Soy and Women’s Health

Mark Messina

February 25, 2013

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The presenter regularly consults for companies/organizations that promote soy and that manufacture and/or sell soyfoods and/or isoflavone supplements.
Soy and Women’s Health

- Isoflavones
- CVD
- Osteoporosis
- Hot flashes
- Skin health
- Breast cancer
## Estimated Soy Isoflavone Intake

<table>
<thead>
<tr>
<th>Location</th>
<th>mg/d</th>
<th>Type of soyfood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shanghai²</td>
<td>30-50</td>
<td>Unfermented</td>
</tr>
<tr>
<td>Japan²</td>
<td>30-50</td>
<td>50% unfermented</td>
</tr>
<tr>
<td>Korea</td>
<td>20-30</td>
<td>70% unfermented</td>
</tr>
<tr>
<td>Singapore</td>
<td>15-20</td>
<td>Unfermented</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>10-15</td>
<td>Unfermented</td>
</tr>
</tbody>
</table>

¹Aglycone equivalent wt ²Upper intake, 100 mg/d.
~3.5 mg/g protein traditional soyfoods; 1 serv.=~25 mg
Food Intake (g/d) in Different Chinese Provinces

Soybean Isoflavone Aglycones

### Phytoestrogens

<table>
<thead>
<tr>
<th>Isoflavone</th>
<th>R₁</th>
<th>R₂</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genistein</td>
<td>H</td>
<td>OH</td>
<td>50</td>
</tr>
<tr>
<td>Daidzein</td>
<td>H</td>
<td>H</td>
<td>40</td>
</tr>
<tr>
<td>Glycitein</td>
<td>OCH₃</td>
<td>H</td>
<td>10</td>
</tr>
</tbody>
</table>

Genistein

Estradiol
Isoflavones classified as SERMs*

Preferentially bind to and transactivate estrogen receptor beta (ERβ) compared with estrogen receptor alpha (ERα)

*Selective Estrogen Receptor Modulators
ER$\alpha$ vs. ER$\beta$

- Different tissue distributions
- Different functions
Comparison of the Clinical Effects of Soybean Isoflavones with Estrogen on Selected Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Isoflavones</th>
<th>Estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal tissue(^1)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Breast tissue(^2)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Endothelial function(^3)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin</td>
<td>Yes?</td>
<td>Yes?</td>
</tr>
</tbody>
</table>

\(^1\) Vaginal maturation index \(^2\) Density & cell proliferation \(^3\) Flow mediated dilation
Soy and Women’s Health

- Isoflavones
- CVD
- Osteoporosis
- Hot flashes
- Skin health
- Breast cancer

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CVD Risk Factors Favorably Affected by Soy

- LDL-cholesterol
  - Fatty acid profile
  - Soy protein
    - FDA health claim
- Endothelial function
  - Flow mediated dilation
  - Endothelial progenitor cells
CVD Risk Factors Favorably Affected by Soy

- LDL-cholesterol
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  - Soy protein
    - FDA health claim

- Endothelial function
  - Flow mediated dilation
  - Endothelial progenitor cells
### Decrease in LDLC (%) in Response to Soy Protein: Results of Recently Published Meta-Analyses

<table>
<thead>
<tr>
<th>Reference</th>
<th>Studies</th>
<th>(N)</th>
<th>LDLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson</td>
<td>20</td>
<td>1946</td>
<td>5.5</td>
</tr>
<tr>
<td>Jenkins</td>
<td>22</td>
<td>757</td>
<td>4.3</td>
</tr>
<tr>
<td>Harland</td>
<td>10</td>
<td>2913</td>
<td>6.0</td>
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<tr>
<td>Reynolds</td>
<td>36</td>
<td>1387</td>
<td>4.0</td>
</tr>
<tr>
<td>Zhan</td>
<td>33</td>
<td>1749</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Endothelial Dysfunction
A Marker of Atherosclerotic Risk
Piero O. Bonetti, Lilach O. Lerman, Amir Lerman

Endothelial Function
ATVB 23: 168, 2003
Clinical trials involving isoflavones have produced inconsistent results.
**Effects of Isoflavones on FMD\(^1\) in PostM Women: Meta-analysis Results**

<table>
<thead>
<tr>
<th>Studies</th>
<th>(N)</th>
<th>WMD ↑(^2)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>525</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Impaired endothelium</strong> (baseline FMD &lt;5.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>233</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Healthy endothelium</strong> (baseline FMD ≥5.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>292</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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\(^1\)Flow mediated dilation \(^2\)Weighted mean difference.  *AJCN 91: 480, 2010*
Effects of Isoflavones on FMD\(^1\) in PostM Women: Meta-analysis Results

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<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>525</td>
<td>1.75</td>
<td>0.0002</td>
</tr>
<tr>
<td>Impaired endothelium (baseline FMD &lt;5.2%)</td>
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<td></td>
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\(^1\)Flow mediated dilation \(^2\)Weighted mean difference. AJCN 91: 480, 2010
## Effects of Isoflavonones on FMD<sup>1</sup> in PostM Women: Meta-analysis Results

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<td></td>
<td></td>
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<tr>
<td>5</td>
<td>233</td>
<td>2.22</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Healthy endothelium</strong> (baseline FMD ≥5.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>292</td>
<td>0.24</td>
<td>0.87</td>
</tr>
</tbody>
</table>

<sup>1</sup>Flow mediated dilation  <sup>2</sup>Weighted mean difference. AJCN 91: 480, 2010
CVD Risk Factors Possibly Favorably Affected by Soy

- Blood Pressure
- Arterial stiffness
- Carotid intima-media thickness

- 4 meta-analyses of RCTs
- Systematic review (4 trials)
- 3 year trial, 350 postM women
CVD Risk Factors Possibly Favorably Affected by Soy

**Blood Pressure**
- 4 meta-analyses of RCTs

**Arterial stiffness**
- Systematic review (4 trials)

**Carotid intima-media thickness**
- 3 year trial, 350 postM women
Soy and Blood Pressure: Meta-analyses of RCTs*

27 studies

2.2 mm ↓ SBP
1.4 mm ↓ DBP

BJN 106:317, 2011

11 studies

2.5 mm ↓ SBP
1.5 mm ↓ DBP

Nutr Metab CVD 22:463, 2012

* Secondary outcome in many studies
Effects of Isoflavone-Rich Soy Protein on CIMT Progression

- 3 year study, 350 postM women
- Age: average, 60.9 y; range, 45-92
- White, 67%; 33% ethnic minority
- Isolated soy protein (25 g/d, 99 mg isoflavones) vs milk protein (25 g/d)
Carotid artery intima-media thickness progression rates

Results analyzed by linear effects model.
Stroke 42:3168, 2011
Carotid Artery Intima-Media Thickness Progression Rates

<table>
<thead>
<tr>
<th>Subjects</th>
<th>N</th>
<th>Control</th>
<th>Soy</th>
<th>% ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>325</td>
<td>5.68</td>
<td>4.77</td>
<td>16</td>
</tr>
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</table>

Years since menopause

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5-10</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>134</td>
<td></td>
<td></td>
<td></td>
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</table>

\[^1\mu\text{m/year}^2\text{p}=0.05\text{ (analyzed by linear mixed effects model adjusted for CIMT randomization strata Stroke 42: 3168, 2011)}\]
### Carotid Artery Intima-Media Thickness Progression Rates

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<th>N</th>
<th>Control</th>
<th>Soy</th>
<th>%↓</th>
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</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>68</td>
<td>6.79</td>
<td>2.16</td>
<td>68</td>
</tr>
<tr>
<td>5-10</td>
<td>89</td>
<td>6.46</td>
<td>5.36</td>
<td>17</td>
</tr>
<tr>
<td>&gt;10</td>
<td>134</td>
<td>5.24</td>
<td>4.78</td>
<td>9</td>
</tr>
</tbody>
</table>

1µm/year  2p=0.05 (analyzed by linear mixed effects model adjusted for CIMT randomization strata Stroke 42: 3168, 2011

**Timing hypothesis**
- Inhibits bone loss
- Reduces fracture risk
Soy Protein and Fracture Risk among Shanghai Postmenopausal Women

Mean quintile protein intake (g/d)

Adjusted relative risk

N= 24,403; 4.5 y follow up, 1770 fractures
Soy Protein and Fracture Risk among Shanghai Postmenopausal Women

Adjusted relative risk

P for trend, <0.001

Mean quintile protein intake (g/d)

N= 24,403; 4.5 y follow up, 1770 fractures
Soy Protein & Hip Fracture Risk among Singaporean Chinese Aged 45-74

Adjusted relative risk

N= 63,257; 7.1 y follow up, 968 fractures
Soy Protein & Hip Fracture Risk among Singaporean Chinese Aged 45-74

Adjusted relative risk

Men

Quartile protein intake (g/d)

N= 63,257; 7.1 y follow up, 968 fractures
Soy Protein & Hip Fracture Risk among Singaporean Chinese Aged 45-74

Adjusted relative risk

Men

Women

P for trend, <0.005

Quartile protein intake (g/d)

<2.7  2.7-<4.7  4.7-<7.6  ≥7.6

N= 63,257; 7.1 y follow up, 968 fractures
Randomized Clinical Trials

Isoflavones and Bone Density
Meta-analyses of RCTs: Conclusions

“... soy isoflavone supplements significantly increase BMD.”

“Isoflavones are not effective in decreasing bone loss in ... postmenopausal ... women.”
J Womens Health (Larchmt) 2010;19:1609-17

“Soy isoflavone ... supplements increased lumbar spine BMD ...”
Asia Pac J Clin Nutr 2010;19:33-42
Design Elements of the 3 Largest & Longest Isoflavone - BMD Trials

<table>
<thead>
<tr>
<th>Location</th>
<th>Dose (mg/d)</th>
<th>Duration</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>0, 80, 120</td>
<td>3 y</td>
<td>208</td>
</tr>
<tr>
<td>USA</td>
<td>0, 200</td>
<td>2 y</td>
<td>248</td>
</tr>
<tr>
<td>Taiwan</td>
<td>0, 300</td>
<td>2 y</td>
<td>431</td>
</tr>
</tbody>
</table>

No effects on lumbar or hip BMD in postmenopausal women

The Hot Flash Hypothesis

Isoflavones can mitigate the drop in estrogen levels

Herman Adlercreutz, MD, PhD
University of Helsinki, Finland

% of women with hot flashes

<table>
<thead>
<tr>
<th>Country</th>
<th>Japan</th>
<th>Canada</th>
<th>USA</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of women</td>
<td>9.7</td>
<td>30.9</td>
<td>34.8</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Cumulative Number of Hot Flash Studies involving Soy or Isoflavones (1995-2012)

Year of Publication

Mixed results
Effects of Isoflavone Supplements on the Frequency and Severity of Hot Flashes

Meta-analysis — 17 studies

K Taku, National Institutes of Health (Japan), M Melby, University of Delaware; MS Kurzer, University of Minnesota; F Kronenberg, Stanford University; M Messina, Loma Linda University. Menopause 19: 776, 2012
Percent ↓ in Hot Flash Frequency

13 trials
N=1196

Net ↓ 20.62 (p=0.00001)

-100 -80 -60 -40 -20 0

Isoflavones
Placebo

Upmalis, 2000
Scambia, 2002
Penotti, 2003
Nahas, 2007
Khaodhiar, 2008
Hachul, 2010
Gocan, 2007
Ferrari, 2009
Faure, 2002
Evans, 2011
D'Anna, 2007
Crisafulli, 2004
Campagnoli, 2005
Percent ↓ in Hot Flash Severity

- Isoflavones
- Placebo

9 trials
N=988

Net ↓ 26.19 (p=0.001)

Nahas, 2007
Nahas, 2004
Khaodhiar, 2008
Jou, 2008
Ferrari, 2009
Han, 2002
Gocan, 2007
Evans, 2011
D'Anna, 2007
Cheng, 2007
## Decrease in Hot Flash Frequency and Severity: Meta-analysis Results

<table>
<thead>
<tr>
<th>Symptom (Studies/N)</th>
<th>Group</th>
<th>Percent Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (13/1196)</td>
<td>Placebo</td>
<td>29.6</td>
</tr>
<tr>
<td></td>
<td>Isoflavones</td>
<td>50.2</td>
</tr>
<tr>
<td></td>
<td>Net</td>
<td>20.6</td>
</tr>
<tr>
<td>Severity (9/988)</td>
<td>Placebo</td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td>Isoflavones</td>
<td>47.6</td>
</tr>
<tr>
<td></td>
<td>Net</td>
<td>26.2</td>
</tr>
</tbody>
</table>
Isoflavone Profile of Two Commonly Used Soy Supplements

- Soybeans
- Supplements
  - Whole soy
  - Soygerm

- Genistein
- Daidzein
- Glycitein
Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: a critical review of published studies

Patricia S. Williamson, PhD, Brent D. Flickinger, PhD, Mark J. Messina, PhD, and Mark W. Empie, PhD

“... extract products containing a minimum genistein dose ... are more effective at reducing hot flashes.”
Percent ↓ in Hot Flash Frequency

- Placebo
- >18.8 mg genistein (median)

6 trials
N=600

Net ↓ 26.50

Nahas, 2007
Hachul, 2010
Ferrari, 2009
Evans, 2011
D'Anna, 2007
Crisafulli, 2004

P = 0.0008 vs low genistein
Percent ↓ in Hot Flash Frequency

- Placebo
- ≤18.8 mg genistein

7 trials
N=596

Net ↓ 12.47

-70 -60 -50 -40 -30 -20 -10 0

- Upmalis, 2000
- Scambia, 2002
- Penotti, 2003
- Khaodhiah, 2008
- Gocan, 2007
- Faure, 2002
- Campagnoli, 2005

P = 0.0008 vs high genistein

Placebo ≤18.8 mg genistein
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<tr>
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<tr>
<td></td>
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<td>&gt;50.2</td>
</tr>
<tr>
<td></td>
<td>Net</td>
<td>&gt;20.6</td>
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<tr>
<td></td>
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<td>&gt;47.6</td>
</tr>
<tr>
<td></td>
<td>Net</td>
<td>&gt;26.2</td>
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</table>
• J Intern Med Res 33: 267, 2005
• Eur J Clin Nutr 60: 1201, 2006
• Dermatology 20:202, 2007
• Clinics 64:505, 2009
• Br J Pharmacol 60: 1185, 2010
"We have done a lot of research and we know this product works ..."

Patricia Manissier, Innēov

http://www.dailymail.co.uk/news/article-1237305/New-anti-wrinkle-sweet-claims-reverse-signs-ageing-set-sale.html#axzz2KFrB3VRW
14-Week Placebo-Controlled Trial of 101 Women Aged 45-65 Years

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflavones</td>
<td>100</td>
</tr>
<tr>
<td>N-3 FAs</td>
<td>3000</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>500</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>500</td>
</tr>
<tr>
<td>Lycopene</td>
<td>16</td>
</tr>
<tr>
<td>$\beta$-carotene</td>
<td>7</td>
</tr>
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</table>

Results
### 14-Week Placebo-Controlled Trial of 101 Women Aged 45-65 Years

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<td>Lycopene</td>
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</tr>
<tr>
<td>β-carotene</td>
<td>7</td>
</tr>
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### Results
- Sig. ↓ in wrinkles
- More wrinkles, greater benefit
- ↑ collagen synthesis
- Trend, other benefits

No isoflavones, no benefit
Soy for Breast Cancer Survivors: A Critical Review of the Literature

Implications of Phytoestrogen Intake for Breast Cancer

Phytoestrogens: Science, Evidence, and Advice for Breast Cancer Patients

Genistein: Does It Prevent or Promote Breast Cancer?

Phytoestrogens: Potential Benefits and Implications for Breast Cancer Survivors

Point-Counterpoint: Soy Intake for Breast Cancer Patients

Addressing the Soy and Breast Cancer Relationship: Review, Commentary, and Workshop Proceedings

Phytoestrogens and breast cancer – promoters or protectors?

Phytoestrogens: Science, Evidence, and Advice for Breast Cancer Patients

Risks and Benefits of Soy Isoflavones for Breast Cancer Survivors

Soybean Phytoestrogens – Friends or Foes?

Is Soy Consumption Good or Bad for the Breast?

Phytoestrogens and breast cancer: a complex story
Hypothesis

Early Soy (Isoflavone) Intake Decreases Breast Cancer Risk
Hypothesis

Early Soy (Isoflavone) Intake Decreases Breast Cancer Risk

Support

- Rodent data
- Epidemiologic data
- Proposed mechanisms
## Genistein & Chemically-induced Rat Mammary Cancer

<table>
<thead>
<tr>
<th>Exposure period</th>
<th>Tumors/Rat</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>8.9</td>
</tr>
<tr>
<td>Prenatal (in utero)</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>
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</table>
# Early Soy Intake & Breast Cancer Risk: Epidemiologic Research

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Location</th>
<th>(N)</th>
<th>% Risk ↓</th>
</tr>
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<tbody>
<tr>
<td>Shu, 2001</td>
<td>Shanghai</td>
<td>3015</td>
<td>49</td>
</tr>
<tr>
<td>Wu, 2009</td>
<td>USA</td>
<td>345</td>
<td>28</td>
</tr>
<tr>
<td>Korde, 2009</td>
<td>USA</td>
<td>255</td>
<td>60</td>
</tr>
<tr>
<td>Lee, 2009</td>
<td>Shanghai</td>
<td>305</td>
<td>43*</td>
</tr>
</tbody>
</table>

*Premenopausal only CEBP;10:483, 2001; AJCN 89; 1145 2009;; 18: 1, 2009; AJCN 89:1920, 2009
Proposed Mechanisms for the Protective Effects of Early Genistein Exposure against Breast Cancer

- Increased cell differentiation
- Increased BRCA1 gene expression (enhanced DNA repair)
- Increased ERβ expression
- Decreased ERα expression

Clin Cancer Res 2005;11:981s-ss; Carcinogenesis 2010;31:886-93; De Asis, Cancer Prev Res 2011; Rahal Endocrinol 2011; Mishra et al., ISRN Oncology, 2011
Young girls should be sure to eat ≥1 serving per day

- 1 oz (28 g)
- ½ cup (100 g)
- 1 cup (240 ml)
- ½ cup (100 g)
Is soy safe for breast cancer patients?
Estrogen and Breast Cancer Relationship

Conceptual basis for concern about isoflavones
Risk of Invasive Breast Cancer

EPT $\rightarrow$ $\uparrow$ 26%

E only $\rightarrow$ $\downarrow$ 20%

Adherent subjects $\rightarrow$ $\downarrow$ 33%

7.1 year Follow up; N = 10,739

JAMA 288: 321; 295, 1647, 2006

CEE, 0.625 mg/d; MPA, 2.5 mg/d
“… the use of estrogen alone results in a small reduction in the risk for developing or dying of invasive breast cancer.”

Annals of Internal Medicine
Concerns about Isoflavones

Based on their stimulatory effect on the growth of existing estrogen-sensitive mammary tumors in athymic ovariectomized mice
Ovariectomized Athymic Mice

- Not all studies show stimulatory effects
- Questionable model for evaluating isoflavones

Differences in isoflavone metabolism between mice and humans
Soy and Breast Cancer

Human evidence
Little Effect of Isoflavone Exposure on Markers of Breast Cancer Risk

- Circulating estrogen levels (47)*
- Breast tissue density (8)*
- Breast cell proliferation (5)*

*number of studies
Little Effect of Isoflavone Exposure on Markers of Breast Cancer Risk

- Supportive of safety but not benefit although ...

- Could be protective via mechanisms not identified by these markers
Soy & the Breast Cancer Patient: Epidemiology
Isoflavonone Exposure Associated with Improved Prognosis: Epidemiology

Five studies:
- 4 very favorable, 1 neutral

Two studies:
- 1 very favorable, 1 mostly favorable

One study:
- Mostly favorable

Isoflavone Intake & Breast Cancer Prognosis: Pooled Analysis

- Shanghai Breast Cancer Survival Study
- Life After Cancer Epidemiology (USA)
- Women’s Healthy Eating & Living (USA)
Isoflavone Intake & Breast Cancer Prognosis: Pooled Analysis

- Shanghai Breast Cancer Survival Study
- Life After Cancer Epidemiology (USA)
- Women’s Healthy Eating & Living (USA)

Median follow up, 7.4 years

N = 9514

½ postM
½ White

1171 Deaths
881 BCa-specific deaths
1348 recurrences

AJCN 2012;96:123
## Hazard Ratios for Post-diagnosis Isoflavone Intake and Breast Cancer Prognosis: Pooled Analysis Results

<table>
<thead>
<tr>
<th>Intake (mg/d)</th>
<th>All cause mortality</th>
<th>Breast cancer</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>Recurrence</td>
</tr>
<tr>
<td>&lt;4.0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>4.0-9.99</td>
<td>1.04</td>
<td>1.09</td>
<td>0.99</td>
</tr>
<tr>
<td>≥10.0</td>
<td>0.87&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.83&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.75&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

95% CI: <sup>1</sup>(0.70, 1.10); <sup>2</sup>(0.64, 1.07); <sup>3</sup>(0.61, 0.92)
Hazard Ratios for Isoflavone Intake and Breast Cancer Prognosis: Pooled Analysis Involving non-Asian US Women

<table>
<thead>
<tr>
<th>Intake (mg/d)</th>
<th>All cause mortality</th>
<th>Breast cancer</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>Recurrence</td>
<td></td>
</tr>
<tr>
<td>&lt;4.0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>4.0-9.99</td>
<td>1.00</td>
<td>1.06</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>≥10.0</td>
<td>0.89 (^1)</td>
<td>0.80 (^2)</td>
<td>0.74 (^3)</td>
<td></td>
</tr>
</tbody>
</table>

95% CI: \(^1\)(0.66, 1.20); \(^2\)(0.55, 1.15); \(^3\)(0.56, 0.97)
Soyfoods are safe for breast cancer patients
“... there is the potential for these [soy] foods to exert a positive synergistic effect with tamoxifen.”
<table>
<thead>
<tr>
<th>Intake (mg/d)</th>
<th>Receptor status</th>
<th>Menopausal status</th>
<th>Tamoxifen use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ER-</td>
<td>ER+</td>
<td>Pre</td>
</tr>
<tr>
<td>&lt;4.0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>4.0-9.99</td>
<td>0.86</td>
<td>1.02</td>
<td>0.91</td>
</tr>
<tr>
<td>≥10.0</td>
<td>0.64</td>
<td>0.81</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Interactions for subgroup analysis not significant
Genistein-Related Findings in Ovariectomized Athymic Mice Implanted with MCF-7 Cells

- Efficacy of tamoxifen inhibited
- Efficacy of letrozole inhibited
Isoflavone Intake and Risk of Death among Chinese Breast Cancer Patients (n=113) on Anastrozole

Does soy differentially affect prognosis according to HER2 status?
Can clinicians now assure their breast cancer patients that soyfoods are safe?

**Options**

1. Prohibit intake  
   *(current default position)*

2. Permit for those who already use it or want to begin

3. Recommend for the purpose of improving prognosis

Women's Health (Lond Engl). 2010; 6: 335-8
Soy & Women’s Health: Summary

1. **CVD:** ↓ risk via multiple mechanisms (especially beneficial in postM women)

2. **Bone health:** data unimpressive

3. **Hot flashes:** isoflavones efficacious

4. **Skin health:** very preliminary

5. **Breast cancer:**
   - Prevention: early intake key
   - Patients: soyfoods are safe
THANK YOU