The Role of Observational Studies

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As required, I would like to report that I have no financial relationships to disclose, nor will I discuss off-label or investigational usage of drugs.
Nutritional Epidemiology

- Correlational (ecologic) studies
- Migrant studies
- Secular trend studies
- Case-control (retrospective)
- Cohort studies (prospective)
- Interventions
Randomized Controlled Trials vs. Observational Studies of Cancer

Observational Studies

Each individual study is limited to some degree by weaknesses in size, dietary assessment, potential biases, and (most importantly) the potential for uncontrolled confounding.

The main strength of observational studies is the ability to examine an association in various circumstances, in diverse populations, using multiple approaches (correlational, secular, migrant studies, case-control and cohort studies), combined with understanding of biology, which allows us to construct a “model” that coherently explains most of the data.
4 Critical Issues

- Timing of association
- Dose-response
- Complexity of diet in influencing carcinogenic pathways
- Inter-correlation among single nutrients
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- **Timing of association**
  - Dose-response
  - Complexity of diet in influencing carcinogenic pathways
  - Inter-correlation among single nutrients
Schematic of dominant factors determining the variation in radiation-induced cancer risk with age at exposure.

Effects of Age at Exposure and Attained Age on the Excess Risk of Solid Cancer Incidence Following Exposure to 1 Gy.

Excess Relative Risk (ERR)
Comparison of the dose-response effect on micronucleus induction in cytokinesis-blocked cultured lymphocytes caused by acute exposure to X-rays up to a maximum dose of 20 rad with folic acid.
Nutrient factors that influence genomic integrity are likely to act very early in carcinogenesis, especially for some cancers (e.g. breast cancer)
Nurses’ Health Study
(n=121,700, age 30-55 yr)

Health Professionals Follow-up Study
(n=51,529, age 40-75 yr)
Colorectal Cancer Risk (NHS, HPFS)

Multivariate RR

- 0-4 year lag (P=0.19)
  - Total Folate Intake (mg/day):
    - <250: 1.0
    - 250-399: 0.96
    - 400-499: 1.00
    - 600-799: 0.92
    - >800: 0.88

- 12-16 year lag (P=0.01)
  - Total Folate Intake (mg/day):
    - <250: 0.80
    - 250-399: 0.79
    - 400-499: 0.69
    - >800: 0.65

Colorectal Cancer
(NHS, HPFS)

Breast Cancer
(NHS II, ages 33-53 yrs)


Red Meat Intake in High School (servings / day)

Relative Risk

P trend = 0.03

The association of milk / calcium intake and colon cancer risk demonstrates the complexity of one dietary factor acting at different points in the lifespan.
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Factor</th>
<th>Association with Risk of Colon Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecologic</td>
<td>milk</td>
<td>↑</td>
</tr>
<tr>
<td>Case-control</td>
<td>milk / calcium</td>
<td>↓</td>
</tr>
<tr>
<td>Cohort</td>
<td>milk / calcium</td>
<td>↓</td>
</tr>
<tr>
<td>Intervention (adenoma)</td>
<td>calcium</td>
<td>↓</td>
</tr>
</tbody>
</table>
Colon Cancer Mortality
by Milk and Milk Product Consumption*

*WHO Food and Health Indicators in Europe for 1971 per 100,00 population, ages 0-64

Nonparametric Regression Curve for the Relationship between Total Calcium Intake and Colorectal Cancer
Pooled Cohort Analysis

Cho et al., JNCI 2004
Hypothesis:

Western (meat, dairy) diet

↓

↑ IGF-1

In Utero

Birth
Childhood
Adolescence

↑ apoptosis

Adulthood

Colorectal Cancer Risk:

↑↑↑

↑↓
Boyd Orr Study Cohort (1948-2005)
Colorectal Cancer (n = 76)


P trend = 0.005
4 Critical Issues

• Timing of association

➤ Dose-response

• Complexity of diet in influencing carcinogenic pathways
• Inter-correlation among single nutrients
If a nutrient is causally associated with cancer risk, the effect is likely to occur over a specific range (dose-response)
Nonparametric Regression Curve for the Relationship between Total Calcium Intake and Colorectal Cancer Pooled Cohort Analysis

Cho et al., JNCI 2004
Ranges of Nutrient Intakes Tested in Observational and Randomized Controlled Trials (RCTs) of Calcium

Range in Observational Studies

Range in RCT (ATBC)

Plasma Beta-Carotene (ng/L)

0.0 0.10 0.29

3.00 0.18
Clinical Folate Deficiency

Placebo

Treatment 1 µg/day Folic Acid

RCT of Folic Acid and Colorectal Adenoma

4 Critical Issues

- Timing of association
- Dose-response

- Complexity of diet in influencing carcinogenic pathways
  - Inter-correlation among single nutrients
Two Examples:

- Energy balance (insulin)
- One-carbon metabolism
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- Energy balance (insulin)
  - One-carbon metabolism
WCRF / AICR Cancer Prevention Recommendations:

- Be as lean as possible
- Be physically active
- Avoid sugary drinks, energy-dense foods
- Eat more variety of vegetables, fruits, whole grains and legumes
- Limit red meats and processed meats
- Limit alcoholic drinks
- Limit consumption of salt
- Don't use supplements to protect against cancer
- * Breastfeed exclusively for up to 6 months
- * Cancer survivors should follow the recommendations for cancer prevention
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Excessive Calorie Intake

\[ \uparrow \text{ (Central Adiposity)} \]
- \[ \uparrow \text{free fatty acids} \]
- \[ \downarrow \text{adiponectin} \]
- \[ \uparrow \text{aromatase} \]

Insulin Resistance

- \[ \downarrow \text{SHBG} \]
- \[ \downarrow \text{IGFBPs} \]

\[ \uparrow \text{Bioavailable Sex Hormones} \]
\[ \uparrow \text{Insulin} \]
\[ \uparrow \text{Bioavailable IGF-1} \]

Inflammation

\[ \uparrow \text{Proliferation} \]
\[ \downarrow \text{Apoptosis} \]
\[ \uparrow \text{Genomic Instability} \]
Risk Factors* for Colon Cancer and Adenoma Compatible with Insulin/IGF Hypothesis

- ↑ circulating C-peptide / insulin
- ↑ circulating IGF-1 or IGF-1/BP-3
- Acromegaly (↑ IGF, insulin)
- Type 2 diabetes
- Metabolic syndrome (↑ insulin)
- Tallness (↑ IGF-1)
- ↑ BMI
- ↑ waist circumference
- ↓ physical activity
- Western diet (↑ insulin)

* based on meta-analyses
Physicians’ Health Study

IGF-1 / IGFBP-3:

- Tertile 1
- Tertile 3

Ma et al., 2004
Excessive Caloric Intake → Adiposity → Insulin Resistance

Diet

↑ Insulin

↑ Bioavailable IGF-1

↓ IGFBP

↑ Proliferation

↓ Apoptosis

↑ Genomic instability
Multivariate RR for C-Peptide Dietary Pattern Score and Risk of Colon Cancer by BMI and Physical Activity (NHS; n=66,714)

Fung T.T. et al., submitted.
Dietary factors that predict hyperinsulinemia will likely differ across populations.

Examples:

• **U.S.** → red meat, sweetened beverages ↑; coffee ↓

• **Sweden** → rye bread (lignans) ↓

• **Costa Rica** → beans / white rice ratio ↓
Two Examples:

• Energy balance (insulin)

➤ One-carbon metabolism
1-Carbon Sources
methionine
choline
betaine

1-Carbon Carrier
folate

Co-factors
vitamins B2, B6, B12

Antagonists
alcohol
Interaction of Alcohol with Methyl Transfer

4 Critical Issues

• Timing of association
• Dose-response
• Complexity of diet in influencing carcinogenesis

➢ *Inter-correlation among single nutrients*
Fruits and Vegetables

• Up to the early 1990s, most evidence came from case-control studies

• Suggested benefits led to strong recommendations for total fruit and vegetable intake, and led to focus (including RCTs) on specific nutrients
# Evidence of Decreased Risk

<table>
<thead>
<tr>
<th>Vegetables and Fruits</th>
<th>Convincing</th>
<th>Probable</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetables</td>
<td>Mouth, pharynx</td>
<td>Larynx</td>
<td>Ovary</td>
</tr>
<tr>
<td></td>
<td>Esophagus</td>
<td>Pancreas</td>
<td>Endometrium</td>
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<tr>
<td></td>
<td>Lung</td>
<td>Breast</td>
<td>Cervix</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>Bladder</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Colon, rectum</td>
<td></td>
<td>Liver, Prostate, Kidney</td>
</tr>
</tbody>
</table>

Food, Nutrition and the Prevention of Cancer: A Global Perspective
World Cancer Research Fund, 1997
Randomized trials have offered strong evidence against benefits of relatively high doses of selected nutrients and risk of cancer over approximately a 5-year period before diagnosis:

- selenium
- vitamin E
- vitamin C
- B vitamins
- β-carotene
Results from prospective studies began to be published in the 1990’s
Fruits and Vegetables and Cancer
(NHS and HPFS)

Relative Risk

Servings/day

<1.5 1.5-<3 3-<5 5-<6 6-<8 8+

(n = 6584 W, 2500 M)

Fruits and Vegetables and Cardiovascular Disease (NHS and HPFS)


P for trend < 0.001
Fruits and Vegetables and the Risk of Cancer

<table>
<thead>
<tr>
<th>Decreases Risk</th>
<th>Exposure</th>
<th>Cancer site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convincing</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Probable</td>
<td>Non-starchy vegetables</td>
<td>Mouth, pharynx, larynx</td>
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<tr>
<td></td>
<td></td>
<td>Esophagus</td>
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<tr>
<td></td>
<td></td>
<td>Stomach</td>
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<tr>
<td></td>
<td>Allium vegetables</td>
<td>Stomach</td>
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<tr>
<td></td>
<td>Garlic</td>
<td>Colorectum</td>
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<tr>
<td></td>
<td>Fruits</td>
<td>Mouth, pharynx, larynx</td>
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<td></td>
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<td>Esophagus</td>
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<td></td>
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<td>Lung</td>
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<td></td>
<td></td>
<td>Stomach</td>
</tr>
<tr>
<td></td>
<td>Foods with folate</td>
<td>Pancreas</td>
</tr>
<tr>
<td></td>
<td>Foods with carotenoids</td>
<td>Mouth, pharynx, larynx</td>
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<td>Esophagus</td>
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<td></td>
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<td>Lung</td>
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<td>Foods with beta-carotene</td>
<td>Esophagus</td>
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<td></td>
<td>Foods with lycopene</td>
<td>Prostate</td>
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<td>Foods with vitamin C</td>
<td>Esophagus</td>
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<tr>
<td></td>
<td>Foods with selenium</td>
<td>Prostate</td>
</tr>
</tbody>
</table>

WCRF / AICR, 2007
Total Vegetables and Breast Cancer by ER Status

S. Jung, unpublished data

n = 19,869 ER+, 4821 ER- breast cancer cases; 21 studies

P for common effects for quintile 5 < 0.001

Courtesy of S.A. Smith-Warner, 2011
Suggestions for Future Observational Studies

- Better assessment of diet
- Better conceptualization of diet into relevant carcinogenic pathways
- Large numbers, long follow-up
- Cancer sub-types
- Early life exposures
- Survivorship studies
- Complementary data (e.g. genetics)