Weighing Scientific Evidence

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Disclosure/Disclaimer

- No financial conflicts
- Outside activity: editor-in-chief, JNCI
  - No connection with the NCI or Federal government
- Opinions are mine, not official positions of the Federal Government or National Institutes of Health
“A wise man proportions his belief to the evidence.”

David Hume, Scottish philosopher, 1711-1776
Questions to Ask About Medical Research

1. What is the exposure and what is the outcome?
2. How certain is it that exposure causes outcome?
3. How important is the outcome?
4. How big is the effect?
5. To whom does it apply?
Levels of Decision Making

Level I: “Would you have this done for yourself or for someone else in your immediate family?”
Influenced by one’s personal experience with the disease and capacity to deal with risk.
Affects few people.

Level II: “What would I recommend to my patient/client?”
Physician making a recommendation for his/her patients. Influenced by prior experience, but the scientific evidence may play a greater role.
Affects possibly hundreds of people.

Level III: “What would I recommend to the nation, the world?”
Across-the-board recommendations for a population. Must be based on rigorous assessment of the scientific evidence.
Affects hundreds of thousands, even millions of people.

slide courtesy of Leon Gordis, Ph.D., Johns Hopkins University
Confounding Variables

Exposure \rightarrow \text{R.I.P.} \rightarrow \text{Outcome}

Confounder

Confounding is the death of any study!
Confounding Variables

Volvo

Fewer accidents

High SES
Safety conscious
“Soccer mom”
Age
Confounding Variables

Vitamin/Supplement Intake

Lower rate of Cancer, Heart Disease...

Health consciousness
Health insurance
Access to care
Confounding is a concern in any observational study!

Confounding is more likely when someone’s choice (patient, doctor, etc.) determined who was in the exposed and unexposed group.
Observational Studies

“...are guilty until proven innocent.”

David Ransohoff, M.D., JNCI, 2006
Vitamin D Analytic Framework

1. Health Outcomes
2. Intermediate Endpoints
3. Health Outcomes (dotted line)
4. Toxicities

Interventions:
- Intake
- Sun exposure

Targets Population(s)
Vitamin D: Potential Target Populations

- Children
- Women of reproductive age
- Elderly women
- Elderly men
- Different ethnic groups, skin pigmentation
- Populations at different latitudes (above 37° North in winter)
Vitamin D: “Interventions”

- Dietary intake/fortified foods
- Dietary supplements
- Exclusive breastfeeding
- Sun exposure (UVB light): the main source worldwide
  - Avoidance to protect against skin cancer
  - Sunscreen
  - Protective clothing
Biomarkers/Surrogate Endpoints for Optimal Vitamin D Status

Potential Surrogate Outcomes

- Blood levels
- Bone mineral density
- Polyps
- PTH levels

None validated

- None can substitute for health outcomes
Health Outcomes of Sun/UV Exposure or Vitamin D Intake

• Bone collagen matrix mineralization
  • Fracture
  • Rickets
  • Falls
• Cancers
  • Skin: melanoma, non-melanoma
  • Colorectal
  • Prostate
  • Breast
• Cardiovascular disease
• Autoimmune disease
# A Closer Look at Outcomes

<table>
<thead>
<tr>
<th>Health Outcomes</th>
<th>Surrogate Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very important</td>
<td>Unclear importance</td>
</tr>
</tbody>
</table>

| Fewer deaths, period | Fewer deaths due to specific disease | Fewer complications of disease | Fewer diagnoses of disease | Better test results | Change in risk factor |

Figure adapted from HG Welch
### Discordance Between Surrogate Endpoint Biomarkers and Health Outcomes

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effect on Surrogate Endpoint</th>
<th>Effect on Health Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>High vs. std. dose Paclitaxel</td>
<td>↑ RR &amp; PFS</td>
<td>⇔ Mortality (no effect) ↑ Toxicity</td>
</tr>
<tr>
<td>Encainide, flecainide</td>
<td>↓ Cardiac arrhythmias (PVCs)</td>
<td>↑ Sudden Death</td>
</tr>
<tr>
<td>Postmenopausal Estrogen + Progestin</td>
<td>↓ Cholesterol, ↓ LDL, ↑ HDL</td>
<td>↑ Coronary heart disease</td>
</tr>
<tr>
<td>Intervention</td>
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<td>Effect on Health Outcome</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Low fat, high vegetable diet (Women’s Health Initiative)</td>
<td>↓ Polyps</td>
<td>← Colon Cancer</td>
</tr>
<tr>
<td>Torcetrapib</td>
<td>↑ HDL cholesterol</td>
<td>↑ Deaths, heart failure</td>
</tr>
</tbody>
</table>
“Level of Evidence” for Cancer Prevention
Physician Data Query (PDQ)

Definition: certainty of the editorial board’s estimate of the health effects of implementing an intervention

Steps

I. Description of the evidence (5 Domains)
II. Summary assessment for both benefits and harms
Description of Evidence in PDQ: Five Domains

1. Study design: ranked by design strength
2. Internal validity: “quality” of execution within study design (good, fair, poor)
3. Consistency (coherence)/volume of evidence
   - One vs. multiple studies
   - Small vs. large studies
   - Consistent direction of outcomes
4. Magnitude of effects: prefer absolute vs. relative effects
   - Change from 1% to 0.5%, or from 4/1000 to 2/1000 [Not: 50% decrease]
5. External validity (good, fair, poor)
   - Applicability in usual practice with same effect?
Internal Validity Criteria for Randomized Controlled Trials (RCTs) and Cohort Studies

Initial assembly of comparable groups:
- For RCTs: adequate randomization, including concealment
- For cohort studies: consideration of potential confounders with adjustment in the analysis

Maintenance of comparable groups (attrition, crossovers, adherence, contamination)

Low rates of loss to follow-up (and non-differential)

Outcome measurements: equal, reliable, and valid (includes masking)

Clear definition of interventions

All important outcomes considered

Source: R. Harris et. al., Am J Prev Med 2001
Physician Data Query (PDQ) Summary of Evidence for Cancer Prevention with Vitamins

- **Rationale**: Many different mechanistic pathways for anticancer effects have been invoked.

- **Benefits**: Evidence is insufficient to support the use of multivitamin and mineral supplements or single vitamins or minerals to prevent cancer.

- **Harms**: Two prospective placebo-controlled trials found that smokers and former smokers who received beta carotene supplements had increased lung cancer incidence and mortality.

- **Implications**: Research into the potential anticancer properties of vitamin and mineral supplements is ongoing.
OK, Stranger... What's the circumference of the Earth?.. Who wrote "The Odyssey" and "The Iliad"?.. What's the average rainfall of the Amazon Basin? Bart, you fool! You can't shoot first and ask questions later!
Illusions of knowledge are the obstacles to discovery.

Daniel Boorstin, 1983