Can Food Prevent Cancer? Magic bullets vs. dietary patterns

Nutrition and Health Conference
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American Cancer Society

Study Finds that Fiber Prevents Colon Cancer
Researchers claim that high fiber will keep the doctor away

Brian Carter
Epidemiology

Outline:
- RCTs
- History
- Foods
- ACS Guidelines on nutrition and physical activity for cancer prevention
- Diet patterns

The cancer continuum
- Prevention
- Research
- Early Detection
- Education
- Advocacy
- Treatment
- Dissemination
- Survivorship

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

P. Greenwald, BMJ, 2002

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

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

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th># of studies</th>
<th>↓ risk (% of studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>30</td>
<td>93%</td>
</tr>
<tr>
<td>Lung</td>
<td>13</td>
<td>85%</td>
</tr>
<tr>
<td>Colon</td>
<td>19</td>
<td>79%</td>
</tr>
<tr>
<td>Breast</td>
<td>12</td>
<td>67%</td>
</tr>
<tr>
<td>Prostate</td>
<td>6</td>
<td>17%</td>
</tr>
<tr>
<td>All</td>
<td>196</td>
<td>78%</td>
</tr>
</tbody>
</table>

WCRF, 1997

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

The Lancet · Saturday 28 November 1981

Summary
Intake of vitamin A (carotene) was inversely related to the 15-year incidence of lung cancer in a prospective epidemiological study of 1954 middle-aged men. The relative risk of lung cancer in the first (lowest) to fourth quartiles of the distribution of carotene intake were respectively, 7.0, 5.5, 3.6, 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

Proportion of Cancer Deaths Attributed to Various Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Percent of all cancer deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>35</td>
</tr>
<tr>
<td>Tobacco</td>
<td>30</td>
</tr>
<tr>
<td>Infection</td>
<td>10</td>
</tr>
<tr>
<td>Reproductive/sexual behavior</td>
<td>7</td>
</tr>
<tr>
<td>Occupation</td>
<td>4</td>
</tr>
</tbody>
</table>

Best estimate: 10-70
Range: 25-40
1-7
1-13
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

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

Sources of widely studied compounds

<table>
<thead>
<tr>
<th>Food Sources</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrots, sweet potatoes, winter squash, mango, cantaloupe, pumpkin</td>
<td>Beta-carotene</td>
</tr>
<tr>
<td>Citrus fruits and juices, broccoli, green peppers, bell peppers, strawberries, leafy green vegetables</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Nuts, oils, peanut butter, some fruits and seeds</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Tomatoes, watermelons, pink grapefruit, apples</td>
<td>Lycopene</td>
</tr>
<tr>
<td>Green leafy vegetables, broccoli, beans, peas</td>
<td>Folate</td>
</tr>
</tbody>
</table>

Randomized, controlled trials of dietary supplements for cancer prevention

- Modify only constituents of interest
- Easy to administer, assess compliance
- Public is likely to accept 'prescription' rather than 'proscription'
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 μg)

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

β-Carotene Intervention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Size</th>
<th>Yrs</th>
<th>Dose</th>
<th>Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATBC</td>
<td>29,133 M</td>
<td>5-8</td>
<td>20 mg/d</td>
<td>16% ↑ smokers</td>
</tr>
<tr>
<td>CARET</td>
<td>18,314 MW</td>
<td>3.7</td>
<td>30 mg/d</td>
<td>36% ↑</td>
</tr>
<tr>
<td>PHS</td>
<td>22,071 M</td>
<td>12</td>
<td>50 mg/2d</td>
<td>no dif</td>
</tr>
<tr>
<td>WHS</td>
<td>39,876 W</td>
<td>4.1</td>
<td>50 mg/2d</td>
<td>no dif</td>
</tr>
</tbody>
</table>

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

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


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


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

<table>
<thead>
<tr>
<th></th>
<th>Polyps</th>
<th>Colon</th>
<th>Breast</th>
<th>Prostate</th>
<th>Lung</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Selenium</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>β-carotene</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mixtures of antioxidants</td>
<td>No</td>
<td>No</td>
<td>Weak</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Summary courtesy of Alan Kristal
Do other supplements reduce cancer risk?

<table>
<thead>
<tr>
<th>Fiber</th>
<th>Polyps</th>
<th>Colon</th>
<th>Breast</th>
<th>Prostate</th>
<th>Lung</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Folate</th>
<th>↑ risk</th>
<th>No</th>
<th>No</th>
<th>No</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Calcium</th>
<th>↓ risk</th>
<th>Yes</th>
<th>No</th>
<th>No</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Vitamin D</th>
<th>In trial</th>
<th>In trial</th>
<th>In trial</th>
<th>In trial</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

*New RCT – "VITAL" of 2,000 IU vitamin D: Cancer, Heart Disease and stroke: [http://www.vitalstudy.org/](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

- RCTs
- Foods
- Diet patterns

Food synergy

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

Tomatoes contain:
- Lycopene
- Phytoene
- β-carotene
- Κ-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.

“Food synergy”

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

Liu, R. J Nutr 2004

Systematic review of the literature

VEGETABLES, FRUITS, 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. Judgments are graded according to the strength of the evidence.

What about other aspects of diet?

Ecologic evidence relating colon cancer incidence to per capita meat consumption, women 1975
Trends in Proportions of Energy Available from Meat, Fish, Milk, Eggs in the US and Asia

Red Meat Intake and Colorectal Cancer

Prospective studies (Larsson & Wolk, Int J Cancer, 2006)

Summary of the evidence for foods and cancer

Red & Processed meats and cancer: Biologic mechanisms

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

Outline:
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

Evolution of 'diet patterns' hypothesis in the Dietary Approaches to Stop Hypertension Study

Hypotheses:
- Potassium
- Magnesium
- Calcium
- Fiber
- Fat

Multiple RCTs of individual nutrients, with modest effects (1980's, 90's)
Test overall pattern, emulating original populations (using contemporary foods)

DASH – Dietary Patterns feeding study

Nutrient Targets for DASH Diets

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Control</th>
<th>Fruit/Vegetable</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>kcal/d</td>
<td>2100</td>
<td>2100</td>
<td>2100</td>
</tr>
<tr>
<td>Fat, %</td>
<td>37</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>Sat. Fat, %</td>
<td>16</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Protein, %</td>
<td>15</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>CHO, %</td>
<td>48</td>
<td>48</td>
<td>55</td>
</tr>
<tr>
<td>Fiber, g</td>
<td>9</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Potassium, mg</td>
<td>1700</td>
<td>4700</td>
<td>4700</td>
</tr>
<tr>
<td>Magnesium, mg</td>
<td>165</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>450</td>
<td>450</td>
<td>1240</td>
</tr>
<tr>
<td>Sodium, g</td>
<td>3 - 3.5</td>
<td>3 - 3.5</td>
<td>3 - 3.5</td>
</tr>
</tbody>
</table>

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

Sacks, AJE 1996; Appel NEJM, 1997

Run-in and Intervention Periods

Randomization
- Control
- Fruit / Vegetable

Control Diet
- F&V, Low fat milk, low fat

3 wks Run-in
8 weeks Intervention

Weekly Blood Pressure During Intervention Feeding
- CONTROL
- Fruit
- Combination
Appel NEJM 1997
Can we apply this same approach to evaluate the impact of diet patterns in cancer prevention?

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 & veggies 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
  - 0.4 more serving of grains
  - 0.8 kg more weight loss

Prentice RL, JAMA, 2006

Intervention studies in cancer

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

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

WHI results for low fat diet pattern and breast cancer risk

Prentice, JAMA 2006

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

<table>
<thead>
<tr>
<th>Food Group</th>
<th>&lt;median</th>
<th>≥ median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetables</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Legumes</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fruit</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cereal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fish</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Meat</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dairy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mono:Poly</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol</td>
<td>M: 10-50g=1; F 5-25g=1</td>
<td></td>
</tr>
</tbody>
</table>

Trichopoulou, et al 2003

Healthy diet patterns

High scores

Less healthy diet patterns

Low scorers

Relative Risk of All Cancer Mortality by Mediterranean Diet Pattern Scores

0 0.5 1 1.5

Relative Risk

Healthy diet patterns promote healthy weight

Manios, PH Nutrition, 2010
Dugan, Asia Pacific J Clin Nutr, 2009
Murtagh, JADA, 2007
Newby, AJ CN, 2003
Quatramoni, et al AJDA, 2002
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.

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 Laureates funded)
  - Epidemiology Research
  - Surveillance and Health Policy Research
  - Behavioral Research
  - Statistics and Evaluation

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+ servings 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 (≤2/d men, ≤1/d women)

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


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

<table>
<thead>
<tr>
<th>Behavior</th>
<th>1988</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥30 kg/m²</td>
<td>28%</td>
<td>36%</td>
</tr>
<tr>
<td>Physical Activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>≥12 times/mo.</td>
<td>53</td>
<td>43</td>
</tr>
<tr>
<td>Smoking</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Fruit/Veg ≥ 5/d</td>
<td>42</td>
<td>26</td>
</tr>
<tr>
<td>Alcohol – mod.</td>
<td>40</td>
<td>52</td>
</tr>
<tr>
<td>5 Healthy habits</td>
<td>15</td>
<td>8</td>
</tr>
</tbody>
</table>

This might seem like old fashioned advice (but, recommendations have evolved...)

ACS 2006 Nutrition and Physical Activity Guidelines

**Individuals:**
- Maintain a healthy weight throughout life
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- If you drink alcoholic beverages, limit consumption (≤2/d for men, ≤1/d for women)

**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?