

Should we allow cancer patients to use supplements Pros and Cons

Dr. Peter Sheng

Objectives

- Explore the reasons why opinion leaders say no to supplements
- Learn how to have a positive conversation on this subject
- Discuss helpful metabolic biomarkers to guide the use of supplements
- Explain how pulse diagnosis guides use of Chinese herbs, a personalized medicine

Why “negative” toward supplements?

Most oncologists not in favor

- Negative or conflicting results from cancer prevention trials through dietary intervention or supplements

It does not matter what you eat?

- Opinion leaders (ASCO, NCCN) said no

Expert opinions

- We did not study in school, MOAs not clear
- Time constraint in clinic
- Quacks/quackery do exist
- Potential herb-drug interactions

some theoretical concern, e.g. antioxidant cancel out chemo-XRT

most publications focus on commonly used:

ginger, ginseng, licorice, St John's worts, grapefruit juice----

Quackery

Ginger: the root of cancer therapy?

A patient recently asked if his bowel cancer was the result of a natural deficiency of selenium in the local soil, since his siblings living near land rich in selenium remained fit and well. To an oncologist involved in scientific research this concept seems difficult to rationalise. After all, how could cancer pathogenesis and treatment be simplified in this way? However, our health is largely influenced by genetics, geography, and culture, and why some people can smoke and consume poor diets and far outlive those who adopt a more healthy lifestyle remains largely unresolved.

Inevitably, some people will develop cancer and some apparently more likely candidates will not. Some

use is reflected by its Indian name "maha aushadhi" meaning "the great medicine", but can these properties be scientifically proven? And, if so, what is the mechanism of action?

Ginger contains two distinct chemical groups. The volatile oils account for the aromatic taste of ginger and consist mainly of sesquiterpene hydrocarbons such as zingiberene and curumene. The spicy taste of ginger is due to non-volatile compounds such as gingerols, shogaols, paradols, and zingerone. Ginger also contains many vitamins, minerals, fats, and a potent enzyme called zingibain that are purported to destroy proteins.

Many laboratory studies with cancer cells or in animals with cancer



Garlic Root/Science Photo Library

Lancet Oncology p235
Vol 13 March 2012

Ginger is thought to have possible chemopreventive and anticancer properties

Calcium, Vitamin D, Dairy Products, and Mortality Among Colorectal Cancer Survivors: The Cancer Prevention Study-II Nutrition Cohort

Baiyu Yang, Marjorie L. McCullough, Susan M. Gapstur, Eric J. Jacobs, Roberd M. Bostick, Veronika Fedirko, W. Dana Flanders and Peter T. Campbell[↑]

Post-diagnosis total calcium intake inversely related to all cause mortality and disease-specific mortality an American cancer society study JCO 2014

Heart 2012;98:920-925 doi:10.1136/heartjnl-2011-301345

Calcium and cardiovascular disease

Original article

Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg)

Editor's choice 

Higher MI risk in CA++
Supplements users

B-Carotene & Lung cancer Prevention

two negative trials

Breast Cancer Track

Intervention Trials on β -carotene

- Beta-Carotene and Retinol Efficacy Trial (CARET)
 - Enrolled 18,314 men and women at high risk of developing lung cancer
 - Randomized to the combination of 30 mg β -carotene and 25 000 IU retinyl palmitate (vitamin A) or placebo
- Alpha-Tocopherol, β -Carotene Cancer Prevention Study
 - Enrolled 29,133 male smokers
 - Randomized to one of 4 groups:
 - Placebo
 - Alpha-tocopherol alone
 - Beta-carotene alone
 - Combination

Omenn et al. N Engl J Med 1996; 334:1150-1155

ATBC Cancer Prevention Study Group. N Engl J Med 1994; 330:1029-1035

ASCO

Clinical Trials: Vitamins and Micronutrients

	ATBC	CARET	SELECT	PHS II Vitamin E / C module	PHS II Low dose multivitamin module
N	29,133	18,314	35,533	14,641	14,641
Duration	8 years	7 years	7 years	10 years	11 years
Outcome	Harm	Harm	No benefit	No benefit	Modest benefit

What Makes the News? *"Supplements are Harmful!"* β -carotene and radiation therapy^{1,2}

RCT, N= 540, Stages I-II head/neck cancer, Rx radiation
 β -carotene, α -tocopherol or placebo.

HRs for recurrence/mortality (p<.05)

Variable	Original
Recurrence	1.86
All-cause mortality	1.38
Cancer mortality	ns

Original data made headline news internationally!

But erroneous conclusion!

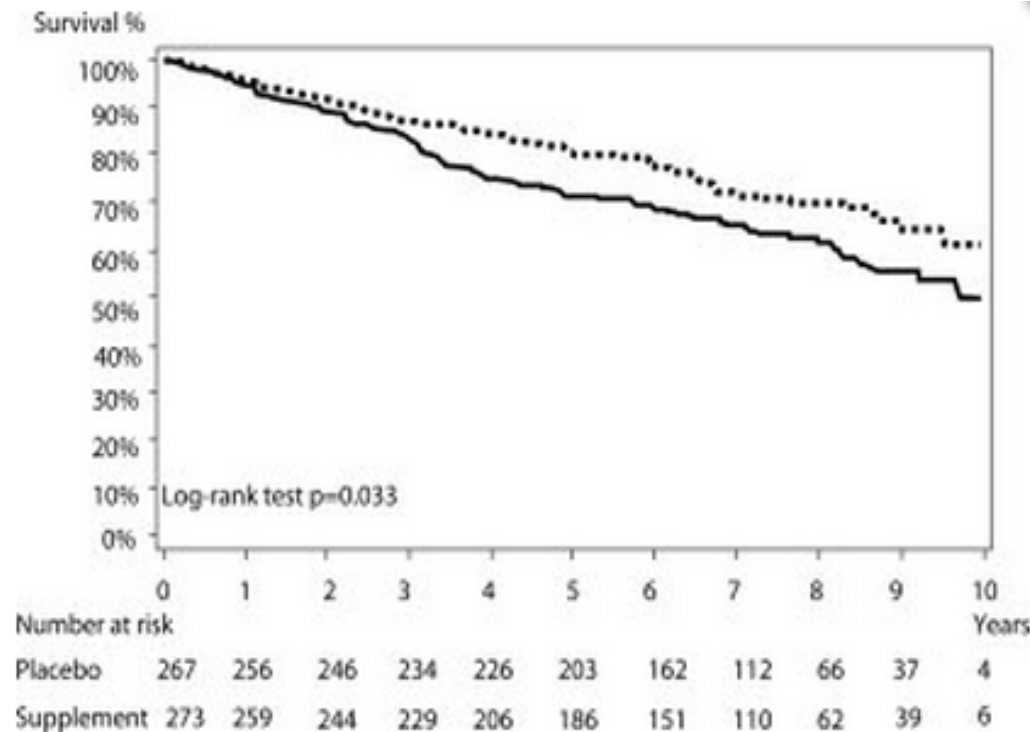


Figure 2. Kaplan-Meier curves of survival until death from any cause among participants randomly assigned to the supplement arm (solid line) or to the placebo arm (dotted line). Data are only shown up to 10 years of follow-up because of the small numbers of participants beyond that time.

540 pts H/N cancer undergoing XRT randomized to 400 IU alpha-tocopherol & 30mg B-carotene for 3 years or placebo. All cause mortality higher in E/A group, HR 1.37

Interpretation of negative trials

- Some walk away with the conclusion
it does not matter what you eat, enjoy life, makes no difference
or, don't do it if it does harm
- Experts in nutrition making a pleading
do not study nutrition like drugs
- Giving a high dose of a vitamin in a nutritionally
depleted individual, it works
as an oxidant, causing more oxidative stress
think of nutrition as whole food nutrition
like a symphony orchestra

Why “yes” for supplements?

- Use is widespread: >60 %
do you tell your teenagers at home not to have a cell phone?
- May do good or harm just like everything else
- Marketing hype, need to help patients
- Need to break down patients into
survivors, active treatment, advanced disease
- Personalized approach not one size fits all
- Living longer & better for all cancer patients
can't do a good job sometimes w/o supplements
- Most of the time, no significant Drug-Herb interaction, except St. John's worts

Suggestion on “physician attitude”

- concern about safety and efficacy
- If limited evidence exists on efficacy, should we discourage pts?
- building a trusting therapeutic relationship
- Physician as a responsive and reliable source of information, an expert guide
- open to pts’ perspectives: empowerment, autonomy
- educate yourself



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- Contraindications
- Adverse Reactions
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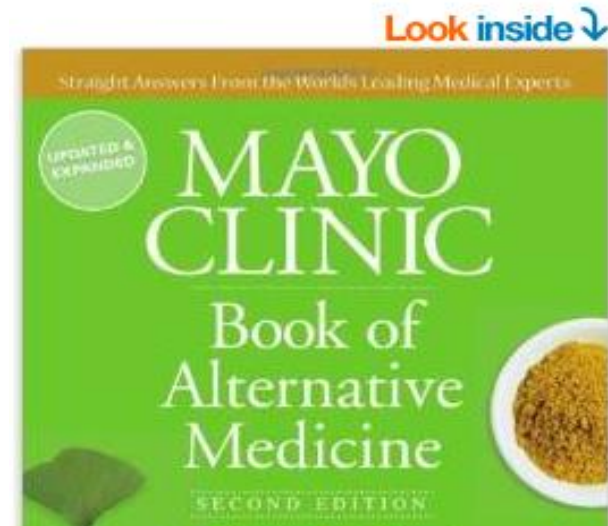
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"Natural Standard has provided just what the doctor ordered - an evidence-based review to tell us what is known, and what is not. Given the clear imperative to talk with our patients about CAM, here's the evidence summary you need."

Harley Goldberg, DO
Medical Director, CAM
Kaiser Permanente

Natural Standard was founded by healthcare providers and researchers to provide high-quality, evidence-based information about complementary and alternative medicine including dietary supplements and integrative therapies. Grades reflect the level of available scientific data for or against the use of each therapy for a specific medical condition.

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Grading System

- A** Strong Positive Scientific Evidence
- B** Positive Scientific Evidence
- C** Unclear Scientific Evidence
- D** Negative Scientific Evidence
- F** Strong Negative Scientific Evidence

Natural Standard provides Decision-support Tools for:

Providers

- Check Interactions & Depletions
- Counsel Patients
- Reconcile LMR

Insurers

- Establish Guidelines
- Maintain Formulary
- Educate Members
- Encourage Prevention

Manufacturers

- Substantiate Claims
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Retailers

- Promote Quality Products
- Generate Loyalty
- Increase ROI

Consumers

- Expert Press Interviews
- Make Safe & Effective Healthcare Decisions
- Trust Provider Recommendations

Evidence-based medicine(EBM)

Do we always need RCT's?
How low can we lower the bar?

Hazardous journey

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

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Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Parachute approach to evidence based medicine

BMJ 2006 ;333 doi: <http://dx.doi.org/10.1136/bmj.333.7570.701> (Published 28 September 2006)

Cite this as: *BMJ* 2006;333:701

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Accepted 19 June 2006

Waiting for the results of randomised trials of public health interventions can cost hundreds of lives, especially in poor countries with great need and potential to benefit. If the science is good, we should act before the trials are done

EBM is to take best care of our patients
Based on the available evidence

How low are we willing to lower the bar?



Sometimes it's best just to jump in

Any RCTs on “smoking & cancer”?

Medscape

Old Medical Advertisements: **THE WORLD WAR II YEARS**

Take a look at these WWII-era medical ads published in the Journal of the American Medical Association, direct-to-physician cigarette ads and all.

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Iletin (Insulin)

Years of research by the manufacturer of Iletin (Lilly) have resulted in methods of preparation that insure perfect coverage. Iletin is a subcutaneous injection, designed as:

- Iletin (Insulin), 100 units per cc., in 10 cc. vials.
- Iletin (Insulin), 500 units per cc., in 2 cc. vials.
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Old Gold
cures
just one thing:
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World's Best
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Challenges facing oncology

- Are we lowering the bar too much
- Toxicity, including a new one: financial
- Quality of life data often missing
- Inability to predict response: biomarkers
- Where is personalized medicine?
- Focusing on the cells, pathways, oncogenic drivers; less on tumor micro-environment & host milieu

Shifting Patterns in the Interpretation of Phase III Clinical Trial Outcomes in Advanced Non–Small-Cell Lung Cancer: The Bar Is Dropping



T

A
F
P
D

Table 1.

Characteristics of Studies Reviewed

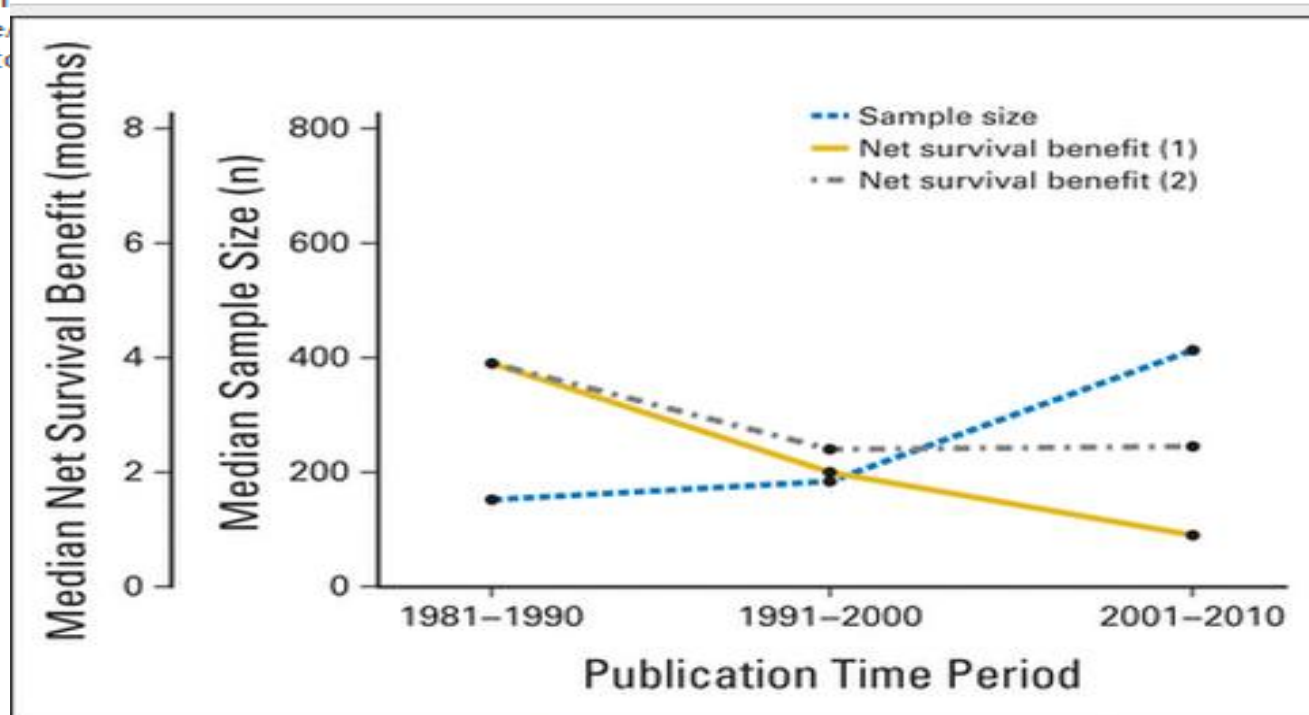
Characteristic	Publication Date					
	1980-1990		1991-2000		2001-2010	
	No.	%	No.	%	No.	%
No. of phase III advanced NSCLC trials identified	32		53		118	
Trial sample size						
Median		152		184		413
Range		38-743		58-680		58-1,725
Mean overall survival across trials, months		6.7		7.9		9.5
Primary end point						
OS	31	97	51	96	96	81
PFS	—	—	—	—	15	13
Other (RR, QOL)	1	3	2	4	7	6
Agent investigated						
Chemotherapy	31	97	43	81	82	69
Singlet	0	0	6	11	16	14
Doublet	12	38	20	38	51	43
Triplet or more	19	59	17	32	15	13
Targeted	0	0	3	3	25	21
Other*	1	3	7	7	11	9
Trials reported as positive	10	31	37	70	88	75
Trials reported as positive for statistically significant improvement in primary survival end point	9	28*	28	53*	38	32*
Trials reported as positive, but did not demonstrate survival benefit	3	9*	9	17*	47†	40*
Trials reported as positive on the basis of:						
Nonsignificant trend in OS	1		—		8	

Shifting Patterns in the Interpretation of Phase III Clinical Trial Outcomes in Advanced Non–Small-Cell Lung Cancer: The Bar Is Dropping

Adrian G. Sacher, Lisa W. Le and Natasha B. Leighl [↑]

+ Author Affiliations

Corresponding author: Natasha B. Leighl, MD, MMSc, Department of Biostatistics, Division of Cancer Control and Prevention, National Cancer Institute, Bethesda, MD, e, 5–105, Toronto



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Fig 1.

Challenges facing oncology

- Statistics, Statistics, Damned Lies

recent editorial in Oncology Times by Dr. D. Reghaven

statistically significant vs. clinically significant

relative or absolute survival benefit

Progression-free survival as end point

well-tolerated treatment ? Reporting of side effects

the new waterfall plot

- The gold standard: Living longer & better

Integrating Dietary Supplements Into Cancer Care

- Curcumin
- Glutamine
- Vitamin D
- Maitake mushroom
- Fish oil
- Green tea
- Milk Thistle
- Astragalus
- Melatonin
- Probiotics

Curcumin

- Major ingredient of Indian spice tumeric
- Anti-inflammatory, chemo-preventive
- Interfere with multiple cell signaling pathways
 - cell cycle (cyclin D1), apoptosis, proliferation, survival, angiogenesis, metastasis, inflammation-----
- Activity against a wide variety of malignancies
- Poor bioavailability, dosage?
- Phase 2 study at M.D. Anderson on pancreatic cancer

MGUS Multiple Myeloma & Curcumin

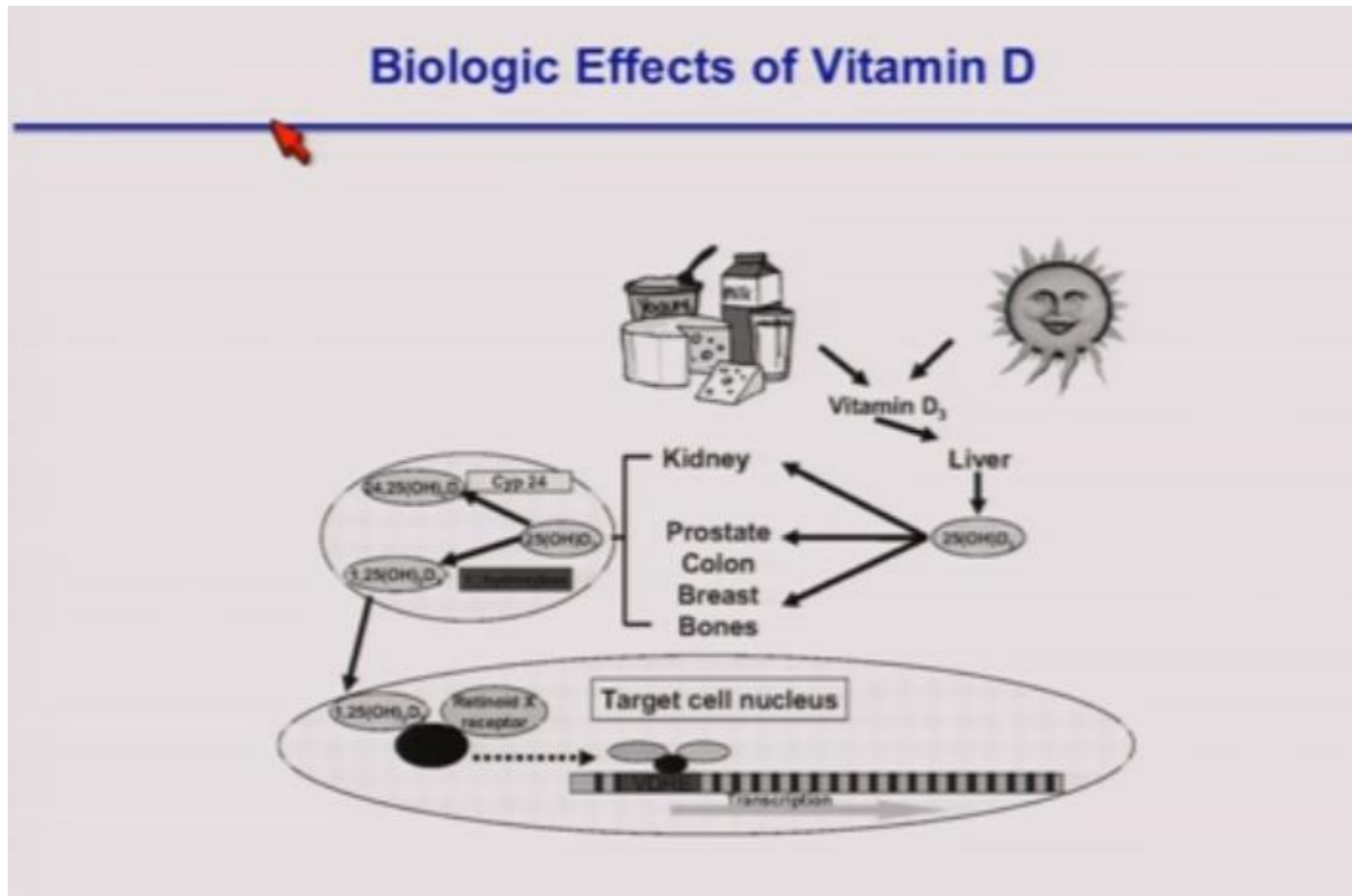
- 36 pts. (n=19 MGUS; 17 SMM) RDBPCT
- Intervention: 4 grams curcumin for 3 month with 8 gm open label extension for 3 additional months
- Results
 - Decreased urinary protein (4 gm 0.03; 8gm 0.04)
 - Decreased Beta 2 microglobulin (4 gm 0.03; 8gm 0.04)
 - Decreased markers of bone breakdown (8 gm 0.07)
 - Decreased creatine (8 gm 0.03)
 - Improved Free Light Chain ratios (0.03)
- Progressive disease risk higher in those with abnormal FLC

Golombick T et al. Am J Hematol 2012 87(5): 455-60

Glutamin

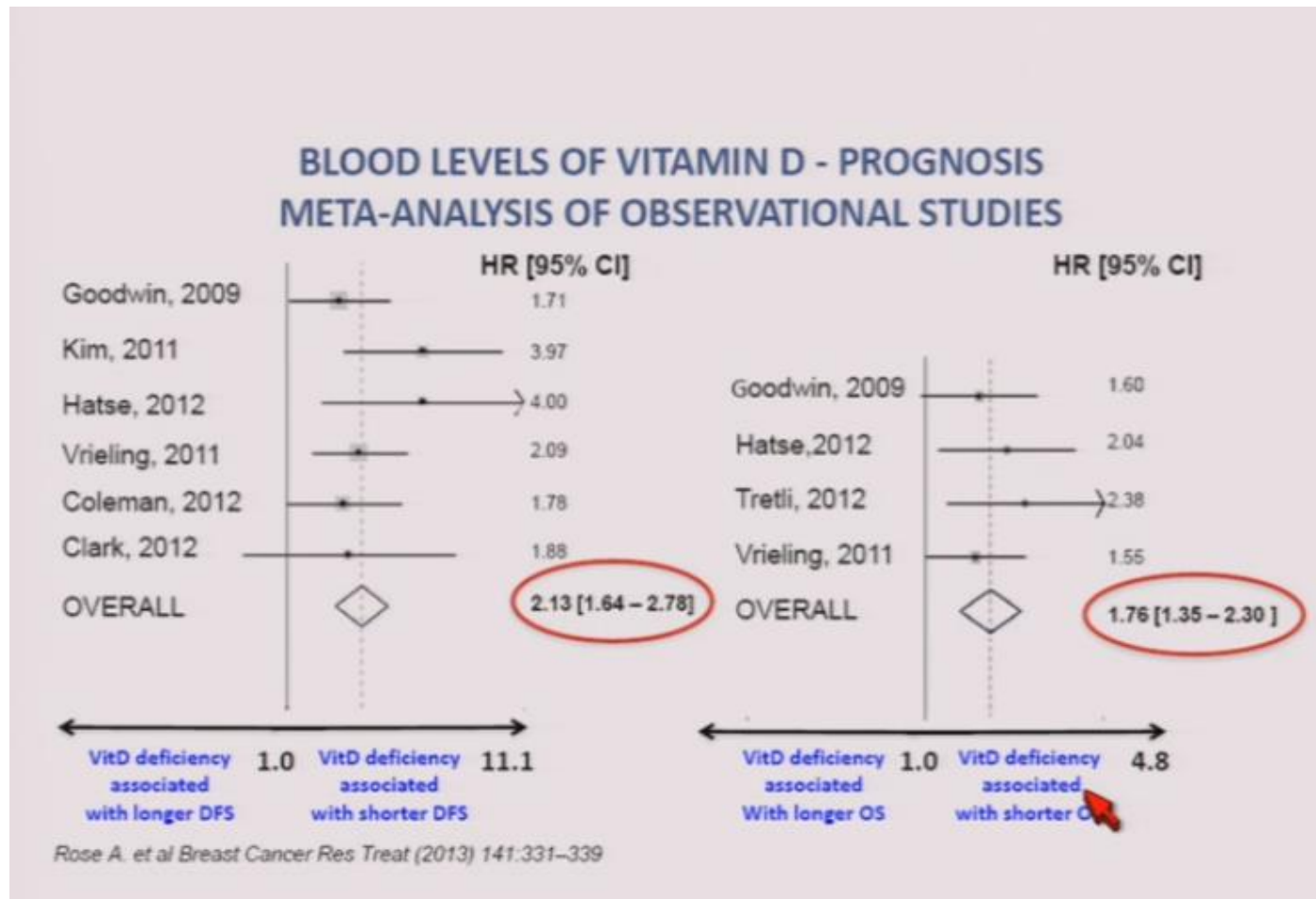
- Reduce cytokine production , improve G-I mucosal barrier
- 10 g PO TID reduces neuropathy, stomatitis
- Interact with other medications?
- Generally safe, a precursor to glutathione
- Caution: source of energy for cancer cells?

Vitamin D



Possible mechanisms: DNA repair, differentiation, regulate gene transcription, Anti-proliferative, apoptosis, anti-angiogenesis, enhancing cytotoxic Rx

Vitamin D & breast cancer prognosis



Vitamin D & cancer risk/prognosis

- Data still inconsistent
- D deficiency very prevalent
- D linked to total body health heart, brain, pain, immune
- Supplementation 1,000-2,000 U/day
- Best guided by blood levels, around 50-60ng/ml
- D2 vs. D3 (25 OH vitamin D), D3 most active
- High D level may increase risk of cancer/death
a U-shaped curve
- No prospective randomized trials

Medicinal mushrooms

including Maitake

A variety of mushrooms, containing β -glucan polysaccharide, function as immune modulators

Best studied is PSK, with several randomized trials involving thousands of pts

Adjuvant therapy improve survival in colon, gastric cancer

May also relieve chemo side effects

Reishi or ganoderma



Fish oil

- Anti-inflammation, anti-proliferative, suppresses NF-kb, apoptosis
- Helpful adjunct during chemo, may improve RR, neutrophil recovery
- 2-3 or 6-8 g a day, look for EPA & DHA
- Treat cancer cachexia w/ celebrex
- Potential interaction with anticoagulant, anti-hypertensive drugs

Green Tea

- *Camilla sinensis*, rich in polyphenol, EGCG the main ingredient
- Multiple anti-cancer mechanisms
- Phase 1 study in CLL: improved lymphocyte count
- Monitor liver enzymes if high dose supplements, G-I toxicities

EGCG and apoptosis

Cell lines: several pancreatic ca cell lines plus 1 lung cancer line.

Effect of EGCG on apoptosis: ↑

Effect of EGCG on ROS: DCF ↑

Apoptosis counteracted by: NAC, CAT

Mechanism: ROS act by impacting on the mitochondrial pathway

Chemotherapy: ↑ doxorubicin effect on hepatoma in vivo

↑ doxorubicin effect on prostate in vivo

↑ gemcitabine effect on cholangio in vivo

Note: EGCG inhibited H1200 **lung cancer in vitro** at IC50 of 20 μM – high. **IC50 in vivo** was only 0.15 μM – longer exposure time.

Milk Thistle

- Treating liver/biliary disorders
- Protection from hepatotoxins
- Silymarin the main extract
- May have activity against HCC
- Decrease liver toxicity from many drugs

Astragalus (Huang Qi)

- Tonifying Qi or energy
- Beneficial when used in conjunction with chemo
- A meta-analysis of 45 trials suggests benefit in HCC
- Typical CHF uses multiple ingredients containing astragalus, and trials of low quality, making evaluation difficult

***Astragalus*-Based Chinese Herbs and Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer: Meta-Analysis of Randomized Trials**

Michael McCulloch, Caylie See, Xiao-juan Shu, Michael Broffman, Alan Kramer, Wei-yu Fan, Jin Gao, Whitney Lieb, Kane Shieh, John M. Colford, Jr

From the University of California, Berkeley School of Public Health, Division of Epidemiology, Berkeley; San Francisco Oncology Associates; Institute of Biophysics, Chinese Academy of Sciences, San Francisco, CA; Pine Street Foundation, San Anselmo; and Institute of Information, China Academy of Traditional Chinese Medicine, Beijing, China

Address reprint requests to John Colford, MD, PhD, University of California, Berkeley, 140 Warren Hall, MC 7360, Berkeley, CA 94720; e-mail: jcolford@berkeley.edu

Purpose Systemic treatments for advanced non-small-cell lung cancer have low efficacy and high toxicity. Some Chinese herbal medicines have been reported to increase chemotherapy efficacy and reduce toxicity. In particular, *Astragalus* has been shown to have immunologic benefits by stimulating macrophage and natural killer cell activity and inhibiting T-helper cell type 2 cytokines. Many published studies have assessed the use of *Astragalus* and other Chinese herbal medicines in combination with chemotherapy. We sought to evaluate evidence from randomized trials that *Astragalus*-based Chinese herbal medicine combined with platinum-based chemotherapy (versus platinum-based chemotherapy alone) improves survival, increases tumor response, improves performance status, or reduces chemotherapy toxicity.

Methods We searched CBM, MEDLINE, TCMLARS, EMBASE, Cochrane Library, and CCRCT databases for studies in any language. We grouped studies using the same herbal combinations for random-effects meta-analysis.

Results Of 1,305 potentially relevant publications, 34 randomized studies representing 2,815 patients met inclusion criteria. Twelve studies (n = 940 patients) reported reduced risk of death at 12 months (risk ratio [RR] = 0.67; 95% CI, 0.52 to 0.87). Thirty studies (n = 2,472) reported improved tumor response data (RR = 1.34; 95% CI, 1.24 to 1.46). In subgroup analyses, Jin Fu Kang in two studies (n = 221 patients) reduced risk of death at 24 months (RR = 0.58; 95% CI, 0.49 to 0.68) and in three studies (n = 411) increased tumor response (RR = 1.76; 95% CI, 1.23 to 2.53). Ai Di injection (four studies; n = 257) stabilized or improved Karnofsky performance status (RR = 1.28; 95% CI, 1.12 to 1.46).

Conclusion *Astragalus*-based Chinese herbal medicine may increase effectiveness of platinum-based chemotherapy when combined with chemotherapy. These results require confirmation with rigorously controlled trials.

Melatonin

- Correlates with circadian rhythms, sleep
- Decline with age
- Growth hormone production, apoptosis, suppression of tumor growth factor, antioxidant, anti-proliferative
- 2 recent meta-analyses show better survival when melatonin used in conjunction with conventional Rx, and less toxicity
- Dose range 0.5 -20 mg, probably higher dose for cancer pts, i.e. 10 mg

Probiotics

- Organisms such as bacteria or yeast to improve health
- Help intestinal function and integrity of intestinal lining
- Chemo & antibiotics kill healthy gut microbiome
- Maintain a strong immune system
- For diarrhea, prevent recurrent C. Diff
- Caution: extreme immune-compromised hosts
 - cases of bacteremia reported

Blood tests guiding use of supplements

- Inflammation: cardio CRP, sed rate, interleukin-8
- Immune regulation: NK activity, T-helper cells, IgG
- Micronutrient status (spectracell lab)
- Oxidative stress: Lipid peroxide, isoprostane
- Cu:Zn ratio: serum copper & zinc, ceruloplasmin
- Glucose/Insulin: BS fasting and 1.5 hr PP, Hgb A1C
IGF-1
- Fibrinogen, D-dimer
- Organic acids in urine, heavy metals

Individualizing Support oncometabolic syndrome

- Mr. A stage 4 NSCLC

HS CRP 14.8

Hgb A1C 5.2

Fibrinogen 450

lipid peroxide high

Vit D3 42

Cu 175

Ceruloplasmin 34

- Mr. B stage 4 NSCLC

HS CRP 3.3

HgbA1C 7.4

Fibrinogen 290

lipid peroxide moderate

Vit D3 20

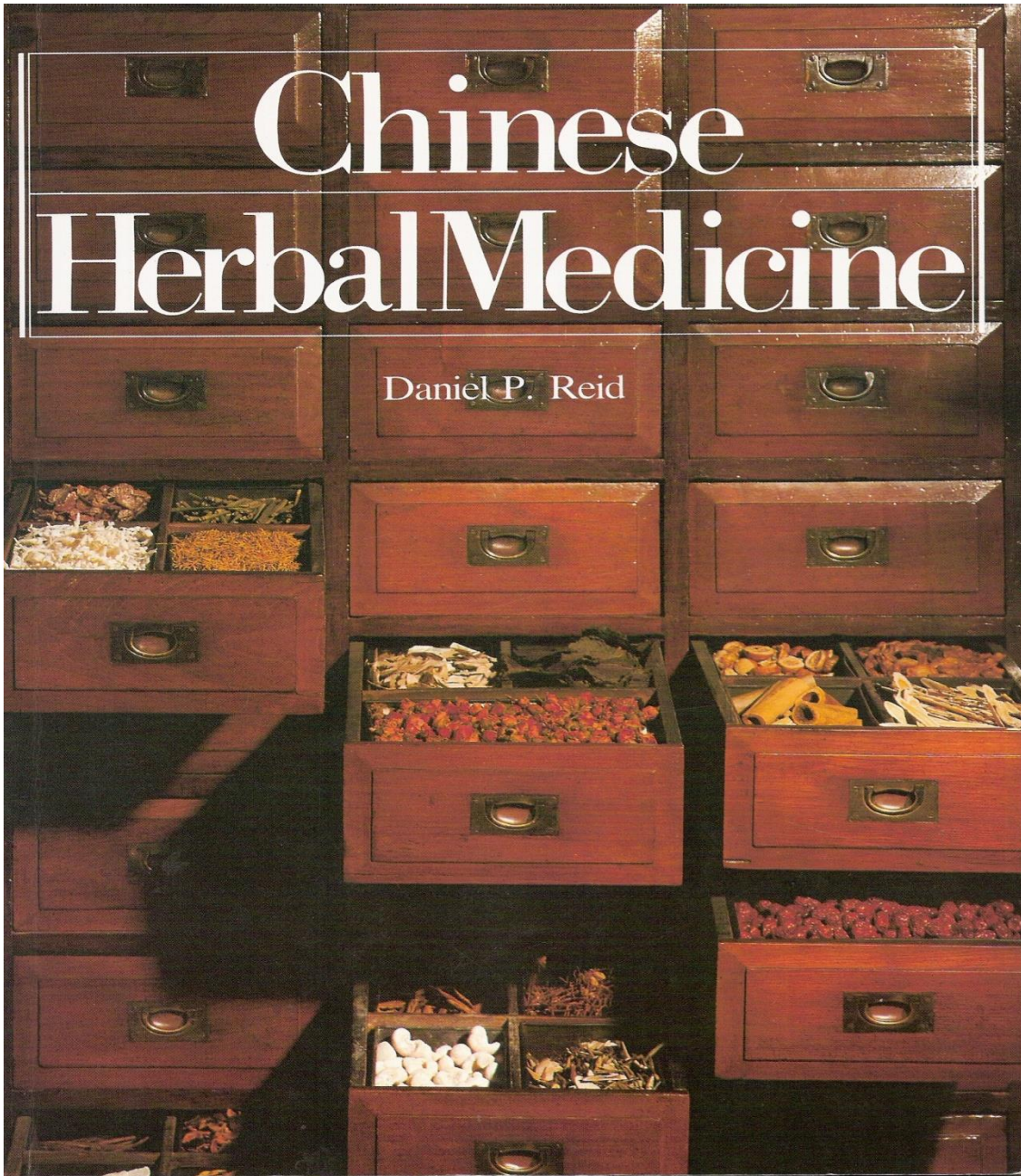
Cu 120

Ceruloplasmin 35

Chinese Herbal Medicine

Daniel P. Reid

Translational doctors
vs.
herbal doctors



Traditional Chinese medicine

- Highly personalized, every individual treated differently
- Based on inspection, history, tongue and pulse
- Very unique theories: yin/yang, 5 elements---etc.
- Acupuncture, herbs, tui na, moxabustion---

Chinese herbal medicine : A Team Work



ADD TO MY GALLERY
Is Andy Dalton, plays

MAG BY SO PRESS

1 week, 6 days ago



DJOKOVIC, THE GRASS-EATER

For the last before the summer holiday, it's Djokovic the grass eater who takes back the lead of the WAT ranking. But he is followed closely by all those who participated, one way or another, to a major sports event. And they are many on the tour.

Fighting cancer takes a team work

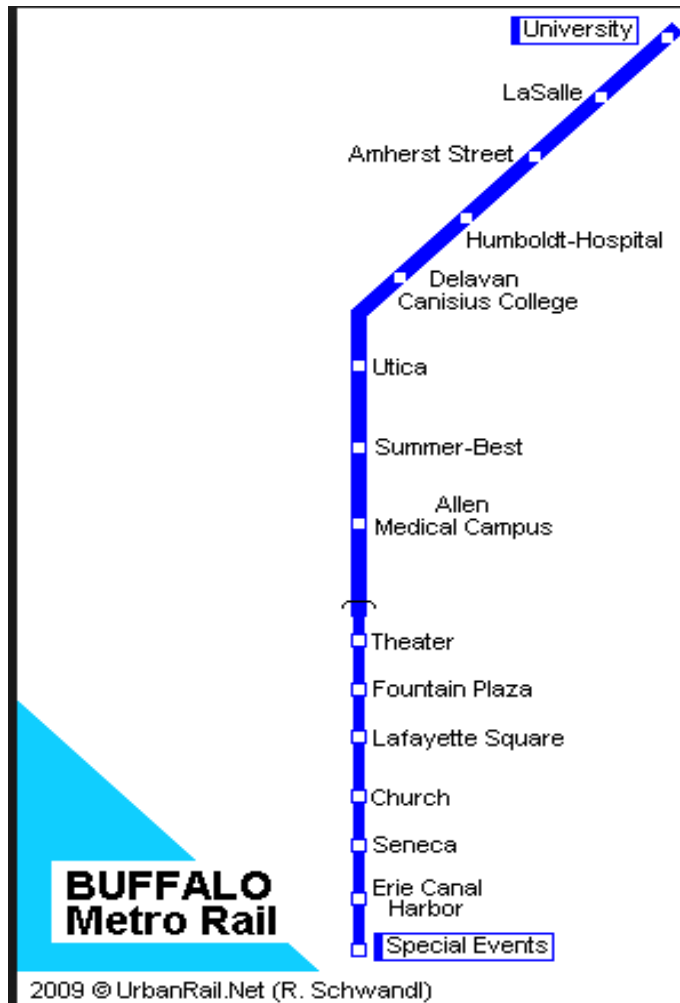
TCM as part of it



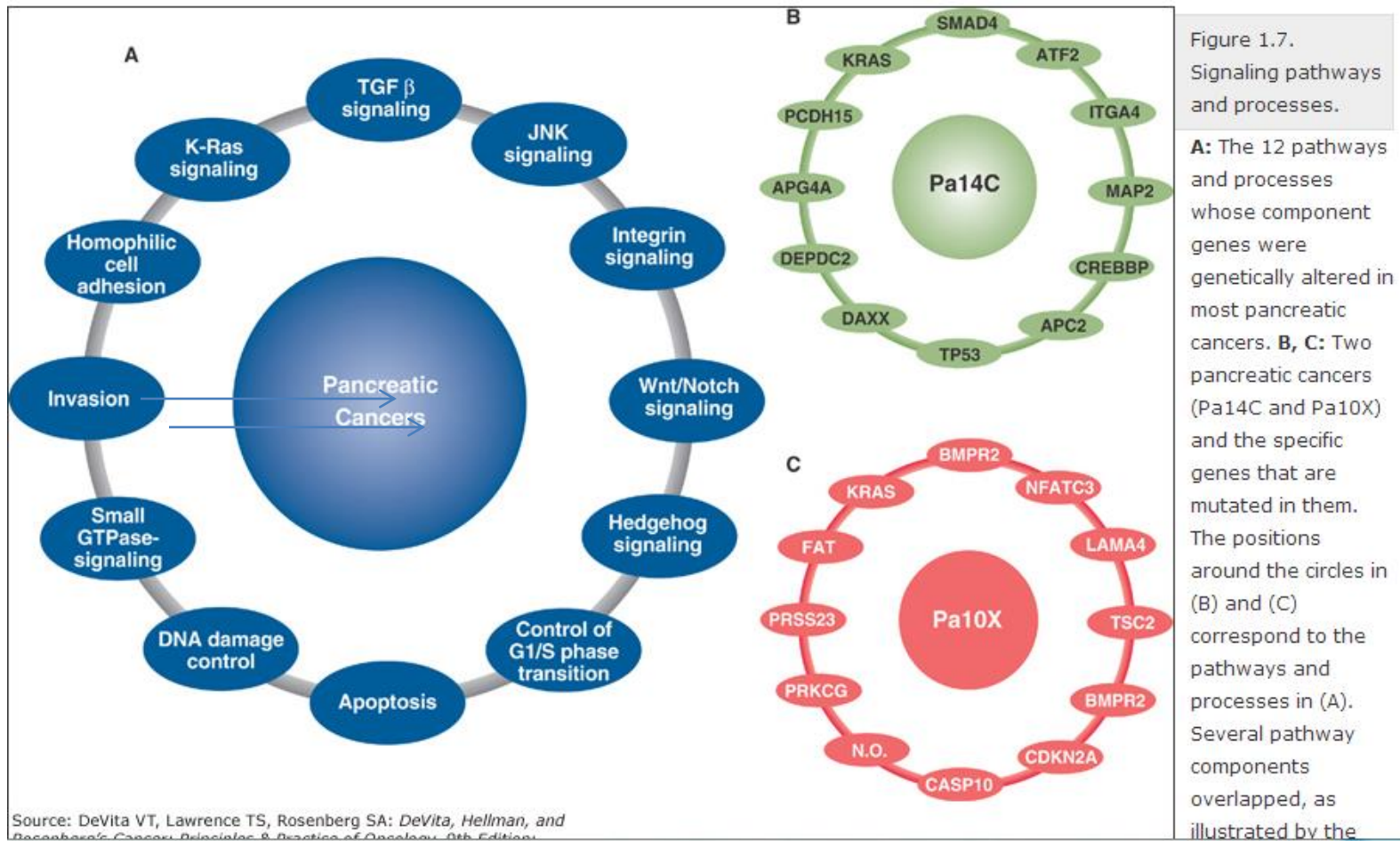
Pathway or Pathways

Buffalo, New York

New York city, New York

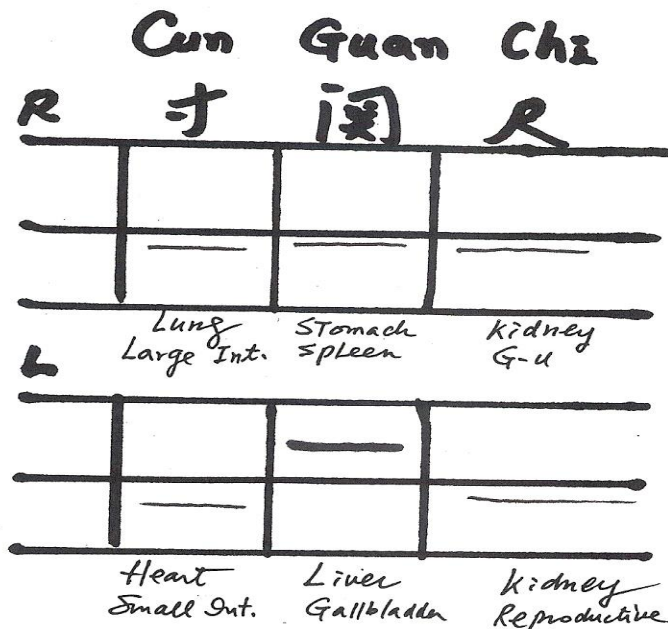


Multiple mutations, Many pathways pancreatic cancer



Pulse Diagnosis

83 year-old retired male physician, hx of gastric lymphoma, in remission
 Complaints: insomnia, cold intolerance, leg swelling, fatigue
 Taking melatonin and other supplements on his own, sleeps 4 hrs per night



Pulse Diagnosis (Finger Position)

- Finger positions
 - Your index finger should be distal to the highest point, which is the styloid process. The styloid process is therefore between your index and middle fingers.



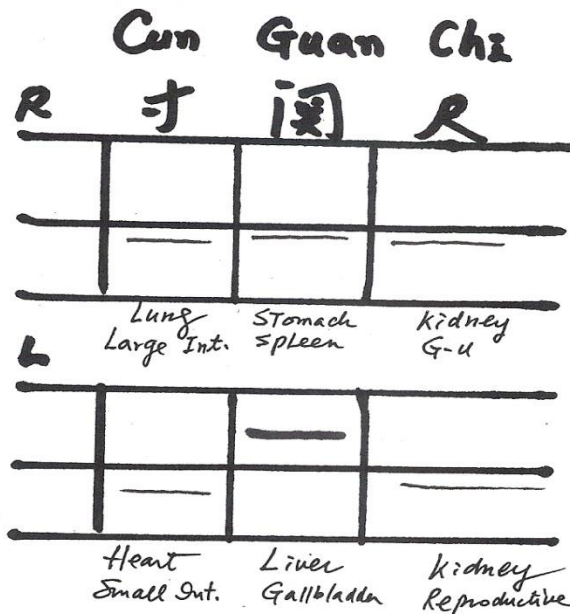
Dramatic improvement after Chinese herbs only after 3 weeks

Case study

- 52 year-old female with bladder cancer
- In remission after chemo-XRT(cisplatin-based), no surgery, one kidney non-functional, GFR 60
- Last treatment 9 months ago
- Completed a 10 week fitness program
- Initial visit: desire to improve or maintain GFR

Case Study (cont'd)

- Pulse dx



Kidney Yang, Heart Blood & Qi deficiency
Liver Qi rising

Improved quickly with 3 acupuncture

Other complaints:

Cold intolerance
Leg swelling
Polydipsia
Polyuria
Low back weakness
Fatigue
Chemo brain
Insomnia
Numbness of feet

Herbal mixture added several weeks later as response to
acupuncture was not fast enough
patient's testimonial

- “As a cancer survivor I was looking for an adjunct therapy to address two issues after exhausting all options offered by traditional Western medicine: neuropathy in my hands and feet and I wanted to maintain the 45% function I had left in my remaining kidney. My research took me to Dr. Peter Sheng. After only six acupuncture treatments, and recently introducing a customized, special blend of Chinese herbs, I have been relieved of all neuropathy in my hands, and only have a miniscule amount remaining in my feet. But even more important to me is the comparison of blood results taken just prior to beginning acupuncture, and again two weeks ago which clearly indicate improved kidney function. As an added bonus, the quality of my sleep has improved and what I used to refer to as “chemo brain” is gone! I can focus now, I can find the right word, I can remember people's names.

Chinese herbal medicine

Drug-herb interaction
very unlikely, theoretically
Very small quantity of each herb
Short term usage common

CHM Processing to Remove Toxicity

Since the early nineteenth century, scientific research has attempted to understand the actions and properties of CHM herbal substances. It was also during this time that most modern drugs were developed. Many herbs sold in the USA are harvested and ground from the original plant form without any TCM processing or preparation. Without the processing to remove toxicity or undesirable side effects, such products could be toxic. In CHM, there



CHM's Multiple Active Ingredients

The skyrocketing rise of healthcare cost and the adverse reaction and side effects incurred from the prescribed drugs have both reinforced such an impression. Herbs in the USA and in many European countries have been prepared as capsules, tablets, teas, lozenges, juice extracts, tincture, and ointments. Most of the herbs are administered as a single herb in the USA and Europe. However, the traditional Chinese herbal medicine contains multiple active ingredients from various herbs and is prepared as concoctions by simmering

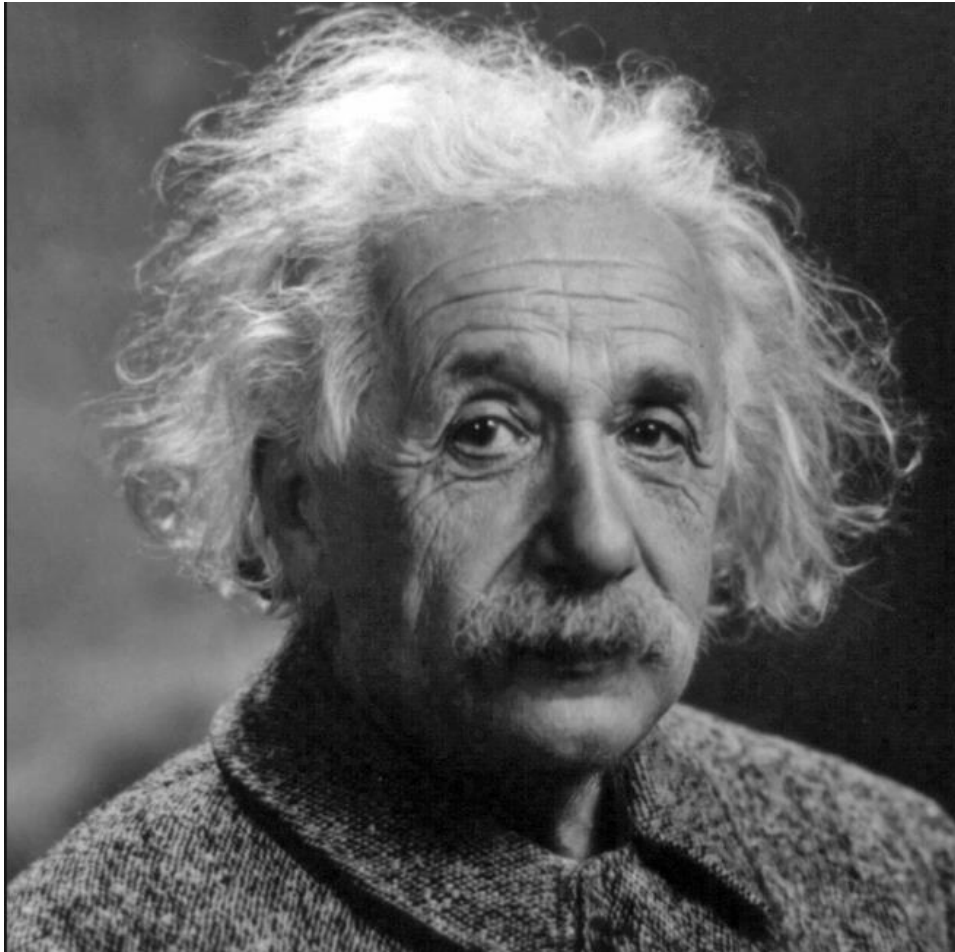


MOAs (mechanisms of action)?

History of medicine is replete of examples where we know things work long before we know how they work.

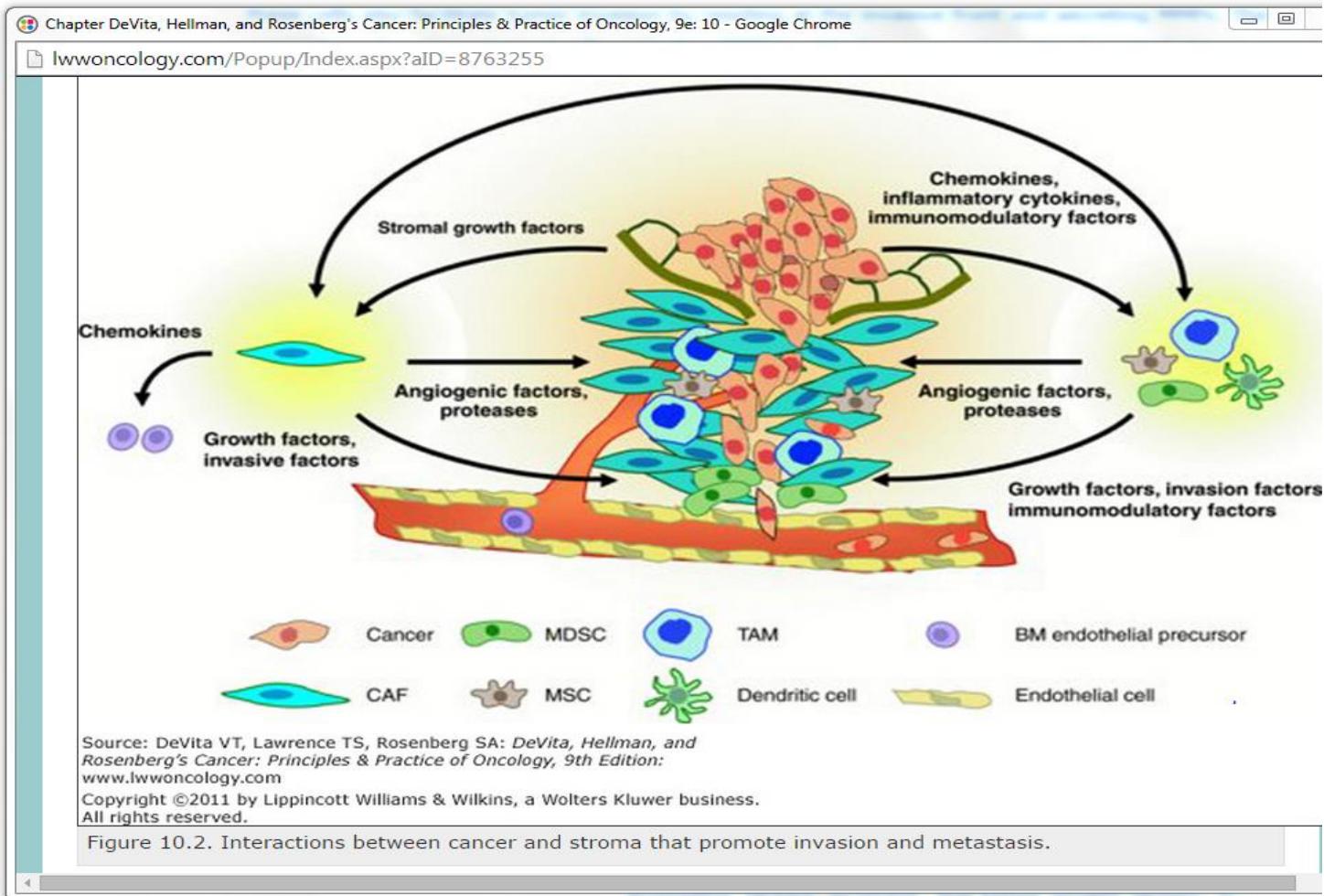
Dr. Sidney Farber

Energy Medicine (Qi or Prana)

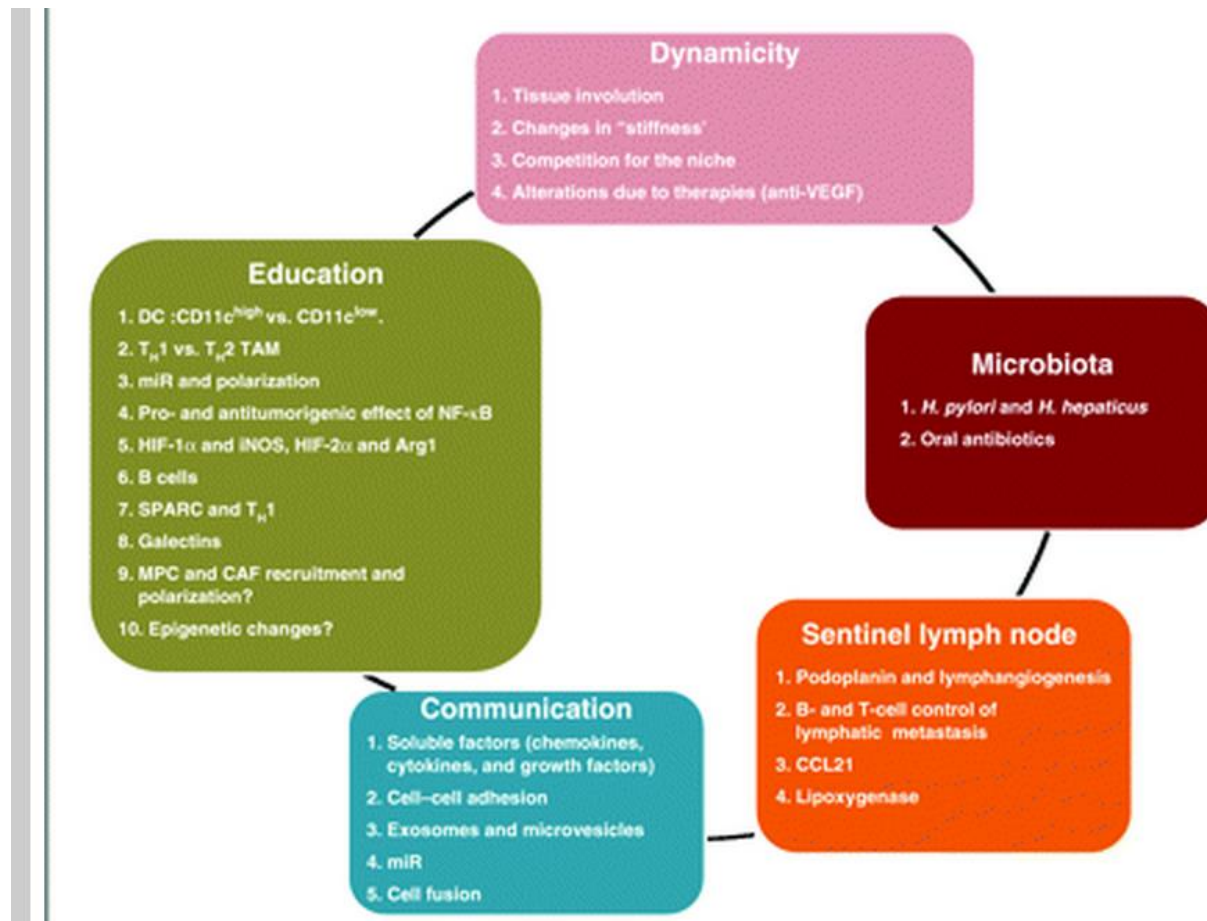


Not everything can
be counted counts;
and not everything
counts can be
counted.

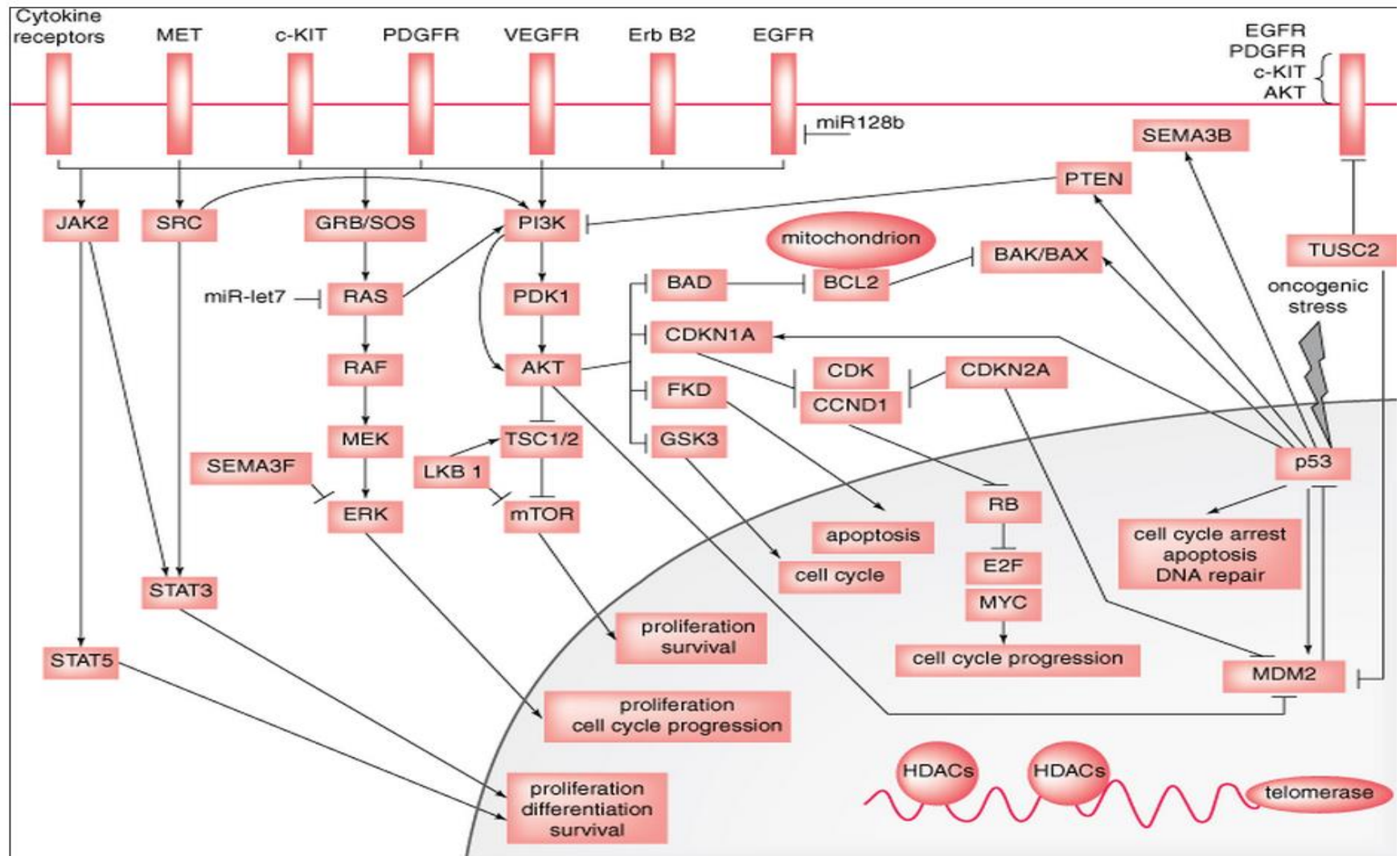
Tumor Microenvironment



Tumor Microenvironment Complexity: Emerging Roles in Cancer Therapy



NSCLC & Pathways



Tumor Macro-environment?

- The host: the mind, co-morbidity
- Performance status
- The outside environment
 - homelessness
 - support group
 - supporting spouse

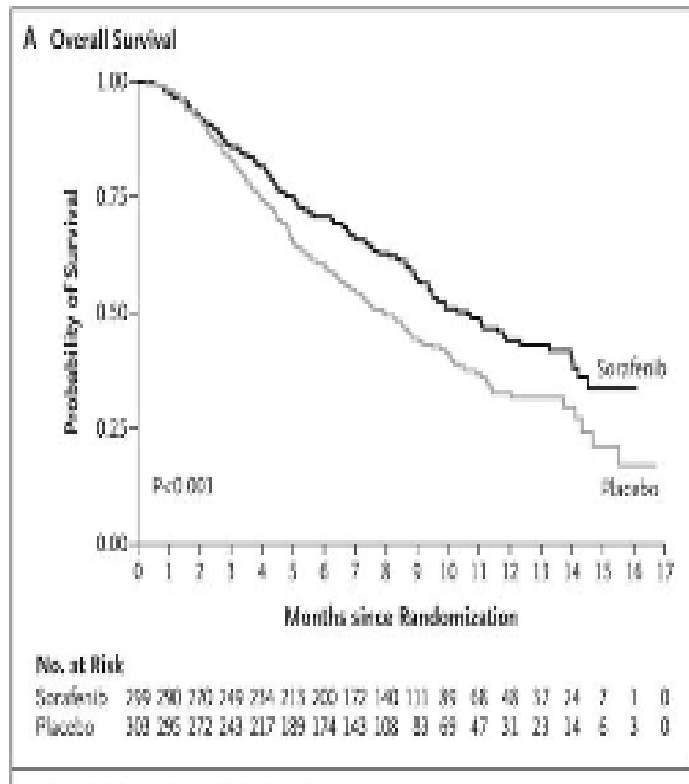
HCC as a possible research project

- HCC, a prevalent cancer, especially in Asia-Pacific area
- Many inoperable and not transplant candidate
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Sorafenib survival benefit

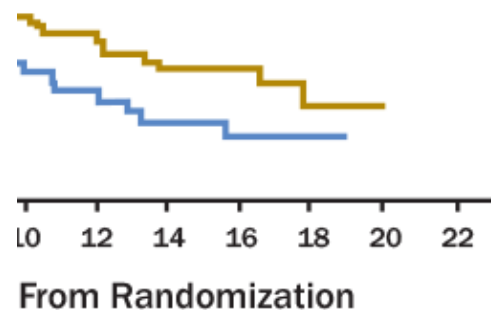
Overall survival consistent with SHARP Trial
SHARP Trial 10.7 vs 7.9 months

Improved overall survival (OS) by 47% vs placebo¹



Overall survival¹

OS: 6.5 months with Nexavar
months with placebo ($P = .014$)



HCC: Integrating WM & CM

- Inoperable HCC patients, after TACE
- Risk stratification
- Sorafenib vs. herbal therapy

herbs tailored to each individual

herbs modified frequently due to body condition change

leeway allowed in study design

Sorafenib as comparator

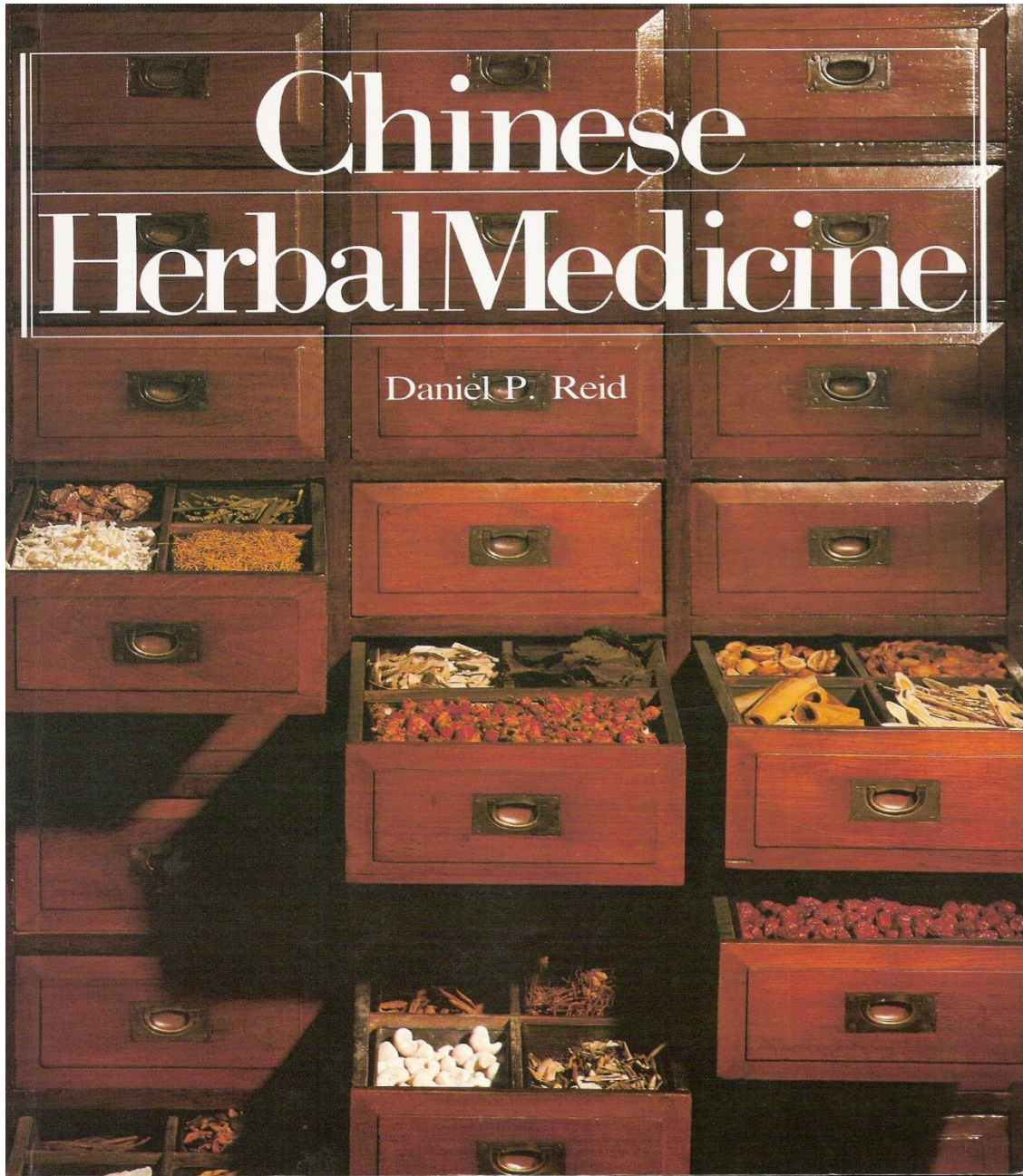
primary endpoint survival

secondary endpoint QoL

Chinese Herbal Medicine

Daniel P. Reid

Pathway /oncogene
doctors or
herbal doctors



Chinese herbal medicine : A Team Work



ADD TO MY GALLERY
Is Andy Dalton, plays

MAG BY SO PRESS

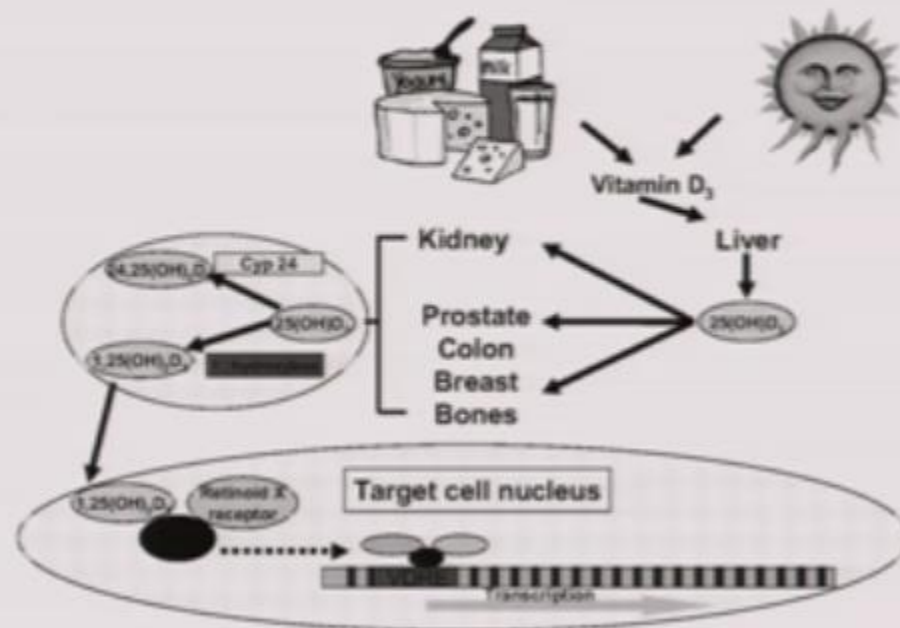
1 week, 6 days ago



DJOKOVIC, THE GRASS-EATER

For the last before the summer holiday, it's Djokovic the grass eater who takes back the lead of the WAT ranking. But he is followed closely by all those who participated, one way or another, to a major sports event. And they are many on the tour.

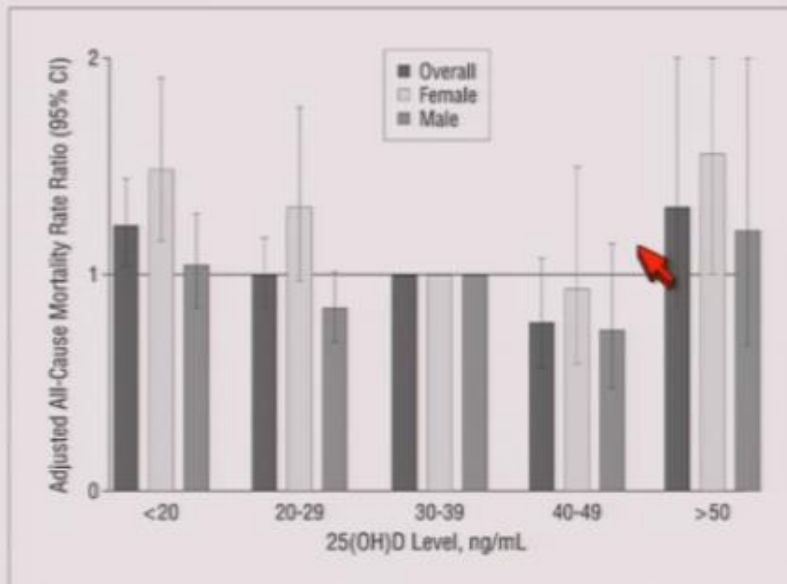
Biologic Effects of Vitamin D



Curvilinear relationship

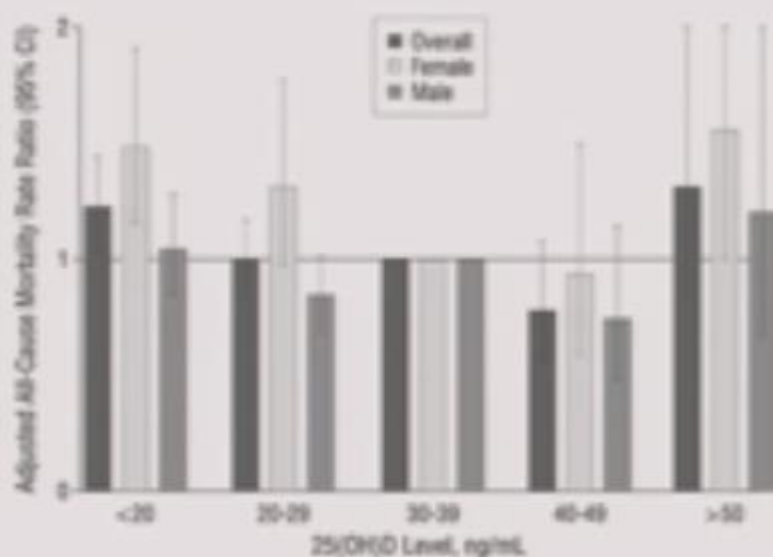
Associations Between 25(OH) Vitamin D Levels and All-Cause Mortality

• n=13,331 participants of the Third National Health and Nutrition Examination Survey



Associations Between 25(OH) Vitamin D Levels and All-Cause Mortality

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META-ANALYSIS OF 42 RCTS:

3 YEARS SUPPLEMENTATION
HR 0.94 (0.90-0.98)

< 3 YEARS SUPPLEMENTATION
HR 1.03 (0.88-1.24)

Zheng Y et al PLOS One 2013

Vitamin D Intake/Exposure



Vitamin D

The body makes vitamin D when it is exposed to Ultraviolet (UV) rays from the sun.

FOOD SOURCES:

Cheese
Margarine
Butter
Fortified Milk
Healthy Cereals
Fatty Fish



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Blood Vitamin D Levels and Cancer Risk

Recent Meta-Analyses

Citation	<u>Tumor Type</u>	<u>Results</u>	
Chowdhury 2014	All cancer	Lower Vitamin D associated with higher risk RR 1.14 (1.01-1.29)	
Chung M 2011	Colorectal	6% lower risk per 10 nmol/L increase in vitamin D	
Liu SI 2013	Pancreas	No association	
Xu Y 2014	Prostate	High(er) Vitamin D associated with increased risk OR 1.17 (1.05-1.30)	
Amir E 2012	Breast (Q1 vs Q4)	Pre-diagnosis blood Post-diagnosis blood	HR 1.10 (1.00-1.20) HR 2.49 (1.93-3.21)
Bauer SR 2012	Breast (per 5 ng/ml increase)	Postmenopausal Premenopausal	HR 0.88 (0.79-0.97) No association

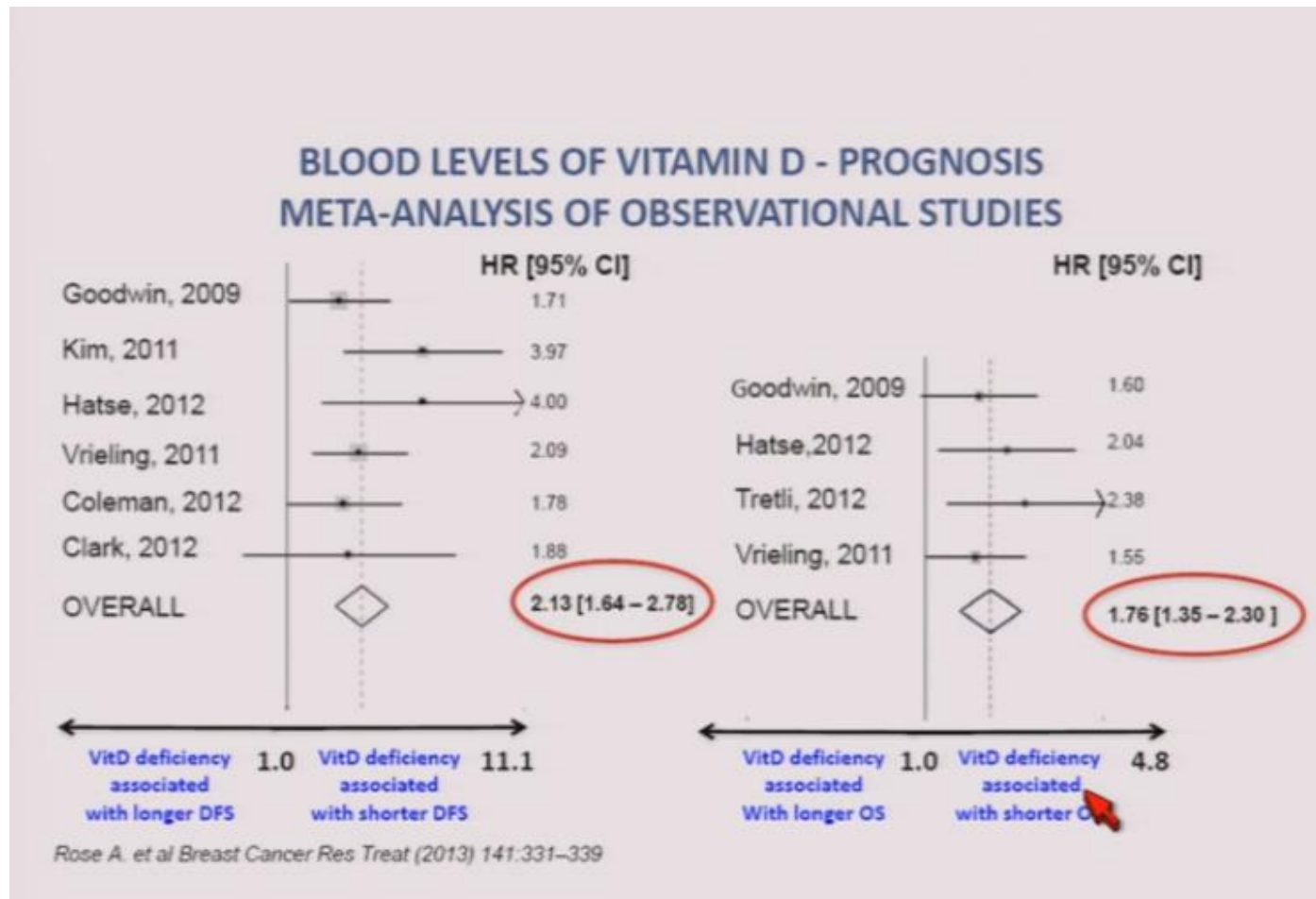
Vitamin may be a marker of overall health



<u>First Author and Publication Year</u>	<u>Type of Randomization</u>	<u>Results for Cancer Incidence</u>
Trivedi 2003 (UK) (n=2682)	<ul style="list-style-type: none"> • 100 000 IU Vitamin D q 4months for 5 years (15 doses in total) • Placebo for 5 years 	HR=1.09 (95% CI, 0.86 to 1.36) (Vitamin D vs. Placebo)
Lappe 2007 (Nebraska) (n=1179)	<ul style="list-style-type: none"> • 1400-1500mg calcium daily for 4 years • 1000 IU Vitamin D + 1400-1500mg calcium daily for 4 years • Placebo for 4 years 	RR 0.40 (95% CI, 0.20 to 0.82) Vitamin D + calcium vs. Placebo (Calcium + Vitamin D vs Calcium – no diff)
Brunner 2011 (WHI)	<ul style="list-style-type: none"> • 400 IU Vitamin D + 1g calcium daily for 7 years • Placebo for 7 years 	RR 0.98 (95% CI 0.90-1.05) RR 0.90 (95% CI 0.77-1.05) (Cancer Mortality)
Chlebowski 2008 (WHI)	<ul style="list-style-type: none"> • Breast cancer events only 	RR 0.96 (0.85-1.09)
Bolland 2011 (WHI) (n=36,282)	<ul style="list-style-type: none"> • Re-analysis according to use/non-use of personal Vitamin D or calcium supplements at randomization 	HR=0.86 (95% CI, 0.78 to 0.96) (Vitamin D + calcium vs. Placebo) (In those not taking personal Vitamin D/Ca supplements at randomization – n/s in those taking supplements)
Avenell 2011 (RECORD) (n=4292)	<ul style="list-style-type: none"> • 800 IU Vitamin D daily for 3 years • 1g calcium daily for 3 years • Placebo for 3 years • Factorial design Vit D vs P/Ca vs P 	HR=1.07 (95% CI, 0.92 to 1.25) Vitamin D vs Placebo

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Vitamin D & breast cancer survival



Vitamin D supplementation

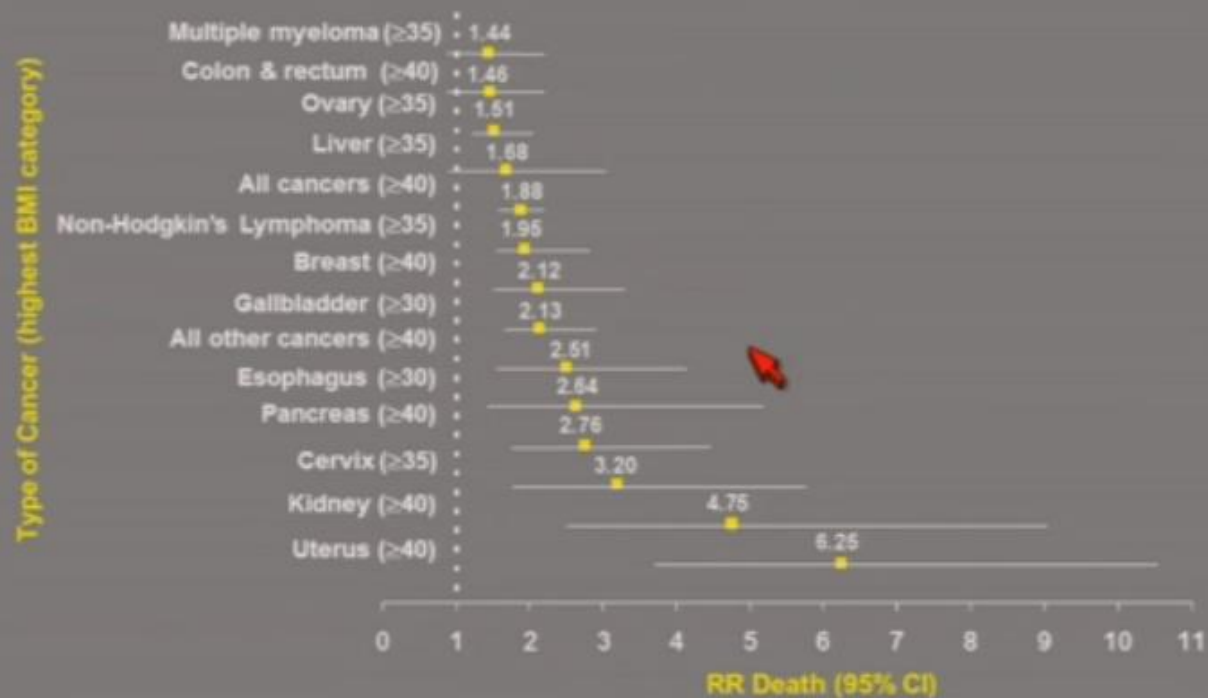
Temporal Changes in Vitamin D in Breast Cancer Patients

Citation	Phase of Disease	#	mean±SD (nmol/L)	25(OH) Vitamin D		
				Deficient (< 50 nmol/L)	Insufficient (50-75 nmol/L)	Sufficient (≥ 75 nmol/L)
Goodwin (J Clin Oncol 2009)	Diagnosis	512	58.1±23.4	37.5%	38.5%	24.0%
Neuhouser (Am J Clin Nutr 2008)	First year * post-diagnosis (avg. 7.5 mos)	597	62.0±26.0	75.6%		24.4%
Crew (J Clin Oncol 2009)	Adjuvant † Chemo	103	42.5	74%	20%	6%
Waltman (Cancer Nurs 2009)	Survivors ‡ (on AI's)	29	64.0±12.3	6.9%	79.3%	13.8%
Cescon * (BCRT 2012)	Within one year of diagnosis	173	88.5 (Toronto) 98.5 (LA)	3.8% (TO) 4.3% (LA)	23.8% (TO) 20.7% (LA)	72.5% (TO) 75% (LA)

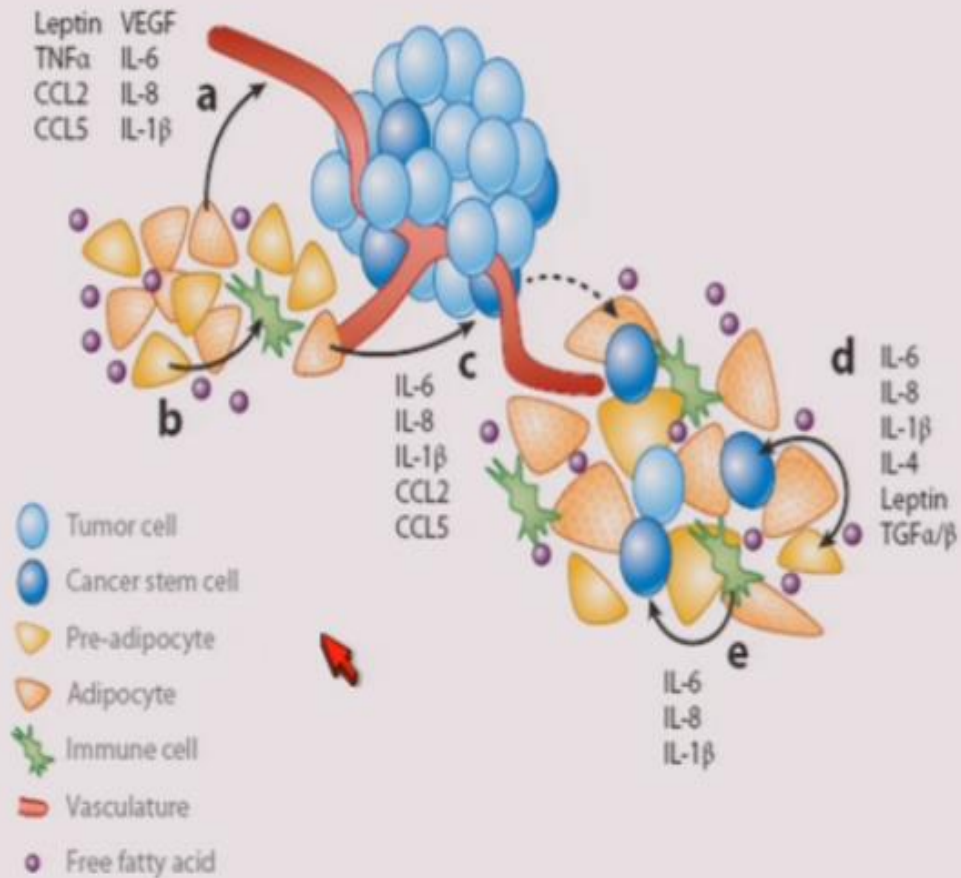
*Cescon et al BCRT 2012

- 84% were taking Vitamin D supplements (mean 1400 IU/day)
- < 10% of those with deficient levels willing to accept randomization

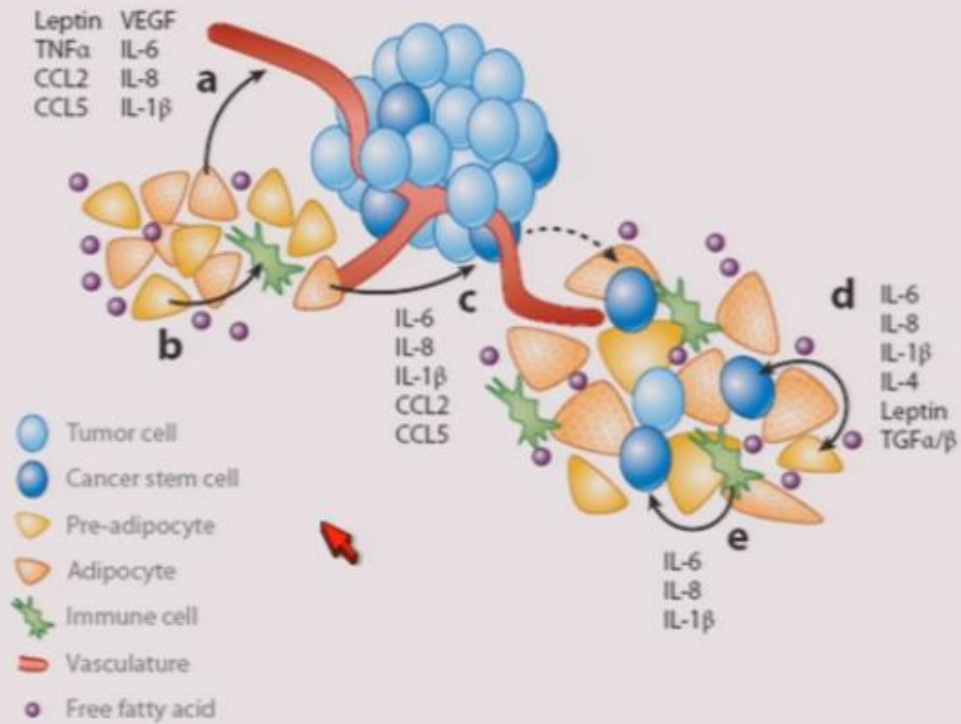
Cancer Mortality in Women – Overweight vs. Normal Weight



Influence of Cytokines Upregulated in Obese Adipose Tissue on Cancer



Influence of Cytokines Upregulated in Obese Adipose Tissue on Cancer



Pulse Diagnosis

83 year-old retired male physician, hx of gastric lymphoma, in remission

Complaints: insomnia, cold intolerance, leg swelling, fatigue

Taking melatonin and other supplements on his own, sleeps 4 hrs per night

Pulse Diagnosis (Finger Position)

■ Finger positions

- Your index finger should be distal to the highest point, which is the styloid process. The styloid process is therefore between your index and middle fingers.



Off- label use of pharmaceuticals

- COX-2 inhibitors: celebrex
- Statins: HMG-CoA reductase
- TM (Tetrathiomolybdate): copper chelation
- Calcitriol: vitamin D if prostate cancer & GBM
- Naltrexone: activate TH1 immune cells

Supplements: Summary

- Select your team members to fight cancer
- Just good nutrition may not be enough
- Learn one supplement at a time (one/wk)
- Combination of dietary supplements/herbs works better (herbal harmony)
thinks about a symphony orchestra
- Personalized medicine


Holistic Medicine



The secret of the secret
noodle soup recipe is that
there is no secret ingredient

Holistic medicine = a
whole list medicine

Marital Status and Survival in Patients With Cancer

Ayal A. Aizer, Ming-Hui Chen, Ellen P. McCarthy, Mallika L. Mendu, Sophia Koo, Tyler J. Wilhite, Powell L. Graham, Toni K. Choueiri, Karen E. Hoffman, Neil E. Martin, Jim C. Hu and Paul L. Nguyen 

 ...

SEER data 2004-2008

734,899 patients w/ 10 cancer types

Being married less likely to have mets, more likely to receive right kind of treatment, and lower cancer-specific mortality

Married men benefit more than women

Survival benefit larger than that of standard chemo

Dr Ayal Aizer JCO Nov 1,2013 Vol 131, p3869-3876

Success is not final and failure is
not fatal, it is the courage to
continue that counts

by Winston Churchill

Integrative Oncology

what else to integrate

- Nutrition
- Strengthening internal biochemistry
- Exercise/rehabilitation
- Psychosocial support
- Micronutrients/supplements
- Other unproven but promising treatment

Conquer cancer Foundation

- The cancer cells: membrane receptors
pathways/oncogenes
effectors
monoclonal Abs & TKI's
genetics & epigenetics
- Tumor micro-environment: immune cells,
blood vessels
fibroblasts
clotting factors
- Tumor macro-environment?

An inexpensive biomarker for Inflammation

High Neutrophil-to-Lymphocyte Ratio Is Associated With Poorer Survival in Solid Tumors Overall and in Individual Cancer Types

By **Matthew Stenger**

Posted: 6/25/2014 4:45:09 PM

Last Updated: 6/25/2014 4:45:09 PM

Key Points:

- High neutrophil-to-lymphocyte ratio was associated with worse survival overall and in each of the individual cancer types, consisting of mesothelioma, pancreatic cancer, renal cell carcinoma, colorectal cancer, gastroesophageal cancer, non-small cell lung cancer, cholangiocarcinoma, and hepatocellular carcinoma.
- High neutrophil-to-lymphocyte ratio was associated with significantly poorer cancer-specific survival, progression-free survival, and disease-free survival.


In a systematic review and meta-analysis reported in *Journal of the National Cancer Institute*, Templeton et al found that high neutrophil-to-lymphocyte ratio, a marker of inflammation, is associated with significantly poorer overall survival in solid tumors overall and by individual category. High neutrophil-to-lymphocyte ratio was also associated with significantly poorer cancer-specific survival, progression-free survival, and disease-free survival.


The meta-analyses included 100 studies (57 published in 2012 or later) comprising 40,559 patients. The median cutoff for high neutrophil-to-lymphocyte ratio was 4.


Worse Overall Survival


Overall, neutrophil-to-lymphocyte ratio greater than the cutoff was associated with a hazard ratio (HR) for overall survival of 1.81 ($P < .001$) for all tumors. Hazard ratios for overall survival were significant for all tumor types examined, including 2.35 (95% confidence interval [CI] = 1.89–2.92) for mesothelioma, 2.27 (95% CI = 1.01–5.14) for pancreatic cancer, 2.22 (95% CI = 1.72–2.88) for renal cell carcinoma,


1.91 (95% CI = 1.53–2.39) for colorectal cancer, 1.66 (95% CI = 1.46–1.88) for gastroesophageal cancer,

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ADVERTISEMENT

HCC as a possible research project

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Early Palliative care Prolongs Life

Palliative care's positive outcomes

Boston-area lung cancer patients receiving outpatient palliative care starting within 12 weeks of diagnosis scored better on measures of cancer symptoms than patients who received standard care, according to a recent study. The patients who got palliative care early were less depressed and anxious and survived longer.

	Oncologic care	Oncologic plus early palliative care
Median survival times	8.9 months	11.6 months
Depressed at 12 weeks	38%	16%
Anxious at 12 weeks	30%	25%

Source: "Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer," *New England Journal of Medicine*, Aug. 19 ([link](#))

Integrative care may make early palliative care even better

One important question to ask

- How do I know I am giving the right supplements?
- Predictive biomarkers? Or metabolic profile?
- Energy/muscle testing?
- Traditional Chinese medicine
 - tongue
 - pulse
 - face
 - ear
 - palm

Parachute approach to evidence based medicine

BMJ 2006 ;333 doi: <http://dx.doi.org/10.1136/bmj.333.7570.701> (Published 28 September 2006)

Cite this as: *BMJ* 2006;333:701

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Malcolm Potts, Bixby professor, population and family planning¹, Ndola Prata (ndola@berkeley.edu), lecturer¹, Julia Walsh, adjunct professor¹, Amy Grossman, research assistant¹

[Author affiliations](#) ▼

Correspondence to: N Prata

Accepted 19 June 2006

Waiting for the results of randomised trials of public health interventions can cost hundreds of lives, especially in poor countries with great need and potential to benefit. If the science is good, we should act before the trials are done

EBM is to take best care of our patients
Based on the available evidence

How low are we willing to lower the bar?



Sometimes it's best just to jump in

Evidence-based medicine(EBM)

Do we always need RCT's?
How low can we lower the bar?

Hazardous journey

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, *professor*¹, Jill P Pell, *consultant*²

¹ Department of Obstetrics and Gynaecology, Cambridge University, Cambridge CB2 2QQ, ² Department of Public Health, Greater Glasgow NHS Board, Glasgow G3 8YU

Correspondence to: G C S Smith gcss2@cam.ac.uk

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Conquer cancer Foundation

- The cancer cells: membrane receptors
pathways/oncogenes
effectors
monoclonal Abs & TKI's
genetics & epigenetics
- Tumor micro-environment: immune cells,
blood vessels
fibroblasts
clotting factors
- Tumor macro-environment?