Biomarkers and Surrogate Endpoints for Evaluating Health Benefits of Food Components: Promises and Perils

J. A. Milner
milnerj@mail.nih.gov

Nutrition Science Research Group
Division of Cancer Prevention
National Cancer Institute
Bethesda, MD 20892
Unprecedented opportunities exist for the expanded use of foods and components to achieve genetic potential, increase productivity and reduce the risk of disease.
5 of the Top 10 Causes of Death of Americans Relate to Dietary Habits

Cancer and Heart Disease Battle for Top Position
DEFINITION

Clinical Endpoint - A characteristic or variable that reflects how a patient feels, functions or survives.

Surrogate Endpoint - a biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.

Source: Biomarkers Definition Working Group -1998
**Surrogate marker**

Is a response variable for which a test of the null hypothesis on no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint.


i.e. A laboratory or physical sign that is used in studies as a substitute for a clinically meaningful endpoint such as pain or death.
Biomarker (Biological Marker)

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

SYSYTEMS BIOLOGY APPROACH TO BIOMARKERS RESEARCH

Discovery

Validation

DETECTION
DIAGNOSIS

BIOMARKERS

PREVENTION

Basic Scientist

Physician/Scientist

Bioinformatics
Technology Developers

Resources/ Biorespository

Pathologist

Resources/ Biorespository
Capturing the Response

Intervention/Treatment → Biomarker → Surrogate Endpoint (Obesity)

Beneficial or Harmful Effects
Not Measured by a Biomarker

IGF

Clinical Endpoint (Diabetes)
Pathway of Disease

Natural History of Disease

Environment + Lifestyle

Genetic Risk

Early Detection

Patient Stratification

Disease Staging

Treatment Options

Biomarkers

Outcomes

Quality Of Life

Treatment History
Fundamental Question Remains if Pathologic Evaluations Reflects What Occurs Normally?
Biomarkers and Other Intermediate Endpoints

Ideal Qualities:

- Readily accessible
- Easily & reliably assayed
- Differentially expressed
- Directly associated with disease progression
- Modulable
- *Predictive*
Multiple Promises and Perils

• Many putative biomarkers
  • few validated
  • lack of criteria for validation
  • more clinical studies needed

Thus biomarkers for disease assessment and early detection are woefully inadequate
<table>
<thead>
<tr>
<th>Health Effects</th>
<th>+ and -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intake of Dietary Constituent</td>
<td>Absorbed Dose</td>
</tr>
<tr>
<td>Susceptibility (Genetic/Environment)</td>
<td>Inactive Metabolite</td>
</tr>
<tr>
<td>Early Biologic Effect</td>
<td>Biologically Effective Dose</td>
</tr>
<tr>
<td>Altered Structure/Function</td>
<td></td>
</tr>
</tbody>
</table>
Numerous Dietary Components May Influence Health

- **Essential Nutrients** - Ca, Zn, Se, Folate, C, E
- **Non-Essential**
  - **Phytochemicals** - Carotenoids, Flavonoids, Indoles, Isothiocyanates, Allyl Sulfur
  - **Zoochemicals** - Conjugated linoleic acid, n-3 fatty acids
  - **Fungochemicals** - Several compounds in mushrooms
  - **Bacteriochemical** - Those formed from food fermentations and those resulting from intestinal flora
Epidemiologic Studies of Soy Components in Diet: Breast Cancer Risk Reduction

Asian

Lee ‘92 (total soy protein)
- p < 0.001 Premenopausal
- NS Postmenopausal

Hirose ‘95 (bean curd, miso)

Yuan ‘95 (tofu, soymilk)
- NS Premenopausal
- NS Postmenopausal
- NS p = 0.44–0.79 Shanghai, Tianjin

Wu ‘96 (tofu)
- p < 0.01 Premenopausal
- p < 0.05 Postmenopausal

Dai ‘01 (soy)
- NS All Breast Cancer
- S Just ER+/PR+

Western

Ingram ‘97 (urinary isoflavones)
- NS Diadzein
- p = 0.009 Equol

den Tonkelaar ‘01 (urinary phytoestrogens)
- NS Postmenopausal

Keinan-Boker ‘02 (food content)
- NS Isoflavones
- S Lignans

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Promises and Perils for Diet Biomarkers

Undeniable limitation in evaluation of eating behaviors

Unclear if markers should focus on nutritional status or dietary intake
Tissue and Leukocyte IQ-DNA Adducts

IQ-DNA Adducts (RAL x 10^7)

* p<0.05

Control

0.20% Indole-3-Carbinol

Leukocyte  Mammary  Colon

IQ= 2-amino-3-methylimidazo[4,5-f]quinoline

Advances in Genomics Are Significantly Changing Views and Strategies for Health Promotion and should help identify responders and non-responders
The Evolution of Biomarkers ??

First Generation
Serum Markers

Gene specific Mutations

Second Generation

Third Generation
Gene Expression Profiles

Fourth Generation
Functional Genomics
The “Omics” of Nutrition and Effect Biomarkers
**Dietary Calcium, VDR FokI Genotype and Colon Cancer Risk**

Influence of Caffeine on Bone Mass May Depend on Genes

Diet-Gene Interactions in Colon Cancer

Yangetal, Cancer Res. 61, 565, 2001
Nutrigenomics today!

- Commercial Nutrition-Gene Test
  - Genelex Sciona 19 genes including MTHFR $395
  - Gene Care CVD nutritional genetic test (South Africa) MTHFR (Hcyst), apoA1 (HDL) +9 others $400

- About 30,000 Genes, 5-8 Million SNPs
Gaps In Science Related to Susceptibility Biomarkers

- Large variation in genetic associations
- Studies often underpowered
- May require more than SNPS, i.e.
  - transcriptomics,
  - proteomics,
  - metabolomics
- Confounders not adequately evaluated
% Reduction in LDL Cholesterol as an Effect Biomarker

- Jenkins et al., JAMA 290: 502-510, 2003
- 4 weeks
- Statins vs. NCEP
  - Step 2 diet vs. a Portfolio eating plan:
    - plant sterols (1g/1000 kcal)
    - almonds (14 g/1000 kcal)
    - viscous fiber (9.8 g/1000 kcal)
    - soy protein (21.4 g/1000 kcal)

Dietary can lower cholesterol as much as cholesterol-lowering drugs
Do Not Over Interpret Biomarkers

MULTIPLE PATHWAYS

One Pathway: Attributable Proportion (AP) equals 1
Two Pathways: Attributable Proportion equals less than 1

AP = S (1-1/R)
Nahta et al., The Oncologist 2003;8:5-17
# A Polymeal For Reducing Cardiovascular Disease Risk

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>Possible % Reduction</th>
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<tbody>
<tr>
<td>Wine</td>
<td>150 ml</td>
<td>32</td>
</tr>
<tr>
<td>Fish</td>
<td>114g 4X wk</td>
<td>14</td>
</tr>
<tr>
<td>Dark Chocolate</td>
<td>100g/d</td>
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<tr>
<td>Fruit/Veg</td>
<td>400g/d</td>
<td>21</td>
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<tr>
<td>Garlic</td>
<td>2.7g/d</td>
<td>25</td>
</tr>
<tr>
<td>Almonds</td>
<td>68g/d</td>
<td>12.5</td>
</tr>
<tr>
<td>Combined effects</td>
<td></td>
<td>76</td>
</tr>
</tbody>
</table>

Components are “complex mixtures” - act synergistically

“Caution: This tomato soup combined with our chicken noodle soup can form a lethal nerve gas.”
Similar to Drugs One Size Does Not Fit All for the Effects of Diet on Cancer Prevention! Identifying Responders from Non-responders to Bioactive Food Components is the Challenge!
Anti-oxidant
Immune Enhancement
Carcinogen Metabolism
Cell Cycle Inhibition
Apoptosis

Typical Intakes

Response

Nutritional
Supranutritional
Toxic

Exposure

Life Style Issues

- What are appropriate assessment at various stages in time?
- What time is most relevant?
- How does diet interact with other lifestyle factors including exercise?
No Perfect Diet Exists That is:

- Desired by everyone
- Ideal for everyone healthwise
Nutritional Preemption
(A Strategy for Health Promotion)

Concept that bioactive food components can be introduced at points of initiation & progression for pathway leading to an unhealthy or lethal phenotype
When I knew all of life’s answers, they changed all the questions!
Success Will Rest With the ability to:

• Identify and validate nutrigenetic, nutritional epigenetic & transcriptomic, proteomic and metabolomic biomarkers of effect and susceptibility

• Communicate effectively its values to the health care community and consumers

• Ensure a responsible bioethical framework