Food Habits, Healthy Lifestyle and Cancer Prevention

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4th Nutrition and Healthy Lifestyles Summit
May 4, 2017
Fauja Singh, 101-year old marathon runner

Started running when he was 89.
He ran his 10th marathon at the age of 101.
Health vs Disease

• Healthy, Happy and Long life
  – Healthy lifestyle (physical activity, healthy diet, lack of stress) + avoidance of tobacco, excessive alcohol, and other harmful environmental physical, chemical, biologic, psychological and social factors

• Unhealthy, Unhappy, Sick
  • Stress – Disease – Stress vicious cycle
  • Lack of physical activity – Obesity vicious cycle
  • Poor dietary habits and unhealthy microbiome
Mechanisms of chronic disease

- Hypertension, Diabetes, Cardiovascular disease, Cancer, Alzheimer’s
- Lack of physical activity, Unhealthy diet, Obesity, Chronic stress
- Mechanisms:
  - Oxidative stress
  - Inflammation
  - Epigenetic changes
  - Metabolic changes
  - Microbiome
Healthy Aging and Disease Prevention

• Physical activity, healthy diet and supplements, low stress, social activity

• Prevention of: muscle loss, bone loss, decreased cognitive function, vision loss, hearing loss, frailty, flexibility, decreased immune function

• Integrative medicine and health policy changes to improve population health and decrease health care expenditures
Integrative Medicine = Healthy Lifestyle

Disease prevention and control, symptom control, quality of life

- **Physical Activity**
- **Diet** (Vegetables, fruit), **Botanicals** (Lycopene, genistein) and other **Natural Compounds**
- **Mind-body approaches**
  - Stress reduction (meditation, yoga)
  - Sleep hygiene (stress, BMI)
  - Acupuncture (pain control)
  - Others (massage, music, thermal spa, and others)
NIH National Center for Complementary and Integrative Health (NCCIH)

Previous name: National Center for Complementary and Alternative Medicine (NCCAM)

The mission of NCCIH is to define, through rigorous scientific investigation, the usefulness and safety of complementary and integrative health interventions and their roles in improving health and health care.

The vision: Scientific evidence informs decision making by the public, by health care professionals, and by health policymakers regarding the use and integration of complementary and integrative health approaches.
Clinical Practice Guidelines

"Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." (Institute of Medicine, 1990)

Issued by third-party organizations, and not NCCIH, these guidelines define the role of specific diagnostic and treatment modalities in the diagnosis and management of patients. The statements contain recommendations that are based on evidence from a rigorous systematic review and synthesis of the published medical literature.

Oncology

- Exercise Guidelines for Cancer Survivors (Med Sci Sports Exerc)
- Integrative Oncology in Lung Cancer (Chest)
- Integrative Oncology: Complementary Therapies and Botanicals (Society for Integrative Oncology)
- Use of Integrative Therapies as Supportive Care in Breast Cancer Patients (Journal of the National Cancer Institute) [391KB PDF]

Allergy and Immunology

- Allergic Rhinitis and Its Impact on Asthma (ARIA) Guidelines: 2010 Revision (Journal of Allergy and Clinical Immunology) [171KB PDF]
- Diagnosis and Management of Food Allergy (Journal of Allergy and Clinical Immunology) [165KB PDF]
- Guidelines for the Diagnosis and Management of Asthma (NHLBI)

Cardiology

- Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NHLBI)
- Management of Stable Ischemic Heart Disease (Annals of Internal Medicine) [PDF]
NCCIH's programs and organization incorporate three long-range goals:

1. Advance the science and practice of symptom management.

2. Develop effective, practical, personalized strategies for promoting health and well-being.

3. Enable better evidence-based decision making regarding complementary and integrative health approaches and their integration into health care and health promotion.
Five major objectives serve the NCCIH’s long-term goals:

1. **Advance research** on mind and body interventions, practices, and disciplines.

2. **Advance research** on natural products for complementary and integrative health.

3. **Increase understanding** of “real world” patterns and outcomes of complementary and integrative health approaches and their integration into health care and health promotion.

4. **Improve the capacity** of the field to carry out rigorous research.

5. **Develop and disseminate** objective, evidence-based information on complementary and integrative health interventions.
Let food be your medicine.
Hippocrates
Hippocrates
460 BC, Kos, Greece
370 BC, Larissa, Greece
The Father of Western Medicine
Mediterranean Diet

• Vegetables
• Fruit
• Fish
• Olives and olive oil
• Nuts, seeds, herbs, spices, whole grain
  • Secret ingredients: physical activity, social life, mindfulness, love and compassion
  • Integrative medicine (phytochemicals, mind-body)
Food habits and health

• Too little food (starvation)
• Too much food (caloric intake)
• Specific food ingredients (vegetables, fruit, grains, seeds, meats, fish)
  • Macronutrients (fats, carbohydrates, proteins)
  • Micronutrients (vitamins, minerals)
  • Non-nutritional botanical supplements
  • Eating habits (eat slow, mindful, social)
Food habits and cancer

- Dietary fats (good vs bad)
- Sugar and carbohydrates (good vs bad)
- Proteins (animal vs plant)
- Vegetables and fruit
- Micronutrients (e.g. vitamin D, Zn)
- Calories, Obesity and Cancer
- Alcohol
Mechanisms of food and cancer

- Mechanisms:
  - Oxidative stress
  - Inflammation
  - Epigenetic changes
  - Metabolism
  - Microbiome
  - Immune system
Gene expression in mammary gland after diet and exercise


AL = ad lib; CR = calorie restricted; EX = exercise
Gene expression in mammary gland after diet and exercise

<table>
<thead>
<tr>
<th>Factor or class of factors</th>
<th>Best estimate</th>
<th>Range of acceptable estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>30</td>
<td>25-40</td>
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<tr>
<td>Alcohol</td>
<td>3</td>
<td>2-4</td>
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<tr>
<td>Diet</td>
<td>35</td>
<td>10-70</td>
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<tr>
<td>Food Additives</td>
<td>&lt;1</td>
<td>-5 -2</td>
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<td>Reproductive &amp; sexual behavior</td>
<td>7</td>
<td>1-13</td>
</tr>
<tr>
<td>Occupation</td>
<td>4</td>
<td>2-8</td>
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<tr>
<td>Pollution</td>
<td>2</td>
<td>&lt;1-5</td>
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<tr>
<td>Industrial products</td>
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<td>&lt;1-2</td>
</tr>
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<td>Medicine &amp; medicinal procedures</td>
<td>1</td>
<td>0.5-3</td>
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<tr>
<td>Geophysical factors</td>
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<td>2-4</td>
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<tr>
<td>Infection</td>
<td>10 ?</td>
<td>1- ?</td>
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<tr>
<td>Unknown</td>
<td>?</td>
<td>?</td>
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<tr>
<td>Cancers</td>
<td>Vegetables</td>
<td>Fruits</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Mouth &amp; pharynx</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Larynx</td>
<td>2</td>
<td>2</td>
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<td>Oesophagus</td>
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<td>3</td>
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<tr>
<td>Lung</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Stomach</td>
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<td>3</td>
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<tr>
<td>Pancreas</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Colon, rectum</td>
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<td></td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ovary</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Endometrium</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prostate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

3=Decreases risk convincing 2=Decreases risk probable 1=Decreases risk possible

*World Cancer Research Fund, 1997*
Nurses’ Health Study (n=121,700)


Ocs
Smoking
Weight/Ht
Med. Hist.

Health Professionals Follow-up Study (n=52,000)


Diet Nails Diet Diet Diet Blood Diet

Nurses’ Health Study II (n=116,000)

1989 1991 1993 1995 1997 1999

Diet Diet Blood Diet

Investigators: Frank Speizer, Bernie Rosner, Meir Stampfer, Graham Colditz, David Hunter, JoAnn Manson, Sue Hankinson, Eric Rimm, Edward Giovannucci, Alberto Ascherio, Gary Curhan, Charlie Fuchs, Fran Grodstein, Michelle Holmes, Frank Hu
Fat Consumption and Risk of Breast Cancer in Pooled Analyses

Adapted from Hunter et al., 1996

(Hunter et al. 1996)
## Risk of Major Clinical Outcomes in the WHI

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>$P$ Value</th>
<th>Unweighted</th>
<th>Weighted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>0.91 (0.83-1.01)</td>
<td>.07</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.77 (0.48-1.22)</td>
<td>.26</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td><strong>Total cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>0.96 (0.91-1.02)</td>
<td>.15</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.95 (0.84-1.07)</td>
<td>.41</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td><strong>Total mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.98 (0.91-1.07)</td>
<td>.70</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td><strong>Global index</strong></td>
<td>0.96 (0.91-1.02)</td>
<td>.16</td>
<td>.16</td>
<td></td>
</tr>
</tbody>
</table>

*(Prentice et al. 2006)*
Fat & Postmenopausal Breast Cancer in NHS, 1980-2000 (3537 cases)

RR of Breast Cancer

Cumulative Average Fat Intake (%E)

P, trend test 0.11

(Kim et al. 2006)
Relative Risk of Colon Cancer
Women & Men (937 cases)

(Michels et al. 2000)
Pooled NHS/HPFS Follow-up

Relative Risk

Cancer
P-value, test for trend = 0.77

Relative Risk

Cardiovascular Disease
P-value, test for trend < 0.001

Fruits & Vegetables/Servings per Day

Hsin-Chia Hung, 2004
Breast Cancer Incidence in WHI

HR, 0.91 (95% CI, 0.83-1.01)

P=0.09

(Prentice et al. 2006)

<table>
<thead>
<tr>
<th>Types of Cancer</th>
<th>Body Mass Index</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.5-24.9</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>All cancers</td>
<td>1.0</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>(1.05-1.11)</td>
<td>(1.18-1.29)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1.0</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>(1.01-1.19)</td>
<td>(1.17-1.51)</td>
</tr>
<tr>
<td>Liver</td>
<td>1.0</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>(0.80-1.31)</td>
<td>(0.97-2.00)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>1.0</td>
<td>1.12</td>
</tr>
<tr>
<td></td>
<td>(0.86-1.47)</td>
<td>(1.56-2.90)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1.0</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>(1.00-1.24)</td>
<td>(1.07-1.52)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.0</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>(0.83-0.94)</td>
<td>(0.72-0.92)</td>
</tr>
<tr>
<td>Breast</td>
<td>1.0</td>
<td>1.34</td>
</tr>
<tr>
<td></td>
<td>(1.23-1.46)</td>
<td>(1.44-1.85)</td>
</tr>
<tr>
<td>Corpus &amp; uterine</td>
<td>1.0</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td>(1.26-1.78)</td>
<td>(2.02-3.18)</td>
</tr>
<tr>
<td>Cervical</td>
<td>1.0</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>(0.97-1.96)</td>
<td>(0.71-2.12)</td>
</tr>
</tbody>
</table>
“On the basis of associations observed in this study, we estimate that current patterns of overweight and obesity in the United States could account for 14 percent of all deaths from cancer in men and 20 percent of those in women.”

## Cancer and Physical Activity

<table>
<thead>
<tr>
<th>Site</th>
<th># of studies</th>
<th>Risk Reduction</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>43 of 51</td>
<td>40-50%</td>
<td>Convincing</td>
</tr>
<tr>
<td>Breast</td>
<td>32 of 44</td>
<td>30-40%</td>
<td>Convincing</td>
</tr>
<tr>
<td>Prostate</td>
<td>17 of 30</td>
<td>10-30%</td>
<td>Probable</td>
</tr>
<tr>
<td>Uterus</td>
<td>9 of 13</td>
<td>30-40%</td>
<td>Possible</td>
</tr>
<tr>
<td>Lung</td>
<td>8 of 11</td>
<td>30-40%</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Insufficient data for testis, ovary, kidney, pancreas, thyroid, melanoma

Obesity Trends* Among U.S. Adults
(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)

1991

1995

2000

No Data □  <10%  10%-14%  15-19%  ≥20%  □

### Multivariate RRs of Overall Mortality According to Joint Categories of BMI & Physical Activity


<table>
<thead>
<tr>
<th>Physical Activity (Hour/Week)</th>
<th>≥3.5</th>
<th>1-3.5</th>
<th>&lt;1</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>1.00</td>
<td>1.18</td>
<td>1.55</td>
</tr>
<tr>
<td>BMI 25-30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>1.28</td>
<td>1.33</td>
<td>1.64</td>
</tr>
<tr>
<td>BMI 30+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>1.91</td>
<td>2.05</td>
<td>2.42</td>
</tr>
</tbody>
</table>

*(Hu FB, et al. 2004)*
Diet and Fatal Prostate Cancer in SDA Men, 1960-1980
(n = 99 cases)
(Snowdon et al, 1984)

<table>
<thead>
<tr>
<th>Milk</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 glass/day</td>
<td>1.0</td>
</tr>
<tr>
<td>1-2 glasses/day</td>
<td>1.8</td>
</tr>
<tr>
<td>3+ glasses/day</td>
<td>2.4</td>
</tr>
</tbody>
</table>

*p trend = 0.005*

*(Jacobson et al. 1998)*

<table>
<thead>
<tr>
<th>Soy Milk Consumption</th>
<th>No. of Men</th>
<th>No. of Cases</th>
<th>Relative Risk&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>10,875</td>
<td>190</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;daily</td>
<td>902</td>
<td>21</td>
<td>0.9 (0.5-1.4)</td>
</tr>
<tr>
<td>1/day</td>
<td>395</td>
<td>11</td>
<td>0.7 (0.4-1.4)</td>
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<tr>
<td>&gt;1 time/day</td>
<td>223</td>
<td>3</td>
<td>0.3 (0.1-0.9)</td>
</tr>
</tbody>
</table>

*P*-value for linear trend 0.02

<sup>b</sup> Adjusted for age, body mass index and frequency of consumption of coffee, whole fat milk, eggs and citrus fruits and age at first marriage.
## Carotenoid intake and risk of prostate cancer in HPFS, 1986-92 (Giovannucci et al, 1995)

<table>
<thead>
<tr>
<th>Carotenoid</th>
<th>Quintile (RR)</th>
<th>P-Trend</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>A-carotene</td>
<td>1.0</td>
<td>1.05</td>
</tr>
<tr>
<td>B-carotene</td>
<td>1.0</td>
<td>1.24</td>
</tr>
<tr>
<td>Crypto-xanthin</td>
<td>1.0</td>
<td>0.97</td>
</tr>
<tr>
<td>Lycopene</td>
<td>1.0</td>
<td>0.90</td>
</tr>
<tr>
<td>Lutein</td>
<td>1.0</td>
<td>1.01</td>
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</table>
Lycopene reduces the risk of various types of cancer

Giovanucci, JNCI 91, 317-331 1999
(a) Prostate cancer incidence (b) Prostate cancer mortality
## Prostate cancer incidence and mortality worldwide

### Prostate Cancer Incidence and Mortality Worldwide in 2008 – Summary

<table>
<thead>
<tr>
<th>Estimated numbers (thousands)</th>
<th>Cases</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>World</td>
<td>899</td>
<td>258</td>
</tr>
<tr>
<td>More developed regions</td>
<td>644</td>
<td>136</td>
</tr>
<tr>
<td>Less developed regions</td>
<td>255</td>
<td>121</td>
</tr>
<tr>
<td>WHO Africa region (AFRO)</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>WHO Americas region (PAHO)</td>
<td>334</td>
<td>76</td>
</tr>
<tr>
<td>WHO East Mediterranean region (EMRO)</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>WHO Europe region (EURO)</td>
<td>379</td>
<td>94</td>
</tr>
<tr>
<td>WHO South-East Asia region (SEARO)</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>WHO Western Pacific region (WPRO)</td>
<td>109</td>
<td>33</td>
</tr>
<tr>
<td>IARC membership (22 countries)</td>
<td>611</td>
<td>128</td>
</tr>
<tr>
<td>United States of America</td>
<td>186</td>
<td>28</td>
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<tr>
<td>China</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>India</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>European Union (EU-27)</td>
<td>323</td>
<td>71</td>
</tr>
</tbody>
</table>
Soy Isoflavones

A. Tamoxifen

B. Genistein

C. Estradiol (E₂)
Genistein’s Pleiotropic Effects

Soy isoflavones and cancer

- Epidemiologic studies show an inverse association between dietary soy intake and cancer risk (breast, prostate, lung, and others)
- **Genistein** and daidzein are the most abundant isoflavones in soy
- **Genistein** has activity against a variety of cancer cells in culture, animal model and clinical studies
Genistein and PC3 Proliferation

![Graph showing the effect of different concentrations of genistein on PC3 cell proliferation over 3 days. The x-axis represents days (0, 1, 2, 3), and the y-axis represents the cell proliferation index (%). Four lines, each representing a different concentration (5 µM, 15 µM, 30 µM, 50 µM), show a decrease in cell proliferation over time. Asterisks indicate significant differences.](image)
Apoptosis assay for PC3 cells treated with genistein, docetaxel, cisplatin, adriamycin, or combination

Con: Control;  G: genistein;  D: docetaxel;  Cis: cisplatin;  A: adriamycin
G+D: genistein followed by docetaxel;  G+Cis: genistein followed by cisplatin.
G+A: genistein followed by adriamycin.  *: p < 0.01
EMSA for NF-kB activity in PC3 cells treated with docetaxel or cisplatin

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>2 nM Docetaxel</th>
<th>300 nM Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1h</td>
<td>2h</td>
<td>4h</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

[Image of EMSA experiment results]
EMSA for NF-kB activity in BxPC-3 cells treated with genistein, cisplatin, or combination

<table>
<thead>
<tr>
<th>Supershift</th>
<th>Non-specific competitor</th>
<th>Specific competitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>25nM Cis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50nM Cis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100nM Cis</td>
</tr>
<tr>
<td></td>
<td>20µM Gen</td>
<td>50µM Gen</td>
</tr>
<tr>
<td></td>
<td>20µM Gen &amp; 25nM Cis</td>
<td>20µM Gen &amp; 50nM Cis</td>
</tr>
<tr>
<td></td>
<td>20µM Gen &amp; 100nM Cis</td>
<td></td>
</tr>
</tbody>
</table>

Cis: cisplatin; Gen: genistein.
NFκB

Transcription

- cIAP-1, XIAP, MMP-9, uPA, VEGF, etc.

Growth Factor, Cytokine

NIK → IKK → Akt

IκB Degradation
Ubiquitin-Proteasome

Nuclear Translocation

Active NFκB

Genistein

A

![Graph showing tumor volume over days with control, prevention, and intervention groups.]

- Control
- Prevention
- Intervention

\[ p \leq 0.0001 \]
\[ p = 0.0003 \]

B

![Control group tumor image.]

C

![Prevention group tumor image.]

control

prevention
Fig-8: Genistein enhanced PC-3 bone tumor growth inhibition induced by docetaxel. A: Inhibitory effects of genistein and/or docetaxel on the growth of bone tumors formed by PC-3 cells in SCID-human mice. B: Comparison of the tumor volumes in each group on the day when all mice were sacrificed. (*: p<0.01, Genistein vs Control, Docetaxel vs Control, Genistein+Docetaxel vs Control; #: p=0.01, Genistein+Docetaxel vs Docetaxel). C: Ex vivo bone tumor X-ray showed more osteolysis and tumor growth in control group (a) than in genistein treatment group (b).

Fig-9: OPG expression was up-regulated by genistein and down-regulated by docetaxel. A: Real-time RT-PCR analysis of OPG mRNA expression in genistein or docetaxel treated PC-3 cells. B: Real-time RT-PCR melting curve showing the PCR product of OPG is pure (only one peak). C: Western Blot analysis of OPG protein expression in genistein and/or docetaxel treated PC-3 cells (C: Control; G: 50 μM Genistein treatment; D: 2 nM Docetaxel treatment; G+D: 30 μM Genistein and 1 nM docetaxel combination treatment).

Li Y et al. Cancer Res. 2006
Effect of Dietary Genistein on MMP Gene Expression in Experimental Metastasis
Cluster Analysis According to Biological Function

Numbers of altered genes in different categories in PC3 bone tumors after genistein treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Up</th>
<th>Down</th>
</tr>
</thead>
<tbody>
<tr>
<td>apoptosis</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>cell cycle arrest, negative regulation of cell proliferation and transcription</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>signal transduction, chemotaxis</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>regulation of transcription and protein biosynthesis</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>oncogenesis</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>
**Effects of genistein on gene expression**

Based on in vitro and in vivo gene profiling with and without genistein.
Plot of predicted rise in log PSA with time

- G3
- G2

intervention
Treatment of PC-3 Prostate Tumors with Radiation + Genistein in Nude Mice

Mean Tumor Volume (mm³)

- Control
- Genistein
- Radiation
- Rad+Gen
Effects of Genistein on CpG Methylation and Histone Acetylation Have Been Reported From Several Groups

Reversal of Hypermethylation and Reactivation of $p16^{INK4a}$, RAR$\beta$, and $MGMT$ Genes by Genistein and Other Isoflavones from Soy

Ming Zhu Fang, Dapeng Chen, Yi Sun, Zhe Jin, Judith K. Christman, and Chung S. Yang

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Genistein mediated histone acetylation and demethylation activates tumor suppressor genes in prostate cancer cells

Nobuyuki Kikuno, Hiroaki Shiina, Shinji Urakami, Ken Kawamoto, Hiroshi Hirata, Yuichiro Tanaka, Shahana Majid, Mikio Igawa, and Rajvir Dahiya

1Department of Urology, Veterans Affairs Medical Center and University of California, San Francisco, San Francisco, CA
2Department of Urology, Shimane University School of Medicine, Izumo, Japan

Original Article

Genistein Reverses Hypermethylation and Induces Active Histone Modifications in Tumor Suppressor Gene B-Cell Translocation Gene 3 in Prostate Cancer

Shahana Majid, PhD; Altaf A. Dar, PhD; Varaehm Shahryari, MD; Hiroshi Hirata, MD, PhD; Ardalan Ahmad, MD; Sharanjot Saini, PhD; Yuichiro Tanaka, PhD; Angela V. Dahiya; and Rajvir Dahiya, PhD
Wnt Pathway Inhibitory Genes are hypermethylated in prostate cancer patients

Whole Genome Expression Profiling Of Prostate Cancer Cells Treated with Genistein

Genistein Upregulates Genes Involved in Cell Cycle Responses to DNA Damage
Genistein Downregulates Genes Involved in the TNF-NFKB Pathway
Genistein induces Acetylation of Histone H3K9

Anti-Ac-H3K9 Chromatin Immunoprecipitation

Genistein induces expression of HAT1

Histone Acetyl Transferase 1 (HAT1)

Genistein synergizes with HDACi Vorinostat to inhibit proliferation

Genistein synergizes with HDACi Vorinostat to induce apoptosis

Whole Genome Expression Profiling Of Prostate Cancer Cells Treated with Genistein, Vorinostat, or Genistein plus Vorinostat

Genistein/Vorinostat Upregulates Genes Involved in Cell Cycle Responses to DNA Damage

<table>
<thead>
<tr>
<th>GO Term</th>
<th>Biological Process</th>
<th>Count</th>
<th>p-value</th>
<th>IPA Biological Function</th>
<th>Count</th>
<th>p-value</th>
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<tbody>
<tr>
<td>GO:0006281</td>
<td>DNA repair</td>
<td>45</td>
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<td>DNA Replication, Recombination, and Repair</td>
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<td>GO:0006915</td>
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<tr>
<td>GO:000075</td>
<td>Cell Cycle Checkpoint</td>
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<td>1.45E-06</td>
<td>DNA checkpoint control</td>
<td>13</td>
<td>1.90E-06</td>
</tr>
</tbody>
</table>

AMPK and PPAR agonists are exercise mimetics

- Identify orally active agents that would mimic or potentiate the effects of exercise to treat metabolic diseases. Natural compounds, such as resveratrol and genistein, have endurance-enhancing activities, but their exact metabolic targets remain elusive.

- Endurance capacities of mice in a treadmill running test. PPAR agonist and exercise training synergistically increase myofibers and running endurance in adult mice.

- AMPK agonist AICAR might be sufficient to overcome the exercise requirement. Even in sedentary mice, 4 weeks of AICAR treatment induced metabolic genes and enhanced running endurance by 44%.

- These results demonstrate that AMPK-PPAR pathway can be targeted by oral drugs to enhance training adaptation or even to increase endurance without exercise.

Genistein improves cardiovascular risk factors


54 mg genistein + Ca + vitamin D, was associated with favorable effects on glycemic control and cardiovascular risk markers
Genistein, insulin sensitivity, renal function


**GENISTEIN**
Improved insulin sensitivity
Decreased renal damage

Induced by a high-fructose diet
Genistein and hypertension


GENISTEIN attenuated the hypertensive effects of dietary NaCl in hypertensive male rats
Genistein, insulin sensitivity and memory


In aged ovariectomized female rats

**GENISTEIN**

increased insulin sensitivity

improved spatial memory
Soy isoflavones, but not Premarin, attenuated AD-relevant protein phosphorylation in primate brain.

Epitopes assessed:
- PHF-1
- Tau-1

(from H Kim et al., 2001, BioFactors)
Relationship between neuroprotective actions by soy versus estrogen

Soy?

Estrogens?

Hyperphosphorylated tau

Depolymerized microtubules;

(dysfunctional neuron)

Stable microtubule

(viable neuron)

(Kim, 2001)
Principal Component Analysis indicates that soy+, soy- and casein-based diets, had non-overlapping global effects on brain proteins.
Isoflavones and cognitive function in older women: the Soy and Postmenopausal Health In Aging (SOPHIA) Study

6-month, double-blind, randomized, placebo-controlled clinical trial

Study subjects were in good health, postmenopausal and not using estrogen replacement therapy

Randomized to active treatment (n = 27) two pills per day, each containing 55 mg of soy-extracted isoflavones (110 mg per day) or placebo (n = 26).

Cognitive function tests administered at baseline and follow-up included: Trails A and B, category fluency, and logical memory and recall (a paragraph recall test assessing immediate and delayed verbal memory).

Kritz-Silverstein D; Von Muhlen D; Barrett-Connor E; Bressel M. Menopause. 10:196-202, 2003.
Summary

• Genistein
  – Antioxidant (prevents DNA damage)
  – Anti-inflammatory (IL-1, IL-6 inhibition)
  – DNA demethylation
  – Histone acetylation
  – NFkB, RANKL, VEGF, MMP, EMT inhibition
  – Enhances chemo/RT
  – Reduces toxicities of chemo/RT
  – Potentiates immune function
  – Anti-viral, anti-bacterial
Let food be your medicine.

Hippocrates

okucuk@emory.edu