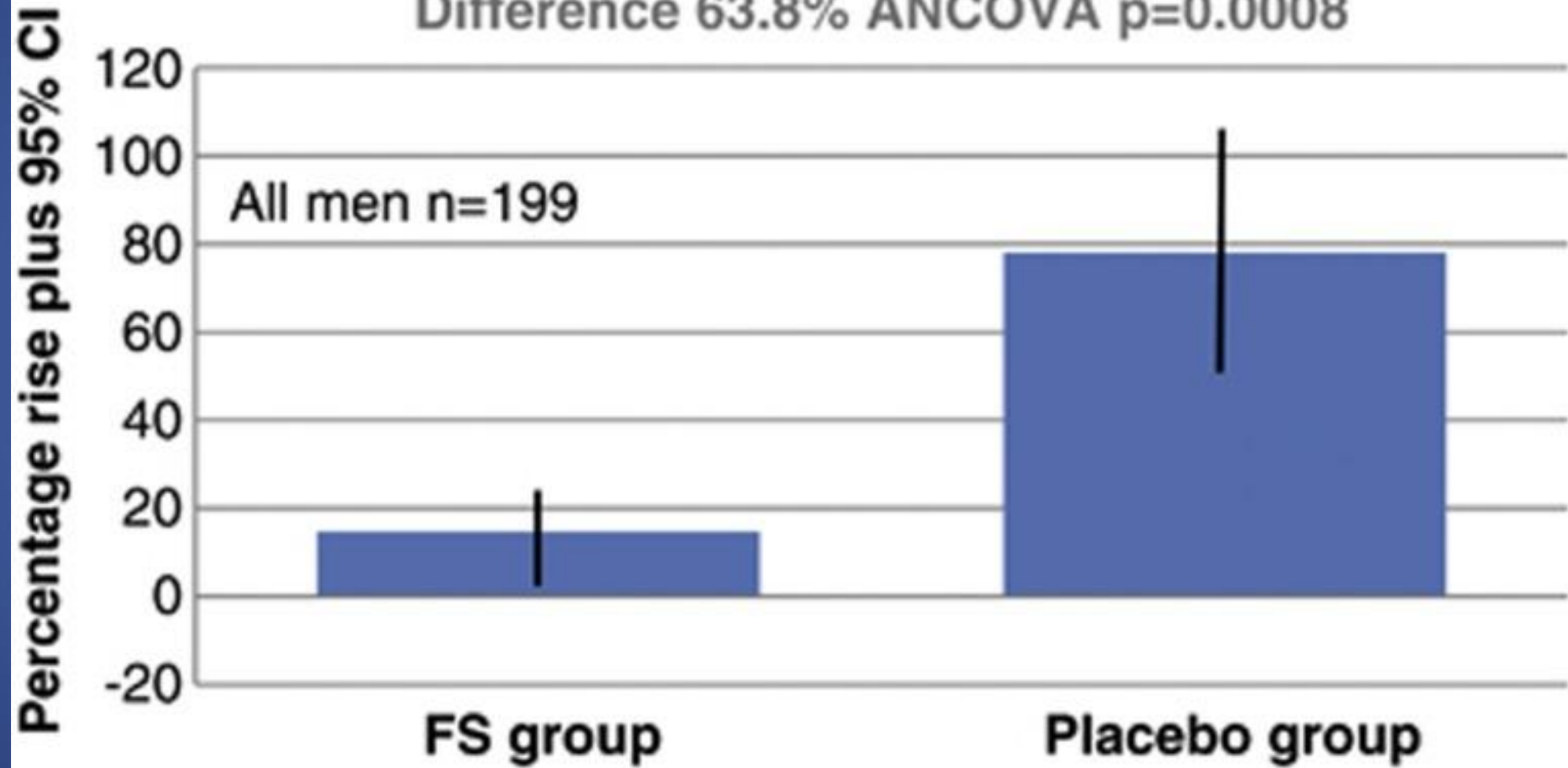
Lost to follow-up (n = 0)
Discontinued intervention (n = 0)

Analyzed (n = 134)
Excluded from analysis (n = 0)

Analyzed (n = 65)
Excluded from analysis (n = 0)

Median percentage PSA change - all men

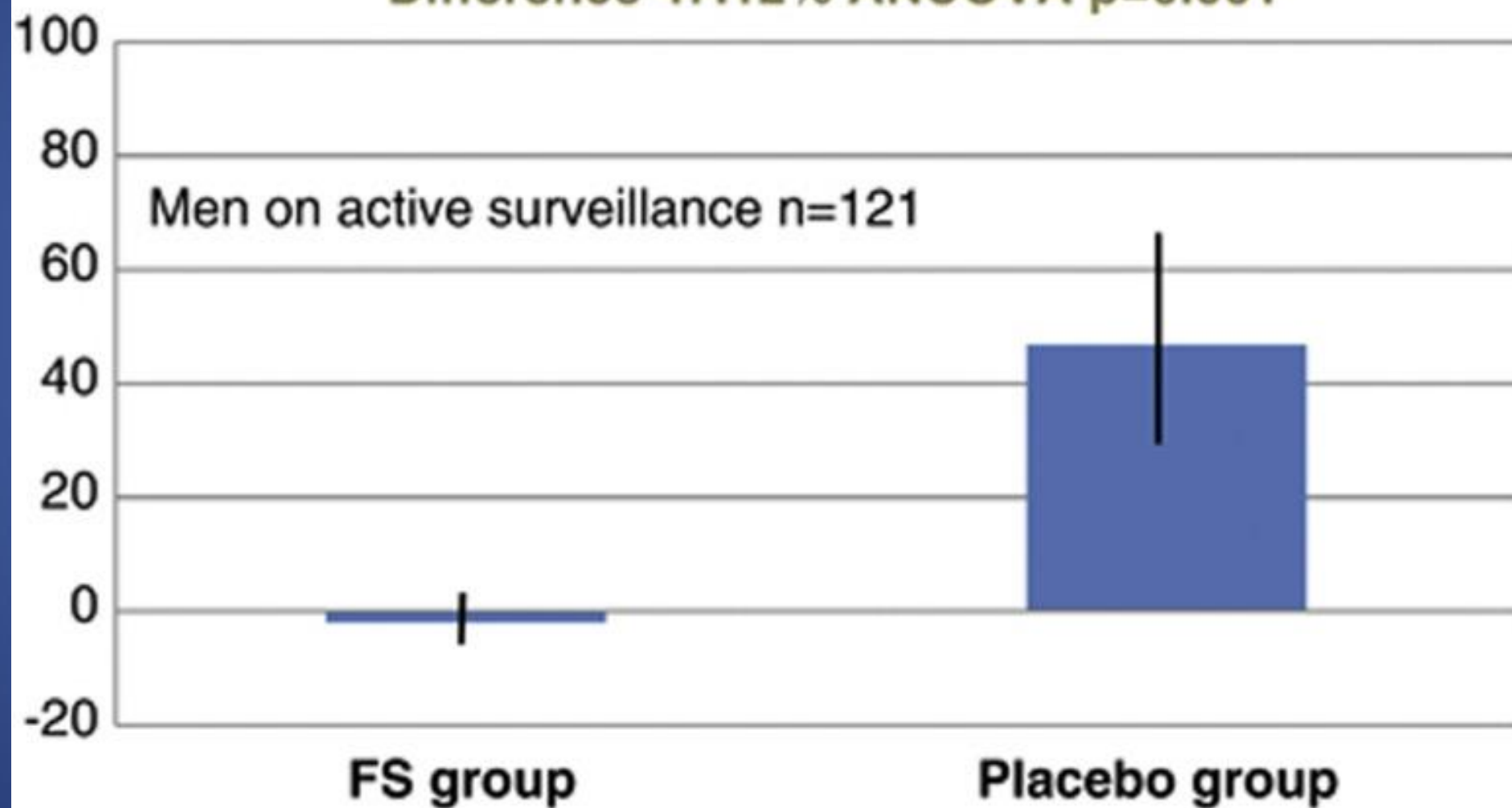
Difference 63.8% ANCOVA p=0.0008



Key: FS = Food supplement, ANCOVA = Analysis of covariance,
— = 95% confidence intervals

Median percentage change in PSA (AS)

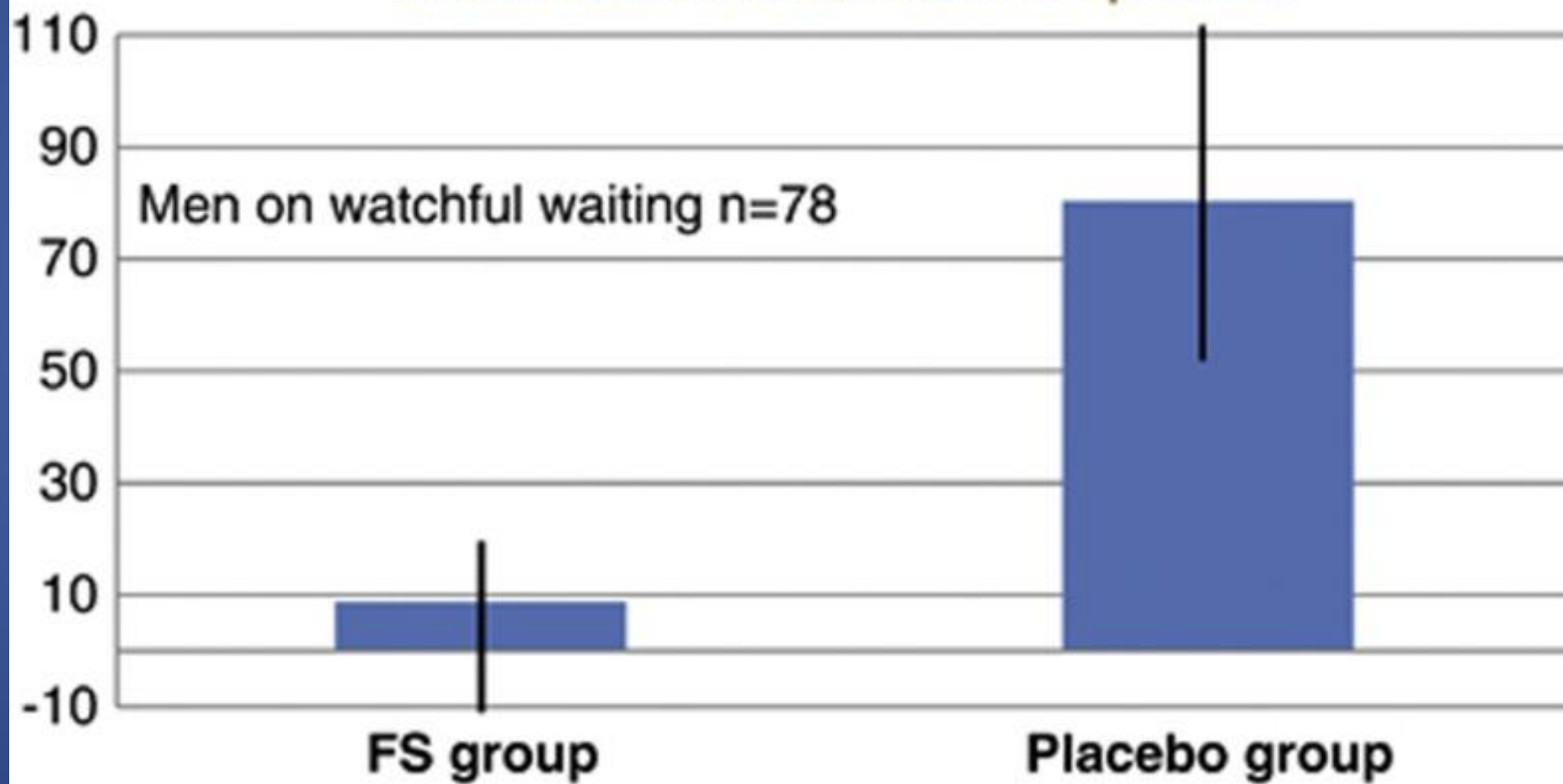
Difference 47.12% ANCOVA p=0.001



Key: FS = Food supplement, ANCOVA = Analysis of covariance,
— = 95% confidence intervals

Median percentage change in PSA (WW)

Difference 71.56% ANCOVA p=0.001



Key: FS = Food supplement, ANCOVA = Analysis of covariance,
— = 95% confidence intervals

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

Journal

Journal of Dietary Supplements >

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REVIEW

Cancer Related to Herbs and Dietary Supplements: Online Table of Case Reports. Part 5 of 5

Amy C. Brown , PhD, RDN

Pages 1-26 | Published online: 05 Oct 2017

- Current listing of potentially life-threatening, cancer-related dietary supplements (DSs; includes herbs) based on PubMed case reports
- Summarized in online tables that can now be updated continually to forewarn United States consumers, clinicians, and DS companies.
- Documented PubMed case reports were used to create a “Toxic Table” related to cancer (1966 to April 2016, and cross-referencing). Keywords included “herb” or “dietary supplement” combined with “cancer” as well as the specific herb “name” combined with “cancer” and sometimes “toxicity.”

- Excluded were herb combinations (some exceptions), Chinese herb mixtures, teas of mixed herb contents, fungi (mycotoxins from molds and mushrooms), poisonous plants, self-harm, excessive doses (except vitamins/minerals), legal or illegal drugs, drug–herb interactions, and confounders of drugs or diseases related to cancer.
- Also included were a few foods related to cancer. Over the past 50+ years, PubMed case reports revealed an increased risk of cancer related to approximately one herb (**guang fang ji**), no dietary supplements (except those containing guang fang ji or aristolochic acid), and two foods (bracken fern, which is sometimes sold as an herbal supplement, and hot maté).

- This online “Toxic Table” can now be continually updated to assist researchers and clinicians in preventing serious adverse events from DSs related to cancer.

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**

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

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**

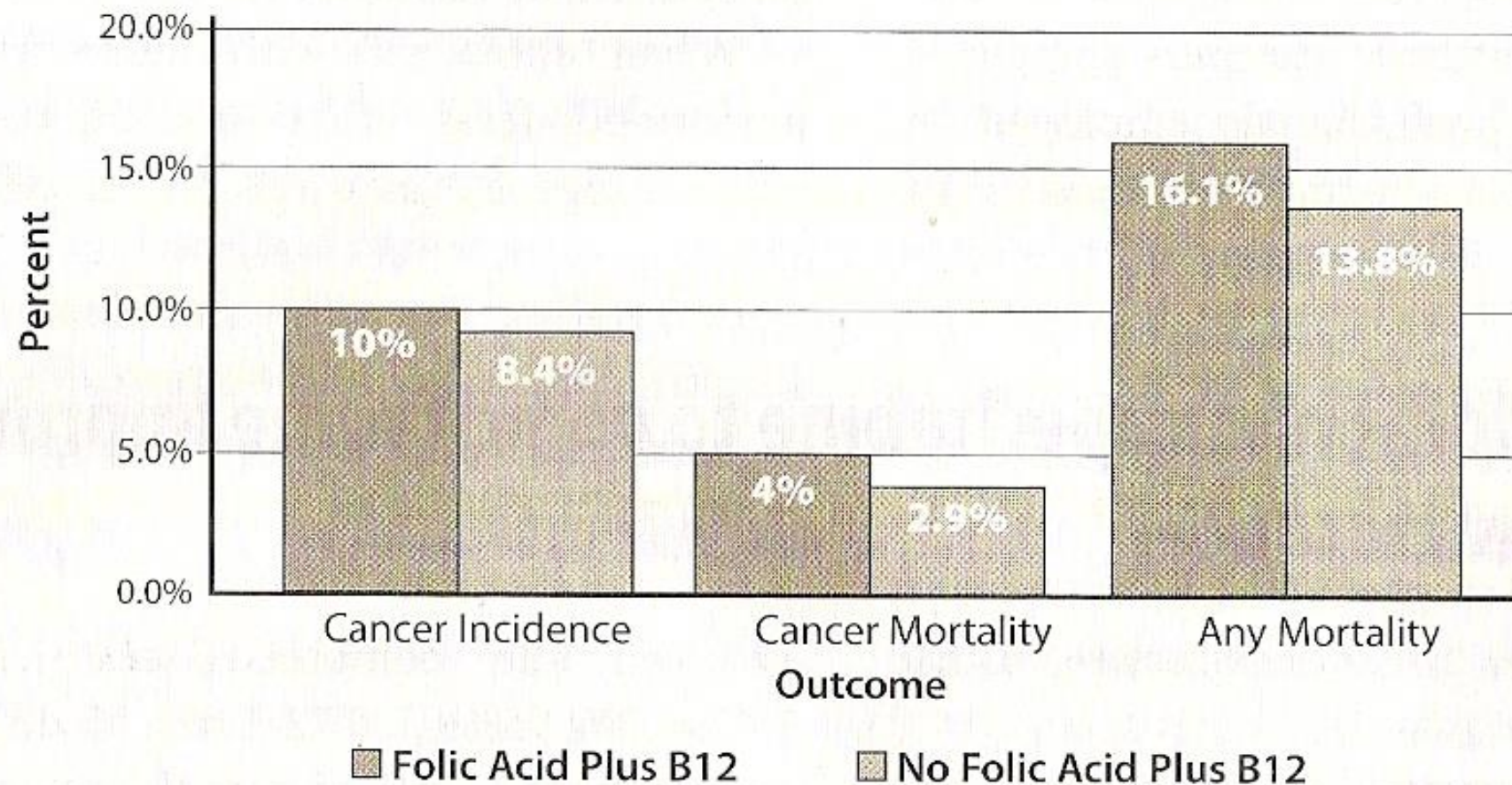
Folic Acid & B12 in Norway

- 6837 people with ischemic heart disease treated with B vitamins or placebo 1998-2005 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

Vitamin B12 and Folate

Folic Acid Plus B12 Linked to Increased Cancer Outcomes, Mortality in Norway



Source: Gil T. *Cancer*. 2009;doi:10.1002/cncr.24638.

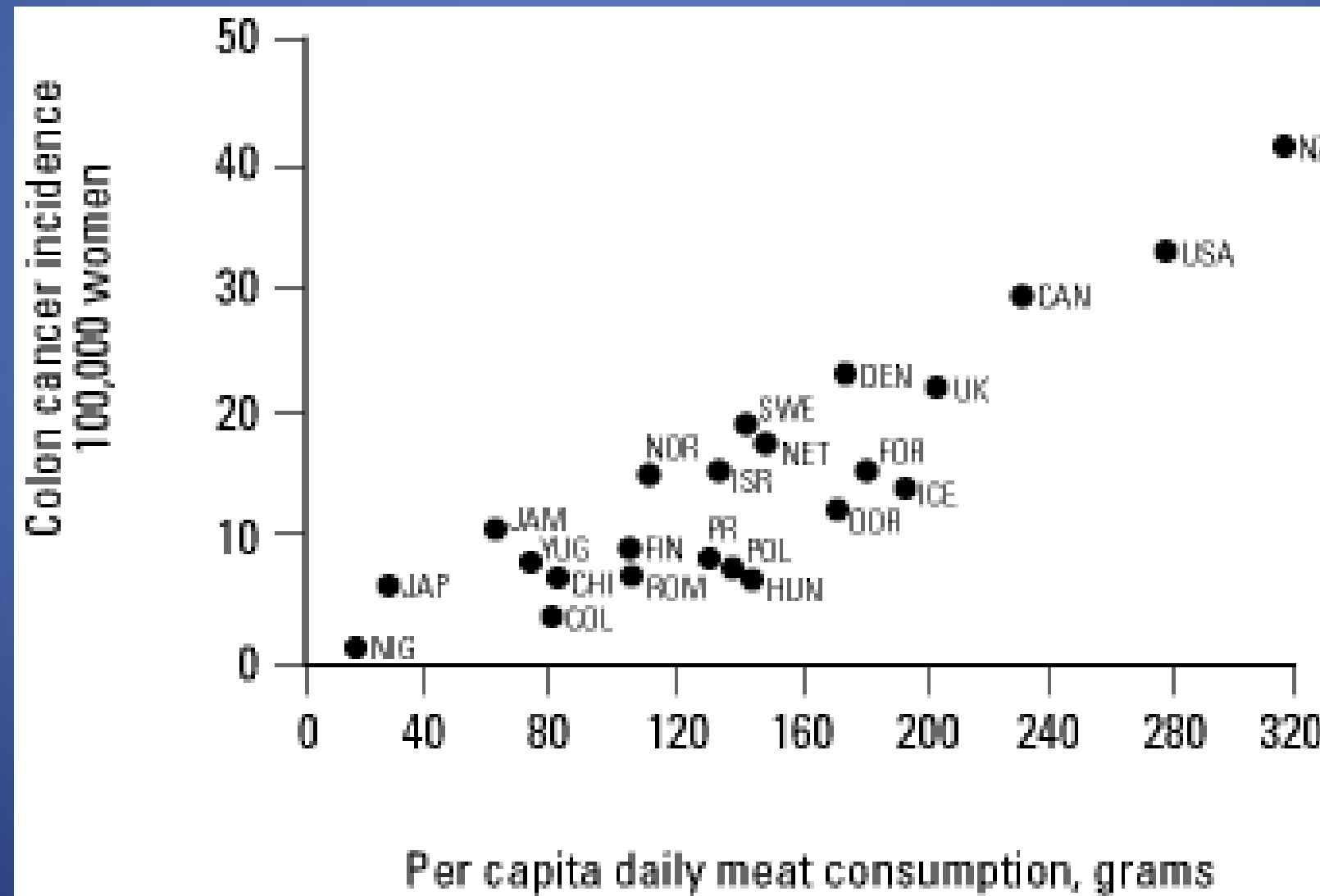
Results mainly driven by increased lung cancer incidence with B vitamins

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 increased breast cancer risk)
- **Don't use supplements to protect against cancer**
- After Rx, cancer survivors should follow the recommendations for cancer prevention

AICR Recommendations to Reduce Cancer Risk

Limit consumption of red meats (beef, pork and lamb) and avoid processed meats



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:

- Strongly Oxidative Chemo

- Cisplatin
- Alkylating agents
- Cyclophosphamide
- Ifosfamide
- Melphalan
- Antitumor antibiotics
- Doxorubicin
- Daunorubicin
- Bleomycin

- Antioxidants:

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

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 - anticoagulation

- CYP3A inhibition

Ginkgo

Piperine

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
- > 50 ng/mL optimal

Vitamin D3 (Cholecalciferol)

Deficiency linked to increased incidence of certain cancers
(**breast, prostate, colon, pancreas**)

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

Vitamin D in Colon Cancer

- Retrospective study of baseline vitamin D levels in newly diagnosed 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

Quality of Supplements Varies

- USP – United States Pharmacopoeia, NSF
 - Third party, batch to batch verification of quality
 - Authenticity, Purity, Potency



Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as Adjunctive Therapy in Advanced Cancer Patients With Chronic Uncontrolled Pain.

Lichtman AH¹, Lux EA², McQuade R³, Rossetti S³, Sanchez R³, Sun W³, Wright S⁴, Komyejeva E³, Fallon MT⁵.

⊕ Author information

Abstract

CONTEXT: Prior phase 2/3 studies found that cannabinoids might provide adjunctive analgesia in advanced cancer patients with uncontrolled pain.

OBJECTIVE: To assess adjunctive nabiximols (Sativex[®]), an extract of Cannabis sativa containing two potentially therapeutic cannabinoids (Δ 9-tetrahydrocannabinol [27 mg/mL] and cannabidiol [25mg/mL]), in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy.

METHODS: Phase 3, double-blind, randomized, placebo-controlled trial in patients with advanced cancer and average pain NRS scores ≥ 4 and ≤ 8 despite optimized opioid therapy. Patients randomized to nabiximols (n=199) or placebo (n=198) self-titrated study medications over a 2-week period, followed by a 3-week treatment period at the titrated dose.

RESULTS: Median percent improvements in average pain NRS score from baseline to end of treatment in the nabiximols and placebo groups were 10.7% versus 4.5% (p=0.0854) in the ITT population (primary variable) and 15.5% versus 6.3% (p=0.0378) in the Per Protocol population. Nabiximols was statistically superior to placebo on two of three quality-of-life instruments at week 3 and on all three at week 5. In exploratory post hoc analyses, US patients, but not patients from the rest of the world (ROW), experienced significant benefits from nabiximols on multiple secondary endpoints. Possible contributing factors to differences in nabiximols efficacy include: 1) the US participants received lower doses of opioids at baseline than the ROW; and 2) the subgroups had different distribution of cancer pain types, which may have been related to differences in pathophysiology of pain. The safety profile of nabiximols was consistent with earlier studies.

Nanoparticle Drones to Target Lung Cancer with Radiosensitizers and Cannabinoids.

Ngwa W^{1,2}, Kumar R^{1,3}, Moreau M^{1,2}, Dabney R⁴, Herman A⁴.

Author information

Abstract

Nanotechnology has opened up a new, previously unimaginable world in cancer diagnosis and therapy, leading to the emergence of cancer nanomedicine and nanoparticle-aided radiotherapy. Smart nanomaterials (nanoparticle drones) can now be constructed with capability to precisely target cancer cells and be remotely activated with radiation to emit micrometer-range missile-like electrons to destroy the tumor cells. These nanoparticle drones can also be programmed to deliver therapeutic payloads to tumor sites to achieve optimal therapeutic efficacy. In this article, we examine the state-of-the-art and potential of nanoparticle drones in targeting lung cancer. Inhalation (INH) (air) versus traditional intravenous ("sea") routes of navigating physiological barriers using such drones is assessed. Results and analysis suggest that INH route may offer more promise for targeting tumor cells with radiosensitizers and cannabinoids from the perspective of maximizing damage to lung tumors cells while minimizing any collateral damage or side effects.

KEYWORDS: cannabinoids; inhalation; intravenous delivery; lung cancer; radiosensitizers; radiotherapy; smart nanoparticles (drones); therapeutic efficacy

Authenticity, Purity, Potency

- Acceptable supplier and contract Brand qualification consisting of: demonstrated cGMP compliance as well as regular on-site audits or established historical relationship. Further, certificate of analyses for Raw Materials and Finished Products are initially validated by conducting full confirmation testing on several subsequent receipts.
- •SOP demonstration of controlled manufacturing processes for all Finished Products and cGMP processes

Authenticity, Purity, Potency

- Use of most appropriate testing methodologies when testing for identity, microbiologicals, heavy metals, pesticides/herbicides (for botanicals), aflatoxins (when applicable), melamine (when applicable), and residual solvents

Future Directions

- Analytical testing on each batch of Raw Material or Finished Product for: identity, potency (label claim) and microbiological contaminants as well as all other applicable analytical tests on ingredients at risk for certain impurities
- •A real time stability program is in use to ensure that all finished products meet label claim throughout shelf life
- •Products contain active ingredients in sufficient quantities to be clinically effective

Integrative Medicine at Memorial

- Provides client-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 Medicine at Memorial

- 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 cure is not

Rationale for the Wellness Model in Cancer 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**

Resources

- MSKCC About Herbs:
 - <https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs/search>
- Natural Medicines Comprehensive Database:
 - <http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=cepd&s=ND&AspxAutoDetectCookieSupport=1>

Contact information:

- asmehta@mhs.net
- Integrative Medicine Clinic:
 - 954-844-9080

Soy Beans

- Numerous nutritional benefits: Isoflavones
 - Daidzein (40%), genistein (50%) and glycetin (10%)
- Essential amino acids
- Fibers
- Poly-unsaturated fatty acids
- Vitamins and minerals

- Isoflavones act as selective estrogen receptor modifiers
- ? Safety of soy products in ER+ women

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 0.48, 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