

# Integrative Oncology: Evidence-Based Supportive Care for Patients during Treatment and Survivorship

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(No Disclosures)

- Objectives:
  - Define Integrative Medicine
  - Describe the role of Integrative Medicine in cancer care and survivorship
  - Present the evidence for nutrition, physical activity, quality sleep, acupuncture and mindfulness recommendations for cancer patients

# Prevalence of CAM

- 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

- 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.

# Integrative Medicine Vs. CAM

- “Complementary and alternative medicine (CAM),”  
“complementary medicine,” “alternative medicine,”
- *“Integrative Medicine”*
- We have all seen these terms on the Internet and in marketing, but what do they really mean?



# Complementary Versus Alternative

- “Complementary” generally refers to using a non-mainstream approach **together with** *conventional medicine*.
- “Alternative” refers to using a non-mainstream approach **in place of** conventional medicine.

# Integrative Medicine

- Unfortunately, some patients gravitate to the use of widely promoted disproved or unproven “alternative” modalities to achieve their goals.
- No less than mainstream cancer therapies in common use, complementary therapies must be evidence-based or, lacking firm evidence, must at least have a rational basis.

# What is Integrative Medicine?

- “Integrative medicine”—increasingly has replaced CAM as a preferred term
- Integrative oncology is a synthesis of mainstream treatment and complementary therapies in cancer care.
  - Noninvasive, nonpharmacologic adjuncts to mainstream treatment that improve patients’ strength and control the physical and emotional symptoms associated with cancer and cancer treatment.
  - Provide patients with a sense of control and self-empowerment at a time when many feel vulnerable and life seems out of control.

Deng, G, Frenkel M, Cohen L, et al: Evidence-based clinical practice guidelines for integrative oncology: Complementary therapies and botanicals. [J Soc Integr Oncol 7:85-120, 2009.](#)



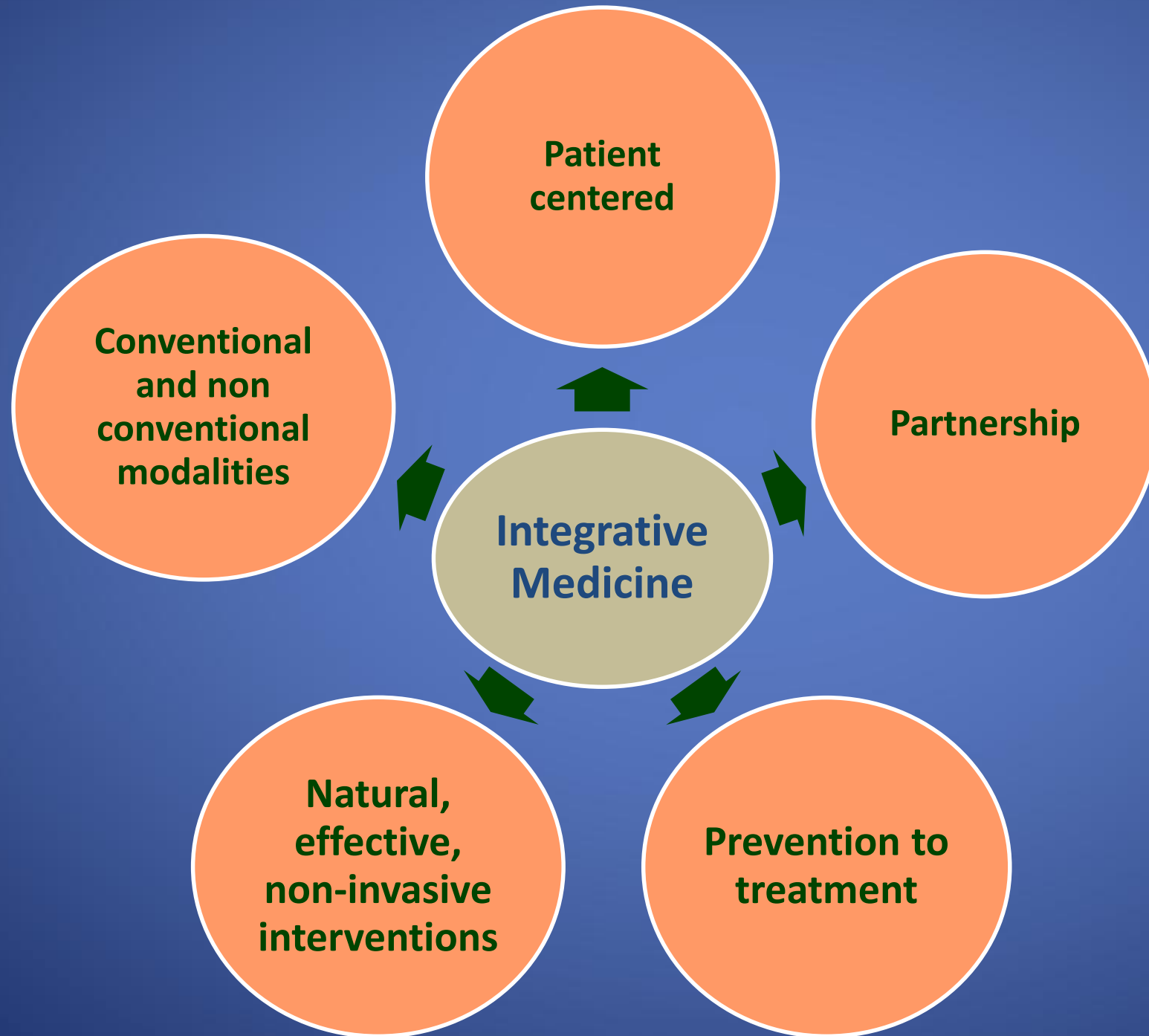
# **Complementary and Alternative Medicine Use in Minority and Medically Underserved Oncology Patients: Assessment and Implications.**

Jones D<sup>1</sup>, Cohen L<sup>1</sup>, Rieber AG<sup>1</sup>, Urbauer D<sup>1</sup>, Fellman B<sup>1</sup>, Fisch MJ<sup>2</sup>, Nazario A<sup>1</sup>.

## 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.

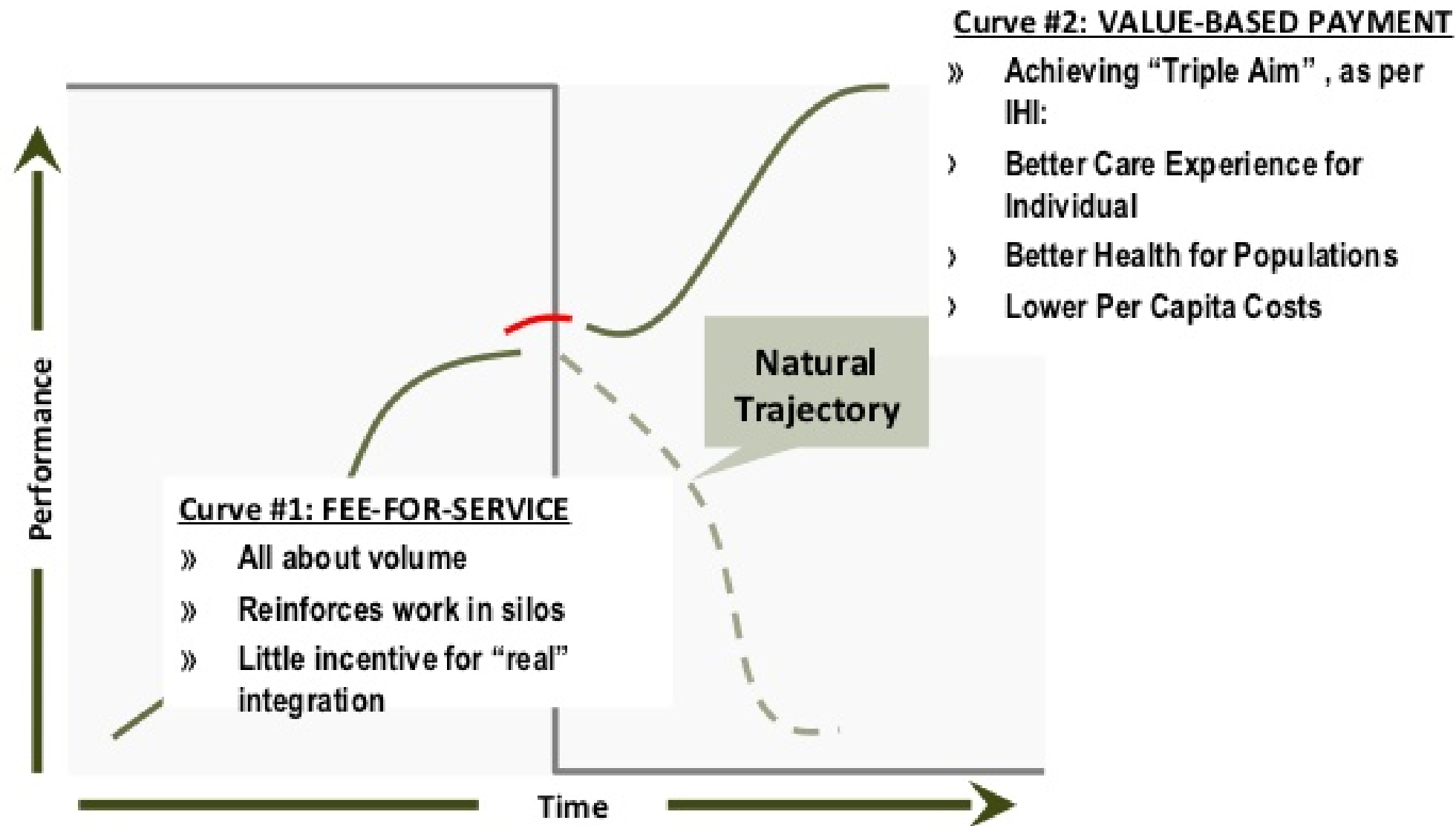
# Integrative Medicine



# Integrative Medicine

- 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

# 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 .

## **A pooled analysis of post-diagnosis lifestyle factors in association with late estrogen-receptor-positive breast cancer prognosis.**

Nechuta S<sup>1</sup>, Chen WY<sup>2,3</sup>, Cai H<sup>1</sup>, Poole EM<sup>2</sup>, Kwan ML<sup>4</sup>, Flatt SW<sup>5</sup>, Patterson RE<sup>5</sup>, Pierce JP<sup>5</sup>, Caan BJ<sup>4</sup>, Ou Shu X<sup>1</sup>.

### **⊖ Author information**

<sup>1</sup>Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, and Vanderbilt-Ingram Cancer Center, Vanderbilt School of Medicine, Nashville, TN.

<sup>2</sup>Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

<sup>3</sup>Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA.

<sup>4</sup>Division of Research, Kaiser Permanente Northern California, Oakland, CA.

<sup>5</sup>Cancer Prevention Program, Moores UCSD Cancer Center, University of California, San Diego, CA.

Associations of **lifestyle factors** with late recurrence and all-cause mortality among 6,295 5-year ER+ Stage I-III breast cancer survivors

Weight gain (>10%), BMI >35, Alcohol intake, Physical activity (<17.4 MET – hr/week), Smoking

**Modifiable lifestyle factors were associated with late outcomes among long-term ER+ breast cancer survivors.**

Int J Cancer. 2016 May 1;138(9):2088-97. doi: 10.1002/ijc.29940. Epub 2015 Dec 9.



## Prolonged Nightly Fasting and Breast Cancer Prognosis.

Marinac CR<sup>1</sup>, Nelson SH<sup>2</sup>, Breen CI<sup>3</sup>, Hartman SJ<sup>4</sup>, Natarajan L<sup>4</sup>, Pierce JP<sup>4</sup>, Flatt SW<sup>3</sup>, Sears DD<sup>5</sup>, Patterson RE<sup>4</sup>.

### ⊖ Author information

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2413 women with breast cancer but without DM, aged 27 to 70 years at diagnosis and participated in the prospective Women's Healthy Eating and Living study between March 1, 1995, and May 3, 2007

Clinical outcomes were invasive breast cancer recurrence and new primary breast tumors during a mean of 7.3 years of study follow-up as well as death from breast cancer or any cause during a mean of 11.4 years of surveillance

Nightly fasting duration was estimated from 24-hour dietary recalls collected at baseline, year 1, and year 4 – sleep duration self reported, archived blood samples used for HgbA1c and CRP

- Fasting < 13 hours per night (lower 2 tertiles of nightly fasting distribution) was assoc with an increase in the risk of breast cancer recurrence compared with fasting 13 or more hours per night (hazard ratio, 1.36; 95% CI, 1.05-1.76)
- Not assoc with higher risk of breast ca mortality or all cause
- Prolonging the length of the nightly fasting interval may be a simple, nonpharmacologic strategy for reducing the risk of breast cancer recurrence. Improvements in glucoregulation and sleep may be mechanisms linking nightly fasting with breast cancer prognosis.

Integr Cancer Ther. 2015 Nov 29. pii: 1534735415617021. [Epub ahead of print]

## **YOCAS® Yoga Reduces Self-reported Memory Difficulty in Cancer Survivors in a Nationwide Randomized Clinical Trial: Investigating Relationships Between Memory and Sleep.**

Janelains MC<sup>1</sup>, Peppone LJ<sup>2</sup>, Heckler CE<sup>2</sup>, Kesler SR<sup>3</sup>, Sprod LK<sup>4</sup>, Atkins J<sup>5</sup>, Melnik M<sup>6</sup>, Kamen C<sup>2</sup>, Giguere J<sup>7</sup>, Messino MJ<sup>5</sup>, Mohile SG<sup>2</sup>, Mustian KM<sup>2</sup>.

Previously showed in a phase III randomized clinical trial that yoga - a program that consists of breathing exercises, postures, and meditation -significantly improved sleep quality in cancer survivors

328 participants from 12 centers who provided data on the memory difficulty item of the MD Anderson symptom inventory included – 8 sessions of yoga for 75 minutes

Sleep quality measured using the Pittsburgh Sleep Quality Index

Yoga significantly reduced patient-reported memory difficulty in cancer survivors

## **Acupuncture As an Integrative Approach for the Treatment of Hot Flashes in Women With Breast Cancer: A Prospective Multicenter Randomized Controlled Trial (AcCliMaT).**

Lesi G<sup>1</sup>, Razzini G<sup>2</sup>, Musti MA<sup>1</sup>, Stivanello E<sup>1</sup>, Petrucci C<sup>1</sup>, Benedetti B<sup>1</sup>, Rondini E<sup>1</sup>, Ligabue MB<sup>1</sup>, Scaltriti L<sup>1</sup>, Botti A<sup>1</sup>, Artioli F<sup>1</sup>, Mancuso P<sup>1</sup>, Cardini F<sup>1</sup>, Pandolfi P<sup>1</sup>.

- 190 women with breast ca randomly assigned and stratified for hormonal therapy
- 12 – week enhanced self care (informational booklet) vs. self care with 10 traditional acupuncture sessions
- Primary outcome: hot flash score (freq X severity)

J Clin Oncol. 2016 May 20;34(15):1795-802. doi: 10.1200/JCO.2015.63.2893. Epub 2016 Mar 28.

- Acupuncture plus enhanced self-care was associated with a significantly lower hot flash score than enhanced self-care at the end of treatment ( $P < .001$ ) and at 3- and 6-month post-treatment follow-up visits ( $P = .0028$  and  $.001$ , respectively).
- Acupuncture was also associated with fewer climacteric symptoms and higher quality of life in the vasomotor, physical, and psychosocial dimensions ( $P < .05$ ).

# JNCI Monograph Nov 2014

## Clinical Practice Guidelines on the Use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer

Searched publications (January 1, 1990–December 31, 2013) and identified 4900 articles, of which 203 were eligible for analysis.

– Greenlee, et al



# JNCI Monograph Nov 2014

## Clinical Practice Guidelines on the Use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer

Meditation, yoga, and relaxation with imagery are recommended for routine use for common conditions, including anxiety and mood disorders (Grade A)

– Greenlee, et al

# JNCI Monograph Nov 2014

## Clinical Practice Guidelines on the Use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer

Stress management, yoga, massage, music therapy and meditation are recommended for stress reduction, anxiety, depression, fatigue, and quality of life (Grade B)

– Greenlee, et al

# JNCI Monograph Nov 2014

## Clinical Practice Guidelines on the Use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer

The majority of intervention/modality combinations ( $n = 138$ ) did not have sufficient evidence to form specific recommendations (Grade I)

# JNCI Monograph Nov 2014

## Clinical Practice Guidelines on the Use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer

Notably, one intervention, acetyl-L-carnitine for the prevention of taxane-induced neuropathy, was identified as likely harmful (Grade H) as it was found to increase neuropathy.

– Greenlee, et al

# Exercise in Cancer Care

**Effects of a Physical Activity Behavior Change Intervention on Inflammation and Related Health Outcomes in Breast Cancer Survivors: Pilot Randomized Trial**

Rogers LQ, Fogleman A, Trammell R, Hopkins-Price P, Vicari S, Rao K, Edson B, Verhulst S, Courneya KS, Hoelzer K.

Southern Illinois University (SIU) School of Medicine, Springfield, IL, USA.

# Exercise in Cancer Care

Chronic  
Exercise  
training

Acute, transient  
release of IL-6 with  
resultant increase in  
anti-inflammatory  
mediators with each  
bout of exercise

Beneficial changes  
in body composition  
with resultant  
changes in  
adipokine levels

Decrease in chronic  
systemic  
inflammation

Less fatigue,  
improved sleep  
quality, **reduced risk  
of breast cancer  
recurrence**



# Symptom Clusters

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

# Integrative Medicine in Cancer Care

Nutrition

Exercise

Mindfulness

Sleep

Acupuncture

Massage

Yoga

# AICR Recommendations to Reduce Cancer Risk

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

# U.S. Diets: Lacking in Fruits and Vegetables

- 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
- 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

# 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 <sup>a</sup>
PSA (mean $\mu\text{g l}^{-1}$ )	6.5	6.5
Gleason grade $\leq 7$	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 $\text{kg m}^{-2}$ )	28.1	28.3
Cholesterol (mean $\text{mmol l}^{-1}$ )	4.87	4.72
BP (mean systolic/diastolic mm Hg)	146/83	150/82
Serum glucose (mean $\text{mmol l}^{-1}$ )	5.15	5.30
C-reactive protein (mean $\text{mg l}^{-1}$ )	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)

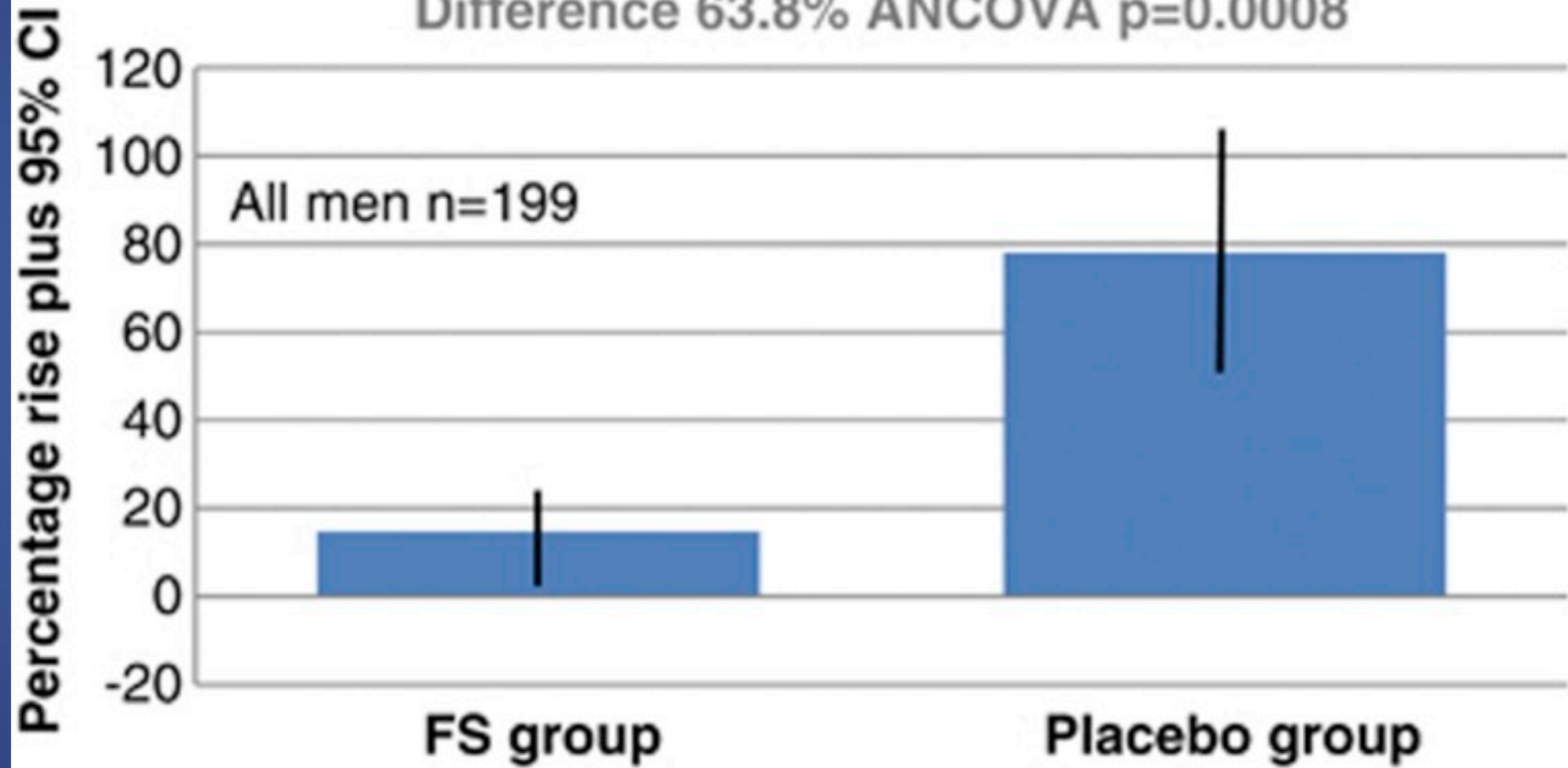
Lost to follow-up (n = 0)  
Discontinued intervention (n = 0)

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

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

### Median percentage PSA change - all men

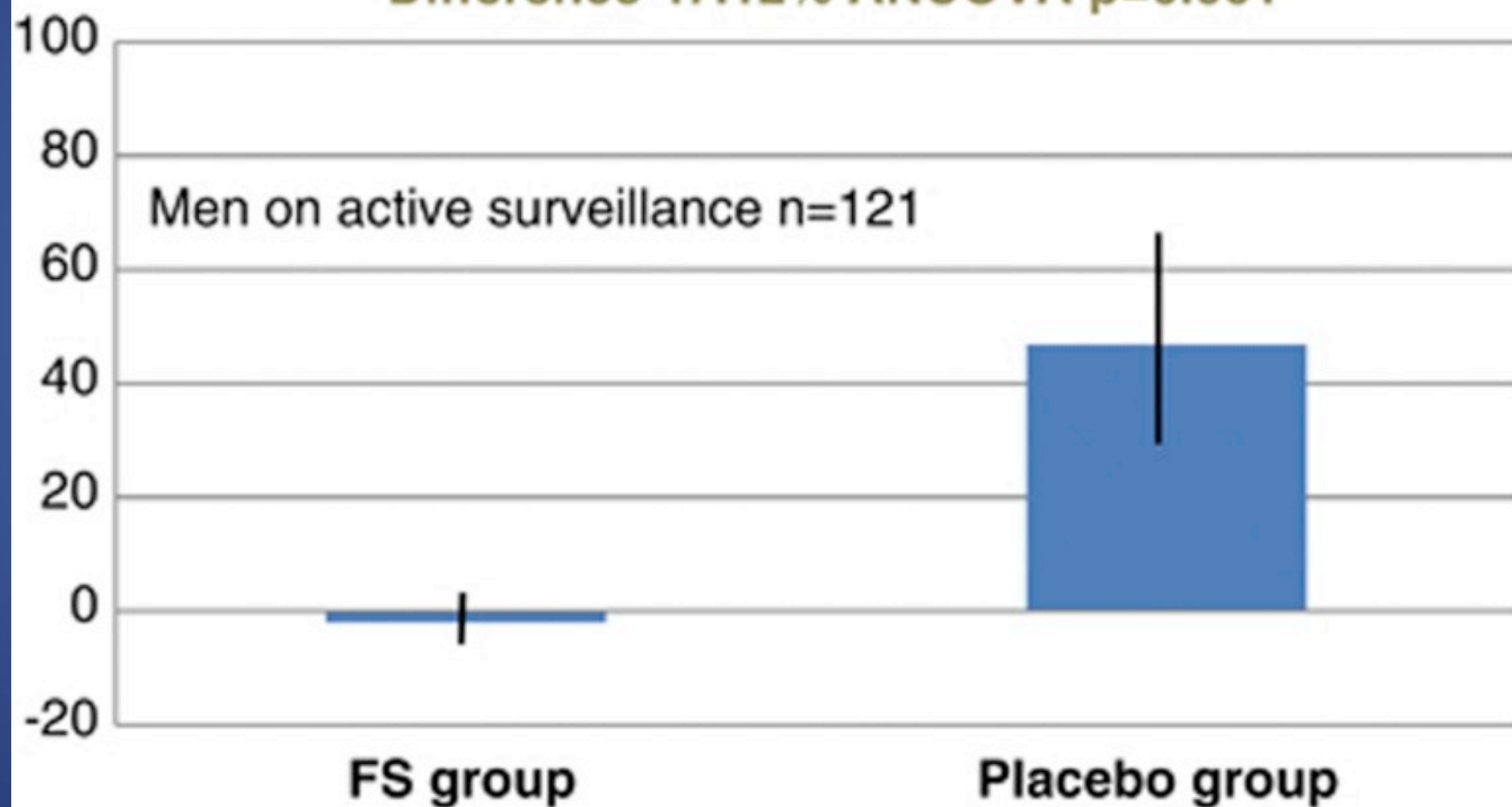
Difference 63.8% ANCOVA p=0.0008



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

### Median percentage change in PSA (AS)

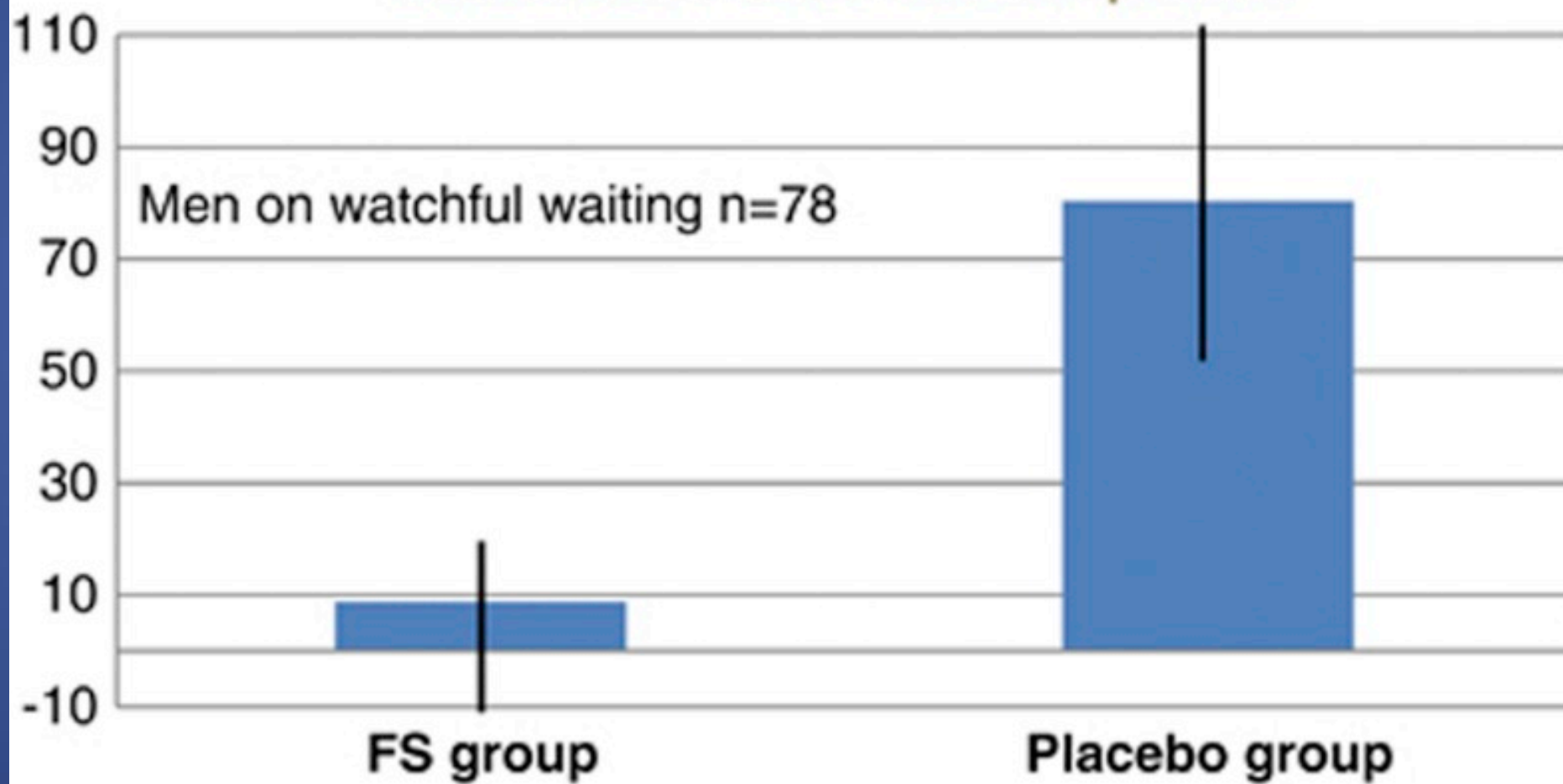
Difference 47.12% ANCOVA p=0.001



**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

# Eat More

- Pomegranate - fruit
- Green Tea - leaf
- Broccoli - flower
- Turmeric - root

# 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

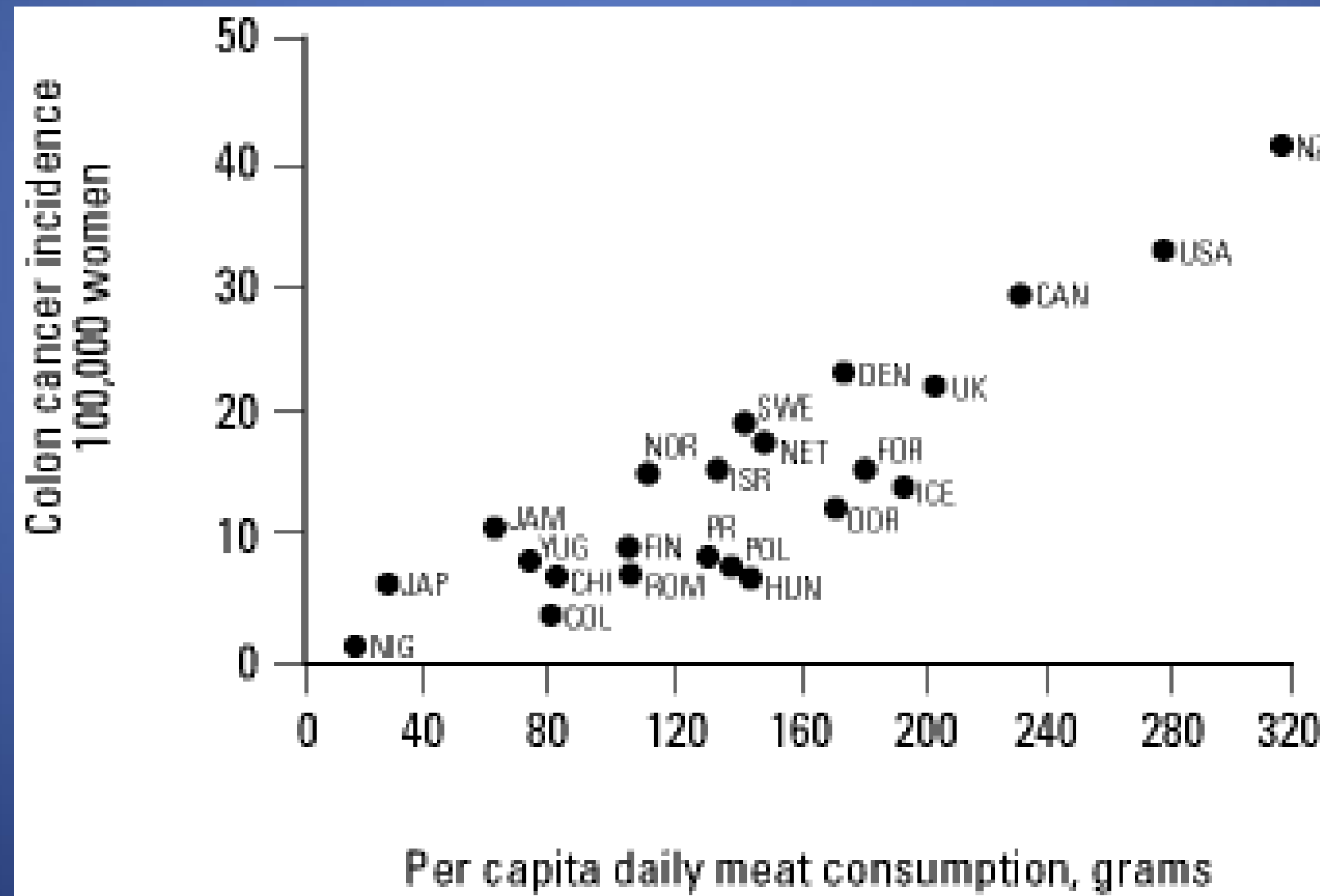
# ADDITIONAL AICR GUIDELINES

- 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

- 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

# 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**

# 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**

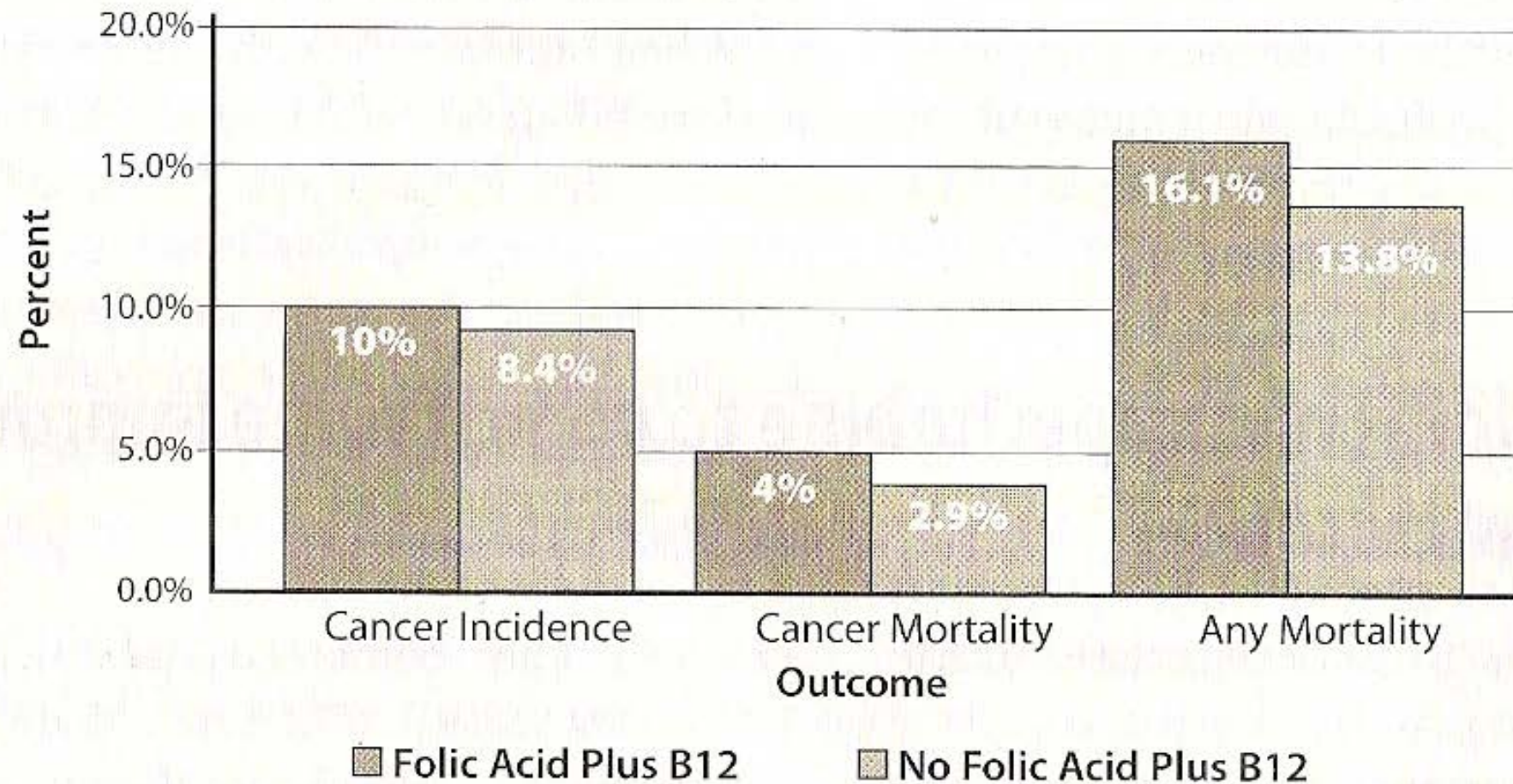
# Folic Acid & B12 in Norway

- 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: *CIT. Cancer*. 2009;doi:10.1002/cncr.24638.

Results mainly driven by increased lung cancer incidence with B vitamins



# 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

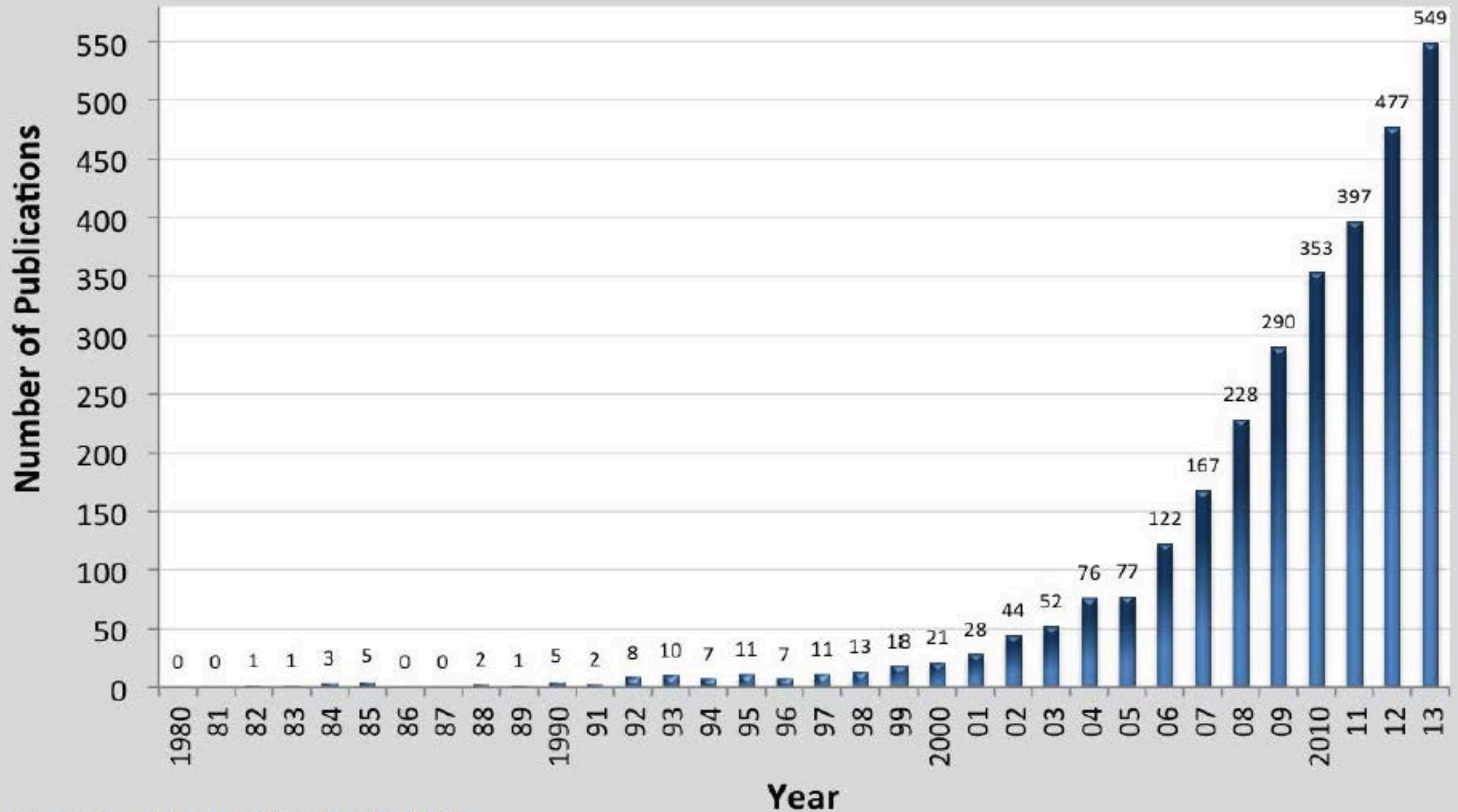
# Vitamin D in Colon Cancer

- 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
  - Third party verification of quality

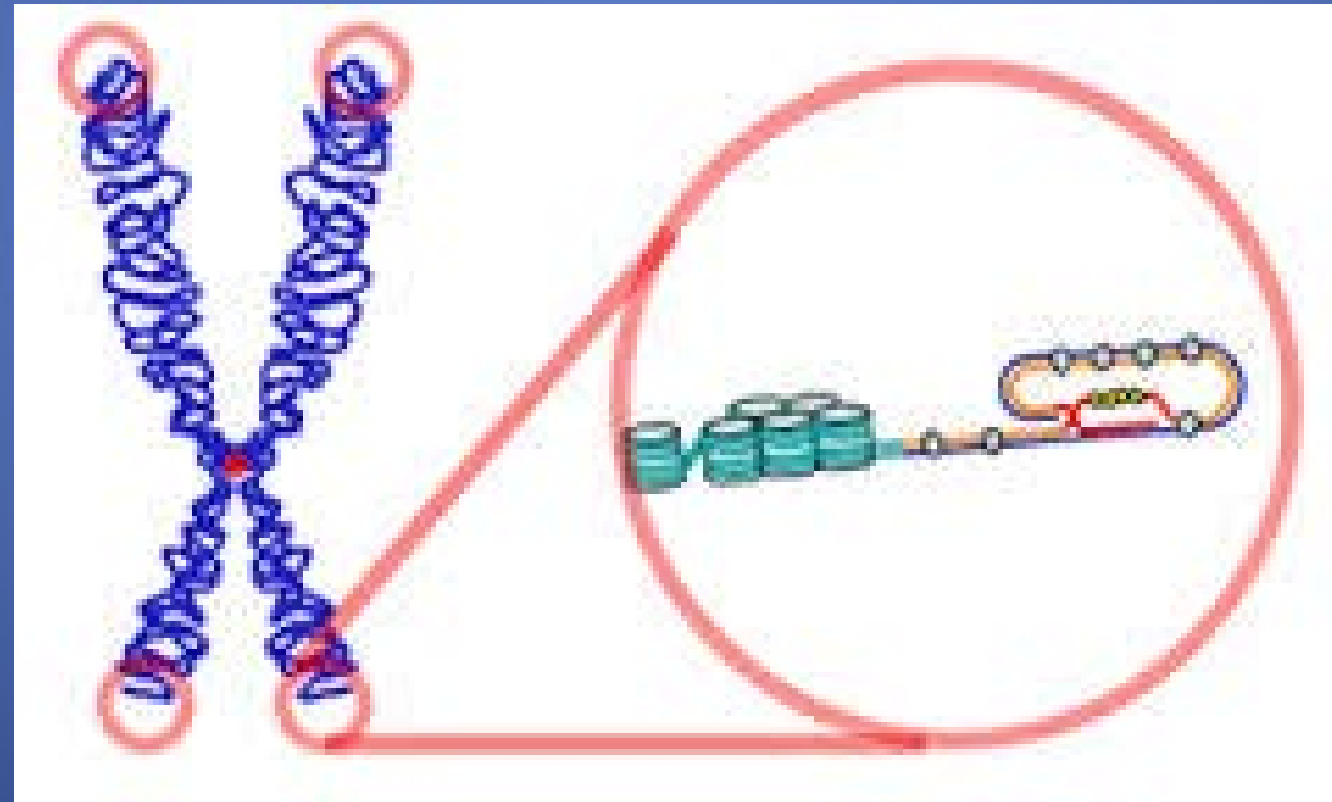
## MINDFULNESS RESEARCH PUBLICATIONS BY YEAR, 1980 - 2013



Source: D.S. Black (2014)

# Mindfulness and Telomeres

- Influence of Mindfulness-Based Stress Reduction (MBSR) on Telomerase Activity in Women With Breast Cancer (BC).



Lengacher CA, et al. Biol Res Nurs, Jan 2014.



# Mindfulness and Telomeres

- Randomized, controlled trial
- 142 breast cancer patients (stage 0-III) after primary treatment – 6 weekly 2 hr sessions
  - Education related to mindfulness
  - Collective practice of meditation
  - Addressing barriers to regular practice
  - Body scan, yoga, walking meditation
- **Increased telomerase activity in meditation group**

# 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**

# Contact information:

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  - 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 acts 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