Personalizing One’s Diet for Cancer Prevention

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No Disclosures
The World Is Changing: Projected Deaths

Cancer - The leading cause of death worldwide (2010)
Increase partially due to aging & growing society!

Do we have the infrastructure in place to deal with this crises?!
What dietary change is best?
Who will benefit and will anyone will be placed at risk??

Dr. Lee Jong-wook, Director General WHO
It has been estimated that about 1/3 of all cancer deaths may be attributable to dietary factors.
Suspect Functional Foods With Health Benefits

- Soy
- Tomatoes
- Spinach
- Broccoli
- Garlic
- Nuts
- Salmon
- Oats
- Blueberries
- Curcumin
- Green tea
- Red wine

Modified Time Magazine: January 21, 2002
Numerous Dietary Components Can Protect Against Cancer

- **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
Bacteria Can Generate New Metabolites from Dietary Components

<table>
<thead>
<tr>
<th>Food Component</th>
<th>Bacterial Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy</td>
<td>Equol</td>
</tr>
<tr>
<td>Fiber</td>
<td>Butyrate</td>
</tr>
<tr>
<td>Plant Lignans</td>
<td>Enterodiol, Enterolactone</td>
</tr>
<tr>
<td>Ellagic Acid</td>
<td>Urolithins A and B</td>
</tr>
<tr>
<td>Hops</td>
<td>8-Prenynlarningenin</td>
</tr>
<tr>
<td>Linoleic Acid</td>
<td>Conjugated Linoleic Acid</td>
</tr>
</tbody>
</table>
Always Questions About How Much Is Needed!

**More**

As progress the response gets better and better, with no end in sight (real life is seldom, if ever, like this. People often assume that if X is good, then 10X is better.

**More**

As increase the effect reaches a plateau, becoming no better with higher doses. This is common with many nutrients. Any excess is not absorbed and excreted (expensive urine / feces)

**More**

As increase effect reaches optimum At some dose it declines, showing that more is better up to a point and then harmful. Applies to some nutrients, e.g. Na⁺ high blood pressure, Fe, Se.
While Diet Linked to Cancer, Much Confusion Exists About What to Eat and Under What Circumstances!!

“Low fat diets don’t work. I eat fish every day and my butt still drags on the ground!”
Can your genes tell you how to focus your diet for cancer prevention?
The Genetic Revolution is Providing New Insights into a Number of Health Issues Including the Role of Diet in Cancer Prevention
The Increasing Complexity of the Central Dogma of Molecular Biology

What is Personalized Medicine?

- Using information about a person's genetic makeup to tailor strategies for the detection, treatment, or prevention of disease.

- Using molecular profiling technologies to assess DNA, RNA, protein, and metabolites to tailor medical care.

- Approach has the promise of delivering the right dose for the right indication to the right patient at the right time.
Recent advances:
Herceptin is a Novel Pioneering Drug for Personalized Medicine Approach Based on Pharmacogenomics to block Her2-neu expression.

Evidence Has Existed for Some Time:
EGCG from Green Tea, Oleic Acid from Olive Oil, n-3 fatty acids from Fish Oil and Apigenin from parsley, thyme, and peppermint may also significantly influence HER2neu expression!
Herceptin and Dietary fish oil increased the latency time to mammary gland tumor development in the HER-2 transgenic mice

Yee LD et al J Nutr 135: 983-8, 2005
The Literature Provides Mixed Conclusions. Epidemiologic Studies of Dietary Soy Components and Breast Cancer Risk

**Asian**
- Lee ‘92 (total soy protein)
  - $p < 0.001$ Premenopausal
  - NS Postmenopausal
- Hirose ‘95 (beancurd, 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$^+$
- den Tonkelaar ‘01 (urinary phytoestrogens)
  - NS Postmenopausal

**Western**
- Ingram ‘97 (urinary isoflavones)
  - NS Diadzein
  - $p = 0.009$ Equol
- Keinan-Boker ‘02 (food content)
  - NS Isoflavones
  - S Lignans

**Estimated Relative Risk**

- Western
  - Inverse
  - Equol
  - Diadzein
  - Lignans
  - Isoflavones
  - Diadzein
  - Equol
  - Lignans
  - Isoflavones

- Asian
  - Beancurd
  - Miso
  - Tofu
  - Soymilk
  - Tofu
  - Soymilk
  - Tofu
  - Soymilk

**Additional Notes**
- Estimated relative risks are shown on a logarithmic scale.
- NS indicates non-significance.
Part of Confusion Arises from Trying to Use Population Information to Predict Individual Responses
If only cancer prevention was this easy…

“Eat less, exercise more, and alter your genetic code with the DNA of thin parents.”
Using the “Oomics” of Nutrition to Identify Responders from Non-Responders

DNA

Nutrigenetics

Nutritional Epigenetics

RNA

Nutritional Transcriptomics

Protein

Bioactive Food Components

Nutrigenomics

Nutritional Omics

Phenotype

Proteomics

Metabolomics

Metabolite
Human Genetic Variation

A Single-base-pair changes

Example: sickle cell disease, A→T in human β-hemoglobin gene

B Insertions and deletions

Example: cystic fibrosis, deletion of 3 base pairs, CTT, in the human CFTR gene

C Structural rearrangements

Example: chronic myelogenous leukemia, chromosome 9 and 22 translocation, BCR-ABL gene fusion
Genomics Can Influence the Response to Diet at Multiple Points

- Food preference
- Food tolerance
- Absorption
- Transport
- Metabolism
- Effect in target tissue

Genetics Can Influence What Types of Foods Are Consumed

<table>
<thead>
<tr>
<th>Food group</th>
<th>Additive genetic effect</th>
<th>Shared environment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat and fish</td>
<td>0.78 (.63-.92)</td>
<td>0.12 (.00-.27)</td>
</tr>
<tr>
<td>Vegetables</td>
<td>0.37 (.20-.58)</td>
<td>0.51 (.30-.66)</td>
</tr>
<tr>
<td>Fruits</td>
<td>0.51 (.37-.68)</td>
<td>0.32 (.16-.46)</td>
</tr>
<tr>
<td>Desserts</td>
<td>0.20 (.04-.38)</td>
<td>0.64 (.46-.77)</td>
</tr>
</tbody>
</table>

n= 103 MZ and 111 DZ twin pairs

Specific Genes Can Influence What We Like to Eat

Knockout Suggest Glucose Transporter Type-2 (GLUT2) Involved

GLUT2 Polymorphism

<table>
<thead>
<tr>
<th>Sugar (g/d)</th>
<th>Thr/Thr</th>
<th>Thr/Ile + Ille/Ile</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td></td>
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</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>125</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Single Nucleotide Polymorphisms in the VDR gene

Human VDR >470 reported SNPs
Distribution and frequency varies among ethnic groups
VDR *FokI* Polymorphism Affects Calcium Homeostasis in Adolescence

Dietary Calcium, VDR *FokI* Genotype and Colon Cancer Risk


Dietary Calcium

- OR for Colon Cancer
- *P for trend=0.004*

VDR Genotype

- FF
- Ff
- ff

Dietary Calcium

- <388 mg/day
- >388 mg/day

Haplotypes in the VDR Gene Influence Colon Cancer Risk

BsmI (b or B), poly (A) S or L, Fok I (f or F) and CDX2 (G or A); 1574 cases and 1970 controls

- Haplotype frequencies varied by ethnic group
- OR for colon cancer varied from 0.06 to 51.12 depending on haplotype

Genetic Information May Assist in Identifying Those Who Will Benefit from Supplemental Intake of Salmon-type Fish

COX-2 (rs5275+6365 T/C) and prostate cancer risk
Sweden: 782 cancer cases and 1,378 controls

- TC/CC Frequency:
  - 62% Euro-Amer
  - 75% African-Amer
  - 33% Chinese-Amer

- Odds Ratio: Prostate Cancer
- COX-2 Genotype

Salmon-type Fish Consumption
- Never
- 1-3 per month
- >1 per week

*P < 0.01

Genetic Information May Also Identify Those at Risk from High Intakes

PPAR\(\gamma\) Genotype, Fish Consumption and Colon Cancer Risk

Odds Ratio

- CC, \(p<0.06\)
- CT +TT, \(p<0.02\)

\(P <0.01\) for interaction

Siezen et al., Carcinogenesis 26:229-457, 2005
Diet Can Modify Genetic Susceptibility to Cancer

Prostate Tumors in *Lady* mice.

Antioxidants = vitamin E, selenium and lycopene

Venkateswaran et al., Cancer Research 64: 5891-5896, 2004
Gene-Nutrient Interactions and Colon Cancer

Yang et al, Cancer Res. 61, 565, 2001

Percent survival vs. weeks for different genotypes and diets.
One Size Does Not Fit All! Genetic Background May Determine Who Will Respond to Specific Bioactive Dietary Ingredients or Foods
Genes Are Only Part Of The Equation

MY GENOME MADE ME DO IT!
Epigenetics Definition

- **genetics**: the study of heritable changes in gene function that occur *with* a change in the DNA sequence

- **Epigenetics**: the study of heritable changes in gene function that occur *without* a change in DNA sequence.
Foods Can Also Influence Epigenetics
Major plants (constituents) with evidence for epigenetic modifications

Histone modifications

Tomatoes (Lycopene)
Apples (Phloretin)
Citrus (Hesperidin)
Turmeric (Curcumin)
Soybean (Genistein)
Coffea (Caffeic acid)
Cinnamon (Coumaric acid)
Tea (EGCG)
Broccoli (Isothiocyanates)
Cashew nuts (Anacardic acid)
Grapes (Resveratrol)
Garlic (Allyl mercaptan)

DNA methylation

Epigenetic Regulation of Cancer

Epigenetics regulates:
- Cell Cycle Control
- DNA Damage
- Apoptosis
- Invasion
- X-Chromosome Inactivation
- Imprinting
- Aging

Factors
- Environmental
  - Diet
- Hormonal
- Genetic

Global Hypomethylation

Site Specific Hypermethylation

Histone Changes Acetylation Changes

DNA Methyl-transferases
- DNMT1
- DNMT3A
- DNMT3B

Noncoding RNA

Bioactive Food Components in the DNA Methylation Process

- Nutrients
  - Polymorphisms
  - SAM
  - SAH

- CpG
  - DNA Methyltransferase

- Me-CpG
  - DNA Demethylation

Nutrients? → Tumor
Maternal Supplements

- zinc
- methionine
- betaine
- choline, folate, B_{12}

LTR Hypomethylated

Yellow Mouse
High risk cancer, diabetes, obesity & reduced lifespan

LTR Hypermethylated

Agouti Mouse
Lower risk of cancer, diabetes, obesity and prolonged life

Genistein Can Also Influence Agouti Phenotype

Viable yellow Agouti (A<sup>vy</sup>) Locus

Histone Modifications Influence Gene Expression

Gene “switched on”: open chromatin, unmethylated cytosines, acetylated histones

Gene “switched off”: closed chromatin, methylated cytosines, deacetylated histones
Histone Modifications Can Be Regulated by Butyrate, Diallyl Disulfide, and Sulforaphane

Acetylated histones H3 and H4 associated with $P21$ and $Bax$ promoters

Transcription of $P21$ and $Bax$ mRNA

$p21$ and Bax protein levels increased

Cell cycle arrest  Caspase activation

APOPTOSIS

HDAC Inhibition by Sulforaphane-rich Broccoli Sprouts in Human Volunteers

Dashwood RH, Ho E. Semin Cancer Biol. 2007
Genetic and Epigenetic Events Can Effect DNA and Therefore Gene Expression
Low-Fat Feeding and Gene Expression in Human Prostate Epithelium

<table>
<thead>
<tr>
<th>HUGO</th>
<th>NAME</th>
<th>PRE-DIET</th>
<th>POST-DIET</th>
<th>AVERAGE RELATIVE EXPRESSION</th>
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<tbody>
<tr>
<td>MMP7</td>
<td>Matrix metalloproteinase 7</td>
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<td>13.1</td>
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<tr>
<td>OLFM4</td>
<td>Olfactomedin 4</td>
<td></td>
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<td>6.9</td>
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<tr>
<td>BF</td>
<td>B-factor properdin</td>
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<td></td>
<td>6.4</td>
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<tr>
<td>IGF-2R</td>
<td>Insulin-like growth factor-2 receptor</td>
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<td></td>
<td>3.5</td>
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<tr>
<td>VMP1</td>
<td>Likely ortholog of rat vacuole membrane protein 1</td>
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<td>3.3</td>
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<td>TGFB1I4</td>
<td>Transforming growth factor beta 1 induced transcript 4</td>
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<td>IER3</td>
<td>Immediate early response 3</td>
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<td>CCT2</td>
<td>Chaperonin containing TCP1, subunit 2 (beta)</td>
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<td>HLA-DRB5</td>
<td>Major histocompatibility complex class II DR beta 4</td>
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<td>CXCR4</td>
<td>Chemokine (C-X-C motif) receptor 4</td>
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<tr>
<td>LUM</td>
<td>Lumican</td>
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<td></td>
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<tr>
<td>CCL2</td>
<td>Chemokine (C-C motif) ligand 2</td>
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<td>DUSP1</td>
<td>Dual specificity phosphatase 1</td>
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<td></td>
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<tr>
<td>IER2</td>
<td>Immediate early response 2</td>
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<td>2.5</td>
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<td>SPARCL1</td>
<td>SPARC-like 1</td>
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<td>TBX3</td>
<td>T-box 3</td>
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<td>ETS1</td>
<td>V-ets erythroblastosis virus E26 oncogene homolog 1</td>
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<td>SLC25A3</td>
<td>Solute carrier family 25 member 3</td>
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<td>PRDX1</td>
<td>Peroxiredoxin 1</td>
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<td>ABAT</td>
<td>4-aminobutyrate aminotransferase</td>
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<td>FOLH1</td>
<td>Folate hydrolase (prostate-specific membrane antigen)</td>
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<td>BPGM</td>
<td>23-bisphosphoglycerate mutase</td>
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<tr>
<td>MGC15937</td>
<td>Similar to RIKEN cDNA 0610008P16 gene</td>
<td></td>
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<td>0.3</td>
</tr>
</tbody>
</table>
Gene Expression Changes in Breast Cancer Cell Lines Treated with Lycopene

A=apoptosis; B= cell cycle; C= receptors; D= oncogenes; E= DNA repair

Chalabi N et al. Pharmacogenomics 7:663-672, 2006
Future is to Focus on the Process Needing Modification
Multiple Food Constituents Can Influence One Nuclear Transcription Factor

Garlic, fish, broccoli, tomatoes

Active Intermediate (radical??)

Caloric Restriction

Agent

nrf2

keap-1

HS SH

Cytoplasm

nrf2

keap-1

Nucleus

ARE

“antioxidant responsive element”

Increased GST, QR
Is There a Best Time for Intervention?

Genistein & Mammary Cancer:

<table>
<thead>
<tr>
<th>Exposure Period</th>
<th>Tumors/Rat</th>
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<tbody>
<tr>
<td>None</td>
<td>8.9</td>
</tr>
<tr>
<td>Prenatal</td>
<td>8.8</td>
</tr>
<tr>
<td>Adult</td>
<td>8.2</td>
</tr>
<tr>
<td>Prepubertal</td>
<td>4.3</td>
</tr>
<tr>
<td>Prepubertal + Adult</td>
<td>2.8</td>
</tr>
</tbody>
</table>

LaMartiniere et al  JNutr 132: 552S, 2002
Linxian Nutrition Intervention Trial
Esophageal cancer mortality by factor D (N=1515)
Factor D= Selenium, β-carotene, vitamin E

Log-rank P=0.024
RR=0.83

Timing Is Very Important
Fundamental Question Remains if Pathologic Evaluations Reflects What Occurs Normally??
Not All Tissues Respond the Same

Plasma and Tissue Levels of Tea Catechins During Chronic Consumption of Tea Polyphenols

Response

Nutritional

Supranutritional

Toxic

Selenium Exposure

Typical Intakes

Response Depends on the Quantity Consumed

Biological Response Depends on the Quantity Consumed

- Antioxidant
- Immune Enhancement
- Cell Cycle Inhibition
- Apoptosis
- Carcinogen Metabolism
- Se-enzymes
- Se-metabolites

How Much Is Enough and Too Much?

Nested Case-Control Prostate Study in Nordic Men (622 cases and 1451 controls)

50 nM = 20 ng/ml

Foods are “complex mixtures” - act synergistically

“Caution: This tomato soup combined with our chicken noodle soup can form a lethal nerve gas.”
Soy Phytochemicals and Green Tea Inhibit Human Mammary Tumors in Mice

Need to Consider Nutrient-Drug Interactions

Indole 3-Carbinol and Tamoxifen In MCF-7 Cells

Integrated Density/Area (pixel value/mm²)

I3C (µM)
- 0
- 50
- 100

µM Tamoxifen

Polymeals May Offer Special Attributes

<table>
<thead>
<tr>
<th>Dietary Component</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wine (150 ml/day)</td>
<td>32%</td>
</tr>
<tr>
<td>Fish (114 g 4x/week)</td>
<td>14%</td>
</tr>
<tr>
<td>Dark Chocolate (100 g/day)</td>
<td>21%</td>
</tr>
<tr>
<td>Fruits and Vegetables (400 g/day)</td>
<td>21%</td>
</tr>
<tr>
<td>Garlic (2.7 g/day)</td>
<td>25%</td>
</tr>
<tr>
<td>Almonds (68 g/day)</td>
<td>12%</td>
</tr>
</tbody>
</table>

76% decreased risk of CVD

Franco et al. BMJ 329:1447-1450, 2004
While I have raised lots of concerns: There is light at the end of the tunnel!
Research Needs: Better Biomarkers

Dietary Exposure → Susceptibility Factors → Early Biological Effect

Absorbed dose → Biologically effective dose → Inactive metabolite

Health Effects + and - → Altered structure/function → Molecular Target
The Future: Personalization

Predictive  ↔  Personalized  ↔  Preemptive

Participatory