

Can Food Prevent Cancer? Magic bullets vs. dietary patterns

Nutrition and Health Conference
May 11, 2010

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Epidemiology Research Program
American Cancer Society



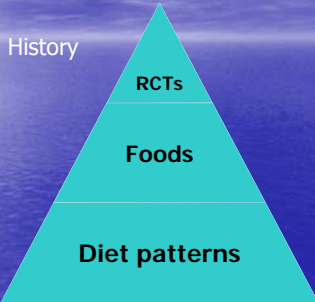
Study Finds that Fiber Prevents Colon Cancer

Researchers claim that high fiber will keep the doctor away

Brian Carter
Epidemiology

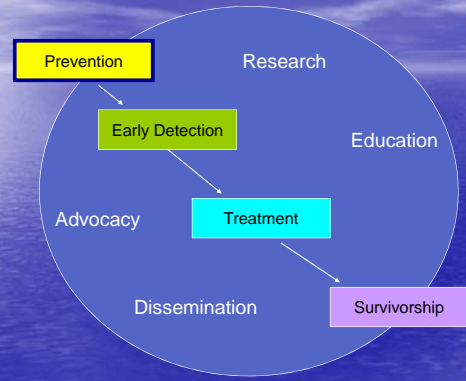


Outline:

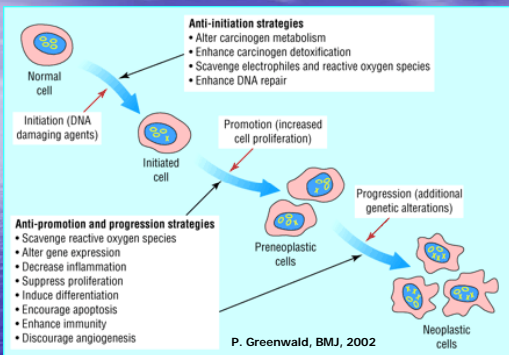


ACS Guidelines
on nutrition and
physical activity
for cancer
prevention

The cancer continuum



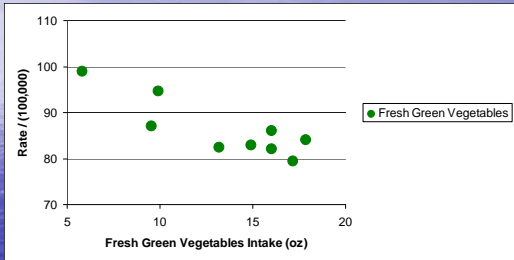
Cancer is a multi-step process which may take years or decades



Diet may play a role in stopping – or promoting growth of tumors

Where does the evidence on diet
and cancer in humans come from?

Ecological study: regional fresh green vegetables intake and colon cancer rates in the U.K. (1969-73)



Data from Bingham, et al 1979

Summary of Case-Control Studies of Fruits and Vegetables and Cancer

Cancer Site	# of studies	↓ risk (% of studies)
Stomach	30	93%
Lung	13	85%
Colon	19	79%
Breast	12	67%
Prostate	6	17%
All	196	78%

WCRF, 1997

The Lancet • Saturday 28 November 1981

DIETARY VITAMIN A AND RISK OF CANCER IN THE WESTERN ELECTRIC STUDY

RICHARD B. SHEKELLE MARK LEPPER
SHUGUEY LIU CAROL MALIZA
WILLIAM J. RAYNOR, JR ARTHUR H. ROSSOF

Departments of Preventive Medicine and of Medicine, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois, U.S.A.

Summary Intake of dietary provitamin A (carotene) was inversely related to the 19-year incidence of lung cancer in a prospective epidemiological study of 1954 middle-aged men. The relative risks of lung cancer in the first (lowest) to fourth quartiles of the distribution of carotene intake were respectively, 7.0, 5.5, 3.0, and 1.0 for all men in the study, and 8.1, 5.6, 3.9, and 1.0 for men who had smoked cigarettes for 30 or more years. Intake of

Study designs for diet and cancer in humans

DEFINITIONS

1. Ecological
2. Case-control
3. Prospective cohort
4. Randomized, controlled trial (RCT)



Increased confidence in causal association

All study designs provide valuable information, and have limitations

Proportion of Cancer Deaths Attributed to Various Factors

Factor	Percent of all cancer deaths	
	Best estimate	Range
Diet	35	10-70
Tobacco	30	25-40
Infection	10 ?	1- ?
Reproductive/sexual behavior	7	1-13
Occupation	4	2-8

<4%: alcohol, geophysical factors, pollution, medicine and medicinal procedures, food additives, industrial products

Doll & Peto, 1981, updated 1992

Interrelationships between diet, physical activity, obesity and cancer risk



Obesity and cancer mortality in women

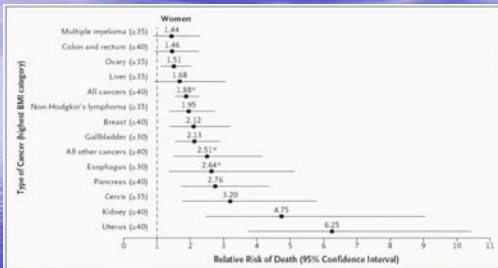
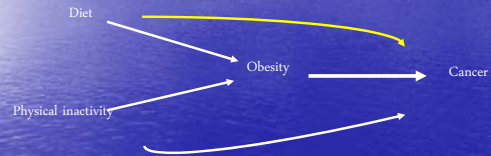


Figure 2. Summary of Mortality from Cancer According to Body-Mass Index for U.S. Women in the Cancer Prevention Study II, 1982 through 1995.
For each relative risk, the comparison was between women in the highest body-mass index (BMI) category (indicated in parentheses) and women in the reference category (body-mass index, 18.5 to 24.9). Asterisks indicate relative risks for women who never smoked. Results of the linear test for trend were significant (P<0.05) for all cancer sites.

Calle et al., New England Journal of Medicine, 2003

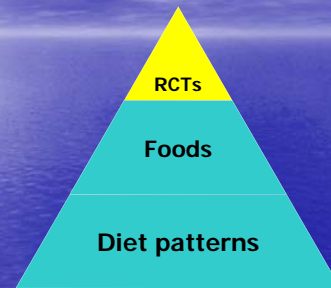
Interrelationships between diet, physical activity, obesity and cancer risk



Reductionism

- Reductionism: "The scientific approach aimed at identifying the molecules involved in biological events and examining them in their purified form or in simple systems" (Zeisel, SH, et al J Nutr 2001)

Outline



Randomized, controlled trials of dietary supplements for cancer prevention



- Modify only constituent/s of interest
- Easy to administer, assess compliance
- Public is likely to accept 'prescription' rather than 'proscription'

Sources of widely studied compounds

Food Sources	Compound
Carrots, sweet potatoes, winter squash, mango, cantaloupe, pumpkin	Beta-carotene
Citrus fruits and juices, broccoli, green peppers, tomatoes, strawberries, leafy green vegetables	Vitamin C
Nuts, oils, peanut butter, some fruits and vegs	Vitamin E
Tomatoes, watermelons, pink grapefruit, apricots	Lycopene
Green leafy vegetables, broccoli, beets, beans	Folate

Linxian Trial



Linxian County, China. Rationale:

- Fruits and vegetables are associated with lower risk of several cancers
- One of the world's highest rates of esophageal and gastric cancer
- **Micronutrient deficient population**

Enrolled 29,584, randomized to one of the following interventions:

- **β -carotene (15 mg), vitamin E (30 mg), Selenium (50 μ g)**

Results: Significantly lower total mortality, cancer mortality, stomach cancer mortality with β -carotene, vitamin E and selenium

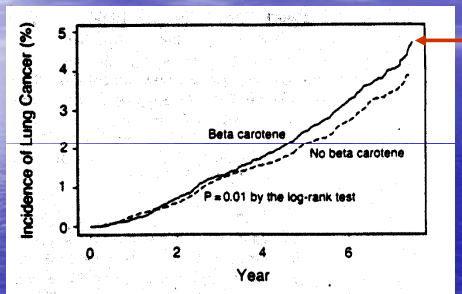
Blot, W. JNCI, 1993

Alpha-tocopherol, beta-carotene (ATBC) trial

- Study design:
 - 50 mg vitamin E, 20 mg β -carotene or both vs placebo
 - Length of follow-up: 5-8 years
 - Participants: 29,133 male smokers aged 50-69
 - Primary outcome: Lung cancer
 - Secondary outcomes: Other cancers

ATBC Cancer Prevention Study Group, NEJM 1994

Results: Cumulative incidence of lung cancer among those who received β -carotene supplements vs those who did not



ATBC Cancer Prevention Study Group, NEJM 1994

β -Carotene Intervention Trials

Study	Size	Yrs	Dose	Lung Cancer
ATBC	29,133 M	5-8	20 mg/d	16% \uparrow
CARET	18,314 MW	3.7	30 mg/d	36% \uparrow
PHS	22,071 M	12	50 mg/2d	no dif
WHS	39,876 W	4.1	50 mg/2d	no dif

} smokers

Why unfavorable results from β -carotene trials??

- Supplement dose
 - Nutritional vs pharmacological
- Choice of study population
 - General population vs high risk (older smokers)
- Type of administration of antioxidants
 - Alone vs with others
- Wrong nutrient?

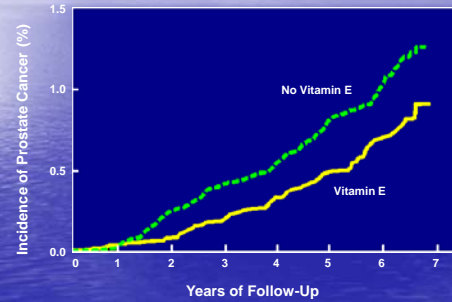
Selenium and Vitamin E

Nutritional Prevention of Cancer (NPC) Selenium Trial

- 1,312 patients with history of basal cell or squamous cell skin cancer
- Participants lived in U.S. counties with low soil Se levels
- 200 micrograms selenium X 10 years
- Results:
- Primary outcome=skin cancer - no effect
- Secondary outcomes:
 - 39% lower total cancer incidence
 - **65% lower prostate cancer incidence**

Clark, L., et al, JAMA 1996

ATBC Study secondary results for vitamin E: Cumulative Prostate Cancer Incidence



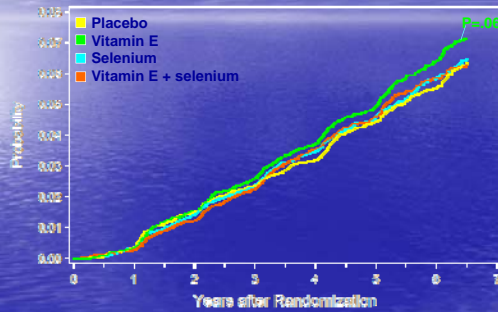
Heinonen et al, JNCI 90:440, 1998

Selenium and Vitamin E Cancer Prevention Trial (SELECT)

- 32,400 men aged 50+ (AA) or 55+ (white)
- Randomized to Se, E, both or placebo
- 200 µg selenium (L-selenomethionine)
- 400 IU/day vitamin E
- Primary outcome=prostate cancer

Lippman S, JAMA 2009

No Effect of Selenium or Vitamin E on Prostate Cancer in SELECT



Lippman, S. M. et al. JAMA 2009;301:39-51

Vitamins get 'F' in cancer prevention

Updated 14 22h ago | Comments 66 | Recommend 14 | E-mail | Save | Print | Reprints & Permissions | RSS



By Liz Szabo, USA TODAY

A bottle of recent studies — including two papers published today — has sunk the notion that individual vitamin supplements prevent cancer.

With so many earlier studies suggesting that people can eat their way to longer lives, experts acknowledge that their latest findings may leave people confused and even frustrated.

Q&A: Which studies should we listen to?
BETTER LIFE: More on supplements and alternative medicine

"A lot of people are looking at this and asking, 'What happened?'" says Lori Minasian, whose study in today's *Journal of the American Medical Association* found that taking vitamin E or selenium does not ward off cancer.

Enlarge
 Vitamin E capsules.
 By Tim Dillon, USA TODAY

Do Antioxidant Supplements Lower the Risk of Cancer or Polyps (RCTs)

	Polyps	Colon	Breast	Prostate	Lung	Total
Vitamin E		No	No	No	No	No
Selenium		No ↓ No-def	No	No	No ↓ Se-def	No ↓ Se-def
Vitamin C		No	No	No	No	No
B-carotene	No	No	No	No	No ↑ smokers	No ↑ smokers
Mixtures of antioxidants	No	No	No	Weak	No	No ↓ Deficient

Summary courtesy of Alan Kristal

Do other supplements reduce cancer risk?

	Polyps	Colon	Breast	Prostate	Lung	Total
Fiber	No					
Folate	↑ risk		No	No		
Calcium	↓ Yes	No	No			
Vitamin D	In trial	No	No			
	In trial	In trial	In trial			In trial

Italicized - from WHI

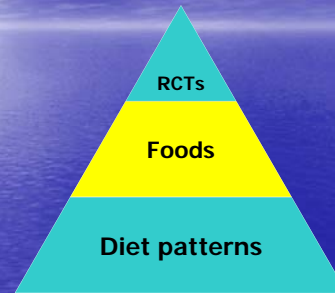
*New RCT – “VITAL” of 2,000 IU vitamin D: Cancer, Heart Disease and stroke <http://www.vitalstudy.org/>

Randomized controlled trials have limitations

- High risk of false negative results
 - Wrong dose, formulation, timing?
 - Study population not susceptible
- Expensive
- Can take several years
- Limited in the number of questions that can be answered
- May not be a ‘gold standard’ for all questions



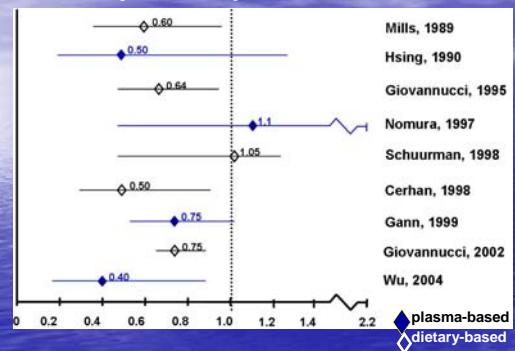
Outline



Food synergy

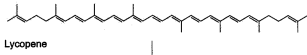
- Food synergy: “Additive or more than additive influences of foods and food constituents on health” (Jacobs DR, AJCN, 2003)

Tomato/Lycopene and Prostate Cancer: Summary of Prospective Studies



Etminan et al., 2004

Lycopene or tomatoes?

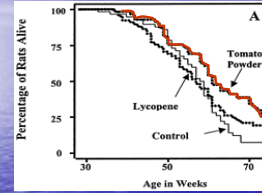


Tomatoes contain:

- Lycopene
- Phytoene
- β-carotene
- γ-carotene
- Ascorbic acid
- Quercitin
- Naringenin
- Glucosinolate
- ...



Prostate carcinogenesis in N-methyl-N-nitrosourea (NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy-restricted diets. (Boileau, et al, JNCI, 2003)



HR (tomato vs lycopene) = 0.74
95% CI = 0.59-0.93

The duration of prostate cancer-free survival was greater for the rats fed tomato powder than for the rats fed either purified lycopene or control diets.

Slide: Peter Gann

"Food synergy"

Mixture of apples, blueberries, grapes, oranges on antioxidant activity

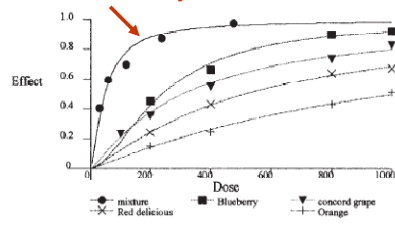


FIGURE 7 Dose-response of antioxidant activity of orange, apple, grape, blueberry and 4-way combination.

Liu, R. J Nutr 2004

Systematic review of the literature

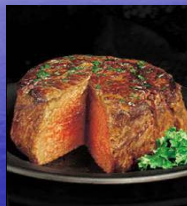
VEGETABLES,¹ FRUITS,¹ PULSES (LEGUMES), NUTS, SEEDS, HERBS, SPICES, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

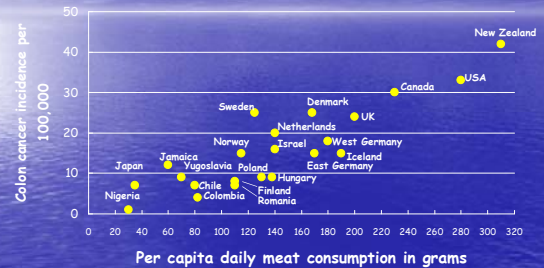
	DECREASES RISK		INCREASES RISK	
	Exposure	Cancer site	Exposure	Cancer site
Convincing				
Probable	Non-starchy vegetables ¹	Mouth, pharynx, larynx Oesophagus Stomach		
	Allium vegetables ¹	Stomach		
	Garlic ¹	Colorectum		
	Fruits ¹	Mouth, pharynx, larynx Oesophagus Lung Stomach		
	Foods containing folate ²	Pancreas		
	Foods containing carotenoids ²	Mouth, pharynx, larynx Lung		
	Foods containing beta-carotene ²	Oesophagus		
	Foods containing lycopene ^{2,3}	Prostate		
	Foods containing vitamin C ^{2,3}	Oesophagus		
	Foods containing selenium ^{2,3}	Prostate		

World Cancer Research Fund/ American Institute for Cancer Research 2007

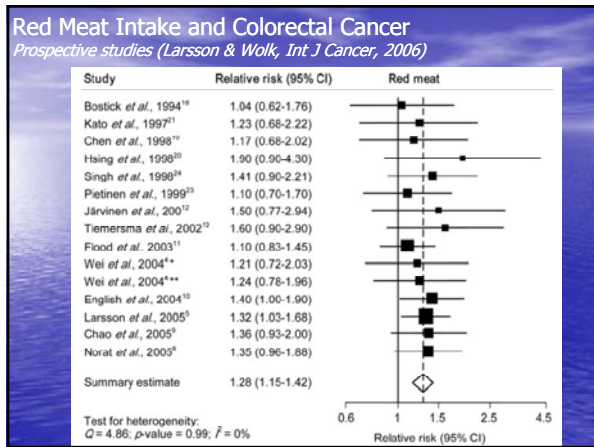
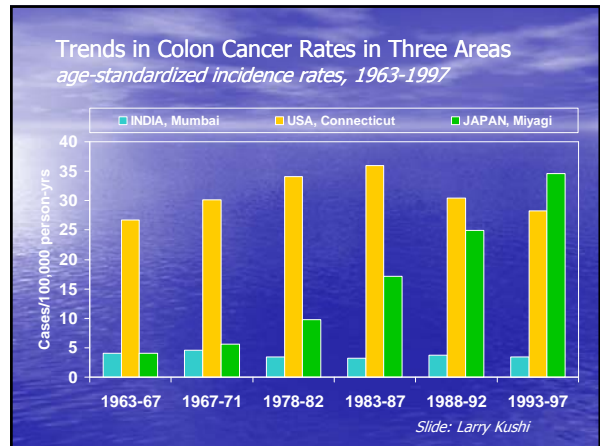
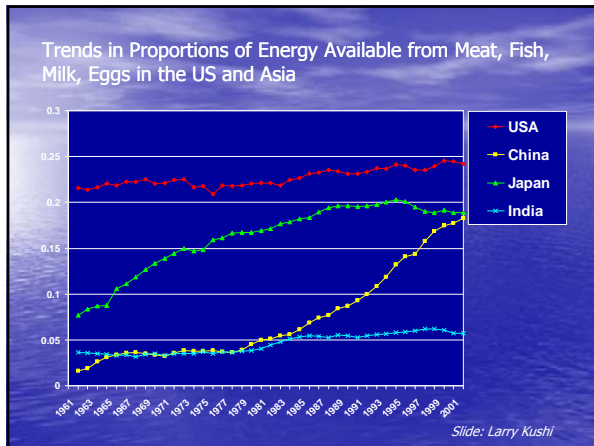
What about other aspects of diet?



Ecologic evidence relating colon cancer incidence to per capita meat consumption, women 1975



Armstrong & Doll, Int J Cancer 1975



Red & Processed meats and cancer: Biologic mechanisms

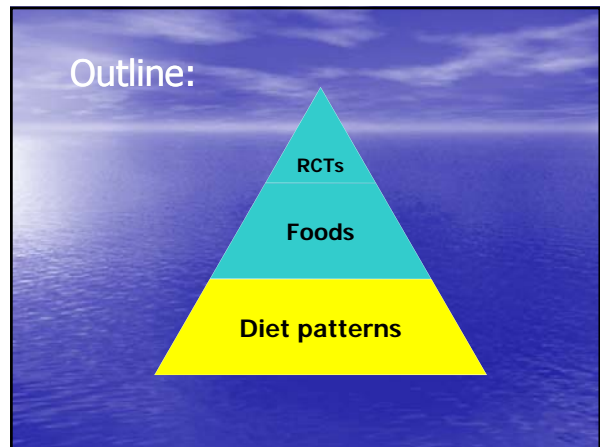
- Carcinogens or their precursors
- Pro-oxidants in meat
- Animal fat (saturated) in meat

Summary of the evidence for foods and cancer

	CRC	Breast	Prostate	Lung	Other
Red or processed meat	↑		↑	↑	↑
Fruit	↓			↓	↓
Vegetables*	↓		↓ lycopene	↓ β-car	↓
Foods high in fiber	↓				
Milk/calcium	↓		↓		
Alcoholic drinks	↑	↑			↑

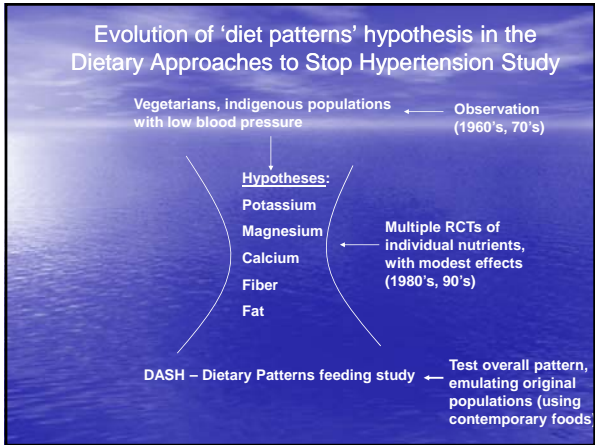
↑ Higher risk ↓ Lower risk Thicker arrow: "Convincing"
Thinner arrow: "Probable"

* Includes sub-types of vegetables Summarized from WCRF report www.dietandcancerreport.org



Diet patterns: actual food consumed in a given period (e.g. day or longer). A measure of the totality of diet composition

- ### Why consider diet patterns?
- It's how people really eat
 - Food components are highly correlated
 - Capture additive & interactive effects of nutrients
 - Guidelines recommendation multiple behaviors

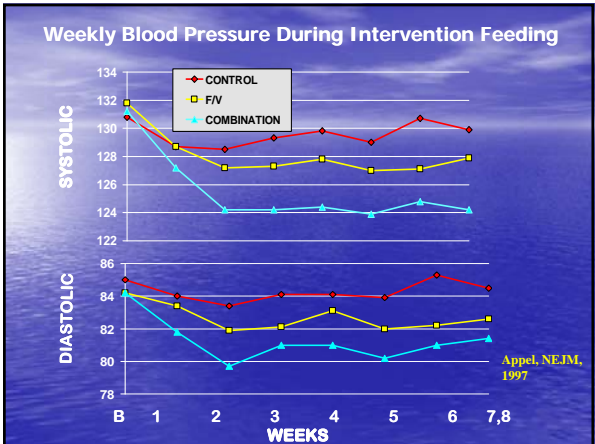
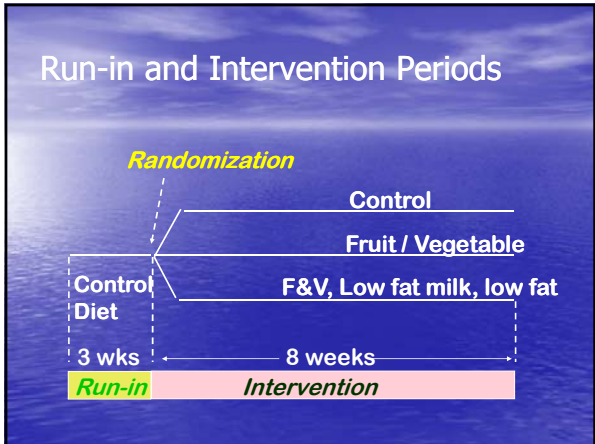


Nutrient Targets for DASH Diets

2100 kcal/d	Control	Fruit/Vegetable	Combination
Fat, %	37	37	27
Sat. Fat, %	16	16	6
Protein, %	15	15	18
CHO, %	48	48	65
Fiber, g	9	31	31
Potassium, mg	1700	4700	4700
Magnesium, mg	165	500	500
Calcium, mg	450	450	1240
Sodium, g	3 - 3.5	3 - 3.5	3 - 3.5

"Typical American" "High fruits and vegetables" "Combination diet" (aka "DASH diet")

Sacks, AJE 1995; Appel NEJM, 1997



Can we apply this same approach to evaluate the impact of diet patterns in cancer prevention?

Intervention studies in cancer

- Long-term feeding studies not practical
- However, you can instruct people how to follow a research diet

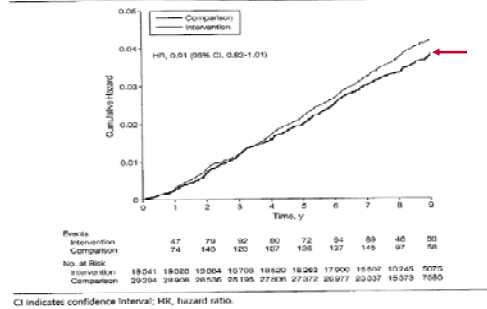
Example: WHI low fat diet and breast cancer prevention

- Randomized, controlled primary prevention trial conducted at 40 US centers from 1993 – 2005
- 48,835 postmenopausal women
- Goal of diet instruction: 20% fat, at least 5 servings of fruits & vegs and 6 servings of grains per day.
- Control group not instructed on dietary change
- Year 6 difference between intervention and control:
 - 8% percent lower total fat intake
 - 1.1 more servings of fruit and vegetables/day
 - .4 more serving of grains
 - 0.8 kg more weight loss

Prentice RL, JAMA, 2006

WHI results for low fat diet pattern and breast cancer risk

Figure 2. Kaplan-Meier Estimates of the Cumulative Hazard for Invasive Breast Cancer



Prentice, JAMA 2006

Evaluate diet patterns using diet questionnaires from large observational datasets ...

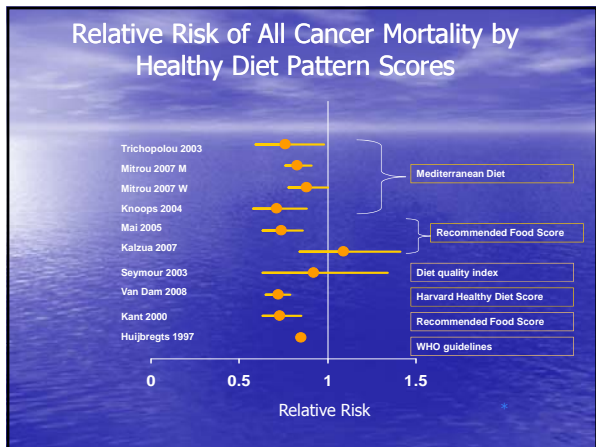
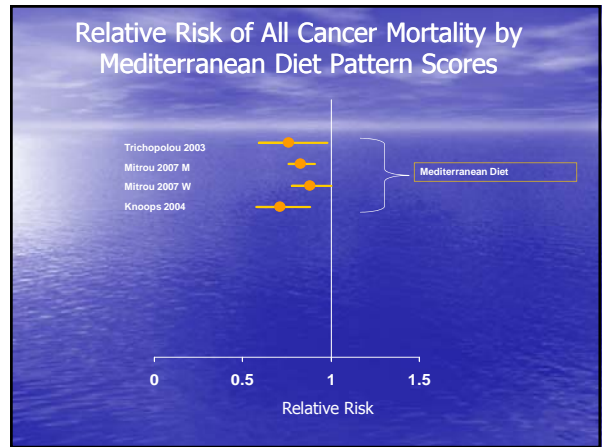
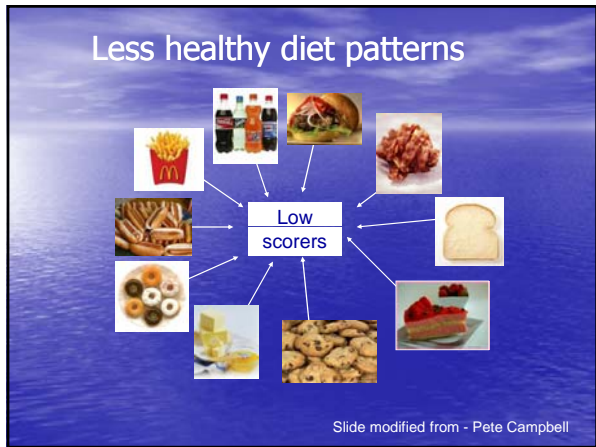
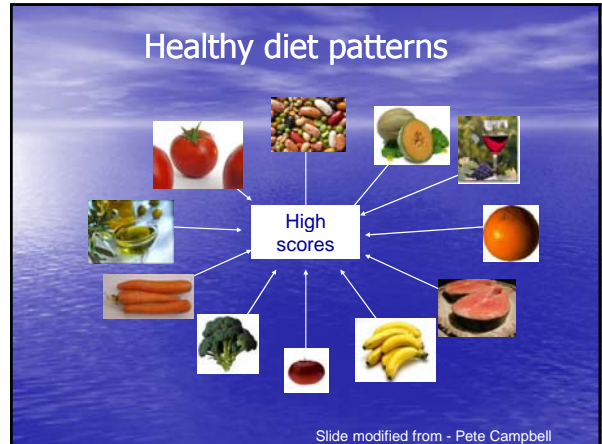
Diet Scores

- Develop scores with criteria developed *a priori*
- Often based on dietary guidelines, or other proposed ideal patterns
- Allows for evaluation of simultaneous adherence to a set of recommendations

Mediterranean diet score

	<median	≥ median
Vegetables	0	1
Legumes	0	1
Fruit	0	1
Cereal	0	1
Fish	0	1
Meat	1	0
Dairy	1	0
Mono:Poly	0	1
Alcohol	M: 10-50g=1; F 5-25g=1	

Trichopolou, et al 2003



Summary of the evidence

- **Nutrients:** Most RCTs of individual nutritional supplements and cancer prevention in humans, especially in well-nourished populations, have not shown benefit
- **Foods:** evidence consistent for certain food groups in cancer prevention, especially limiting red & processed meat
- **Diet patterns** appear to be more strongly related to lower cancer risk

American Cancer Society National Home Office Atlanta, GA



Mission: "Dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives and diminishing suffering from cancer through research, education, advocacy, and service."

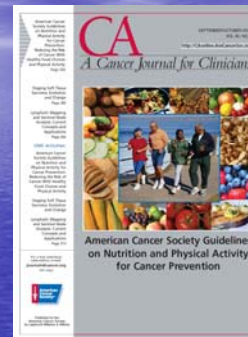


ACS Research Department

- **GOAL:** To determine the cause of cancer and to support efforts to prevent, detect, and cure the disease
- Largest source of private, not for profit cancer research funds in US
 - Extramural grants (44 Nobel Laureats funded)
 - Epidemiology Research
 - Surveillance and Health Policy Research
 - Behavioral Research
 - Statistics and Evaluation



American Cancer Society *Guidelines on Nutrition and Physical Activity for Cancer Prevention*



<http://CAonline.AmCancerSoc.org> - Sept/Oct 2006 Kushi, et al

ACS 2006 Nutrition and Physical Activity Guidelines

Individuals:

- Maintain a healthy weight throughout life
- Adopt a physically active lifestyle
- **Consume a healthy diet, with an emphasis on plant sources**
 - 5+ svgs variety of vegetables and fruits/day
 - Limit red and processed meats
 - Choose whole grains over refined grains and sugars
 - Choose foods and beverages in amounts for healthy weight
- If you drink alcoholic beverages, limit consumption ($\leq 2/d$ men, $\leq 1/d$ women)



Change in prevalence of healthy behaviors over 18 years – U.S. men and women aged 40-74, NHANES (%)

	1988	2006
BMI ≥ 30 kg/m ²	28%	36%
Physical Activity		
None	15	36
>12 times/mo.	53	43
Smoking	27	26
Fruit/Veg $\geq 5/d$	42	26
Alcohol – mod.	40	52
5 Healthy habits	15	8

King, D, et al, Am J Med, 2009

This might seem like old fashioned advice



(but, recommendations have evolved...)

ACS 2006 Nutrition and Physical Activity Guidelines

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Communities:

- Facilitate healthy nutrition, physical activity, and maintenance of a healthy weight at the population level



We need to make it easier for people to access healthy food



Questions?