Soy and Breast Cancer Prognosis
The Epidemiological Evidence

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Outline

- Isoflavones: Background

- **Soy and Breast Cancer Prognosis**: Review of the Epidemiological Literature

- **Important Clinical Questions**
  - Is soy harmful for women with breast cancer?
  - Is soy beneficial for women with breast cancer?
  - Does soy negate benefit of tamoxifen or aromatase inhibitors?
  - Do effects vary by populations, estrogen status, or menopausal status?
Isoflavones and Estrogen

- Soyfoods-only foods to contain nutritionally significant amount of isoflavones
- Isoflavones in soy: Genistein, Daidzein, and Glycitein
- Diphenolic compounds with chemical structure similar to estrogen
- Estrogenic activity of Genistein and other isoflavones well-documented
Isoflavones

- Traditional foods: ~3.5 mg/g protein
  - 1 serving ~25 mg

Genistein (50%)
Daidzein (40%)
Glycitein (10%)
Isoflavones (mg) in Soy foods

- 60 g textured vegetable (soy) protein = 45 mg
- ½ cup Miso = 59 mg
- ½ cup Soybeans, boiled = 47 mg
- 3 oz Tempeh = 37 mg
- 1 cup Soy Milk = 30 mg
- 3 oz Tofu = 20 mg

USDA Nutrient Data Laboratory
Soy Consumption In Different Populations

- Average isoflavone consumption in the U.S. is less than 3 mg/day.
- While older adults in Japan and China consume 25-50 mg/day.

How May Soy Be Related to Breast Cancer Risk or Progression

- There is significant evidence that lifetime endogenous estrogen exposure (ovarian and adipose derived) increase risk of breast cancer.
- Isoflavones activate ERα and ERβ receptors—but with less potency than endogenous 17β-Estradiol—essentially a weak estrogen.
- Also may activate estrogen responsive genes.
Anti-Estrogenic Effect of Isoflavones

- Because of similar structure—also can compete for estrogen receptor-binding sites
- Increase synthesis of Steroid Hormone Binding Globulin
- Inhibits aromatase—helps biosynthesis of estrogen
- Increase clearance of steroids
- Prolongs menstrual cycle
Besides Hormonal Effects- Tumor Inhibitory Effect of Isoflavones

- Inhibit DNA topoisomerase II-stops DNA replication
- Inhibit angiogenesis-growth of blood vessels
- Induce Apitosis –cell death
- Enhance immune system
Soy for Breast Cancer Survivors: A Critical Review of the Literature

Implications of Phytoestrogen Intake for Breast Cancer

Genistein: Does It Prevent or Promote Breast Cancer?

Phytoestrogens: Potential Benefits and Implications for Breast Cancer Survivors

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

Phytoestrogens and breast cancer – promoters or protectors?

Risks and Benefits of Soy Isoflavones for Breast Cancer Survivors

Point-Counterpoint: Soy Intake for Breast Cancer Patients
It may be **unwise** for women, especially those with estrogen receptor positive breast tumors, to increase their **phytoestrogen** intake.
Soy & Breast Cancer

If you are a breast cancer survivor, talk to your health care provider about adding soy into your diet before making any major changes.
Soy & Breast Cancer

- If you’ve had breast cancer, talk to your doctor before supplementing your diet with isoflavone pills. Experts generally consider whole foods containing soy or isoflavones to be healthy and safe, when consumed in moderation.

- The Bottom Line: Phytoestrogens are estrogens, and there’s no evidence that effective doses wouldn’t cause problems similar to those that prescription estrogens are known to raise.

http://www.mayoclinic.com/health/menopause/DS00119/DSECTION=10
Animal studies suggest that genistean, a soy isoflavone, may antagonize the effects of tamoxifen. Therefore patients taking tamoxifen should consult their physicians about the use of phytoestrogens.
Original Concerns Based On In Vitro and Animal Models

- ER positive cell line—estrogenic activity of physiological doses promoted cell growth
- However, larger doses inhibited tumor growth through non-hormonal effects
- Genistein stimulated growth of mammary tumors in ovariectomized mice implanted with ER positive cell lines
- Research from the same model shows that genistein inhibits the effectiveness of tamoxifen and aromatase inhibitors
Is it a question of hormonal (estrogenic) environment?

Isolavones may be both antagonist/agonist and act more like SERMs
Clinical Evidence for Safety

- Majority of clinical trials found that daily intake of isoflavones between 36-100 mg does not lead to increase epithelial cell proliferation
- Soy does not increase breast density
Epidemiological Evidence

Pre-Diagnosis Soy Intake
- Shanghai Breast Cancer Study (Boypati, 2005)
- Long Island Breast Cancer Study (Fink, 2007)

Post-Diagnosis Soy Intake
- LACE (Guha et al 2009)
- WHEL (Caan et al 2011)
- Shanghai Study (Shu et al 2009)
- Harbin Medical Center (Xang et al 2010)
- ABC Pooling Project (Nechuta et al 2011)
Associations of total isoflavones and disease-free survival (Boypati-Shanghai Breast Cancer Study)

Hazard Ratios

Disease-free survival

P for trend = NS
Age adjusted HRs and 95% CIs for the association between flavonoid intake in relation to all-cause mortality by menopausal status (Long Island Study)
LACE Study
Kaiser Permanente

- Prospective cohort of 1954 early stage breast cancer survivors
- Follow-up on average 6.3 years
- Soy intake ~ 2 years post-diagnosis with a 14 item soy questionnaire (Kirk et al.)
- Outcome- Recurrence (N=282)

Guha, N, et al. BCRT, 2009
Soy Isoflavone Intake and Breast Cancer Recurrence (LACE study) - Postmenopausal Breast cancer

Soy Isoflavone Intake and Breast Cancer Recurrence (LACE study) - Tamoxifen Users

Quintiles of intake (cut-points shown in legend)

Hazard Ratios

P for trend
Daidzein 0.10
Genistein 0.13

Breast cancer recurrence among Postmenopausal women using Tamoxifen, according to Daidzein intake

3088 Breast Cancer Survivors (US) enrolled in WHEL (dietary intervention trial)

Median follow-up 7.3 years

FFQ to assess soy intake ~ 2 years post diagnosis

Highest level of isoflavones (16-86mg/day)

Outcomes-Death (N=271: >80% died of BC), New breast events (N= 348)
Adjusted HR (95% CI) for overall mortality and recurrence by baseline isoflavones (WHEL Study)

Hazard Ratios

New Breast Cancer Events

Mortality

P for trend = 0.02

Caan et al. CEBP 2011
Adjusted HR (95% CI) for overall mortality by baseline isoflavones and ER Receptor status (WHEL Study)

Hazard Ratios

- ER+ (n=2144) P for trend = 0.07
- ER- (n=546) P for trend = 0.10

Caan et al. CEBP 2011
Adjusted HR (95% CI) for overall mortality by baseline isoflavones and Tamoxifen use (WHEL Study)

Women who used Tamoxifen (n=1816)

- Isoflavones mg/day 0-0.07: HR = 0.79
- Isoflavones mg/day 0.07-1.01: HR = 0.81
- Isoflavones mg/day 1.01-16.33: HR = 0.26
- Isoflavones mg/day 16.33-86.9: HR = 1.0

Non-users of Tamoxifen (n=884)

- Isoflavones mg/day 0-0.07: HR = 1.0
- Isoflavones mg/day 0.07-1.01: HR = 0.61
- Isoflavones mg/day 1.01-16.33: HR = 0.79
- Isoflavones mg/day 16.33-86.9: HR = 0.68

P for trend = 0.05
P for trend = 0.20

Caan et al. CEBP 2011
Shu et al. Soy Food Intake and Breast Cancer Survival 2009

- 5042 Breast cancer survivors (SBCSS)
- Median follow-up time 3.9 years
- Soy questionnaire capturing multiple time points post-diagnosis going back to baseline cancer diagnosis
- Soy Intake - median 47 mg isoflavone
- Outcome - Death (N=444), Recurrence (N= 534)
Association of Isoflavone Intake with Total Mortality and Recurrence/Breast Cancer-Specific Mortality

(Shanghai Breast Cancer Survival Study)

Hazard Ratios

Recurrence/Breast Cancer-Specific Mortality

Total Mortality

Shu et al. JAMA 2009
Association of Isoflavone Intake with Recurrence/Breast Cancer Mortality by ER
(Shanghai Breast Cancer Survival Study)

No significant interaction

Hazard Ratios

ISOFLAVONES mg/day
≤20.00
20.01-36.50
36.51-62.68
>62.68

ER-negative

ER-positive

ISOFLAVONES mg/day ≤20.00
ISOFLAVONES mg/day 20.01-36.50
ISOFLAVONES mg/day 36.51-62.68
ISOFLAVONES mg/day >62.68

No significant interaction
Isoflavone Intake and Tamoxifen Use in Association with Recurrence Among Women with ER+ Cancer (Shanghai Breast Cancer Survival Study)

Shu, X. O. et al. JAMA 2009

Hazard Ratios

<table>
<thead>
<tr>
<th>Isoflavones mg/day</th>
<th>No Tamoxifen Use</th>
<th>Tamoxifen Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤20.00</td>
<td>0.84</td>
<td>0.71</td>
</tr>
<tr>
<td>20.01-36.50</td>
<td>1.04</td>
<td>0.91</td>
</tr>
<tr>
<td>36.51-62.68</td>
<td>0.71</td>
<td>0.73</td>
</tr>
<tr>
<td>&gt;62.68</td>
<td>0.58</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Kaiser Permanente
Kang et al. Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy, 2010

- 524 Chinese patients form Harbin Medical University who underwent surgery for breast cancer between 2002 and 2003
- Mean follow-up 5.1 years
- Mean isoflavone intake 25 mg
- All were on adjuvant hormonal therapy
- Soy FFQ to determine intake (mean 120 days post diagnosis) and 5 years
- Outcome- Death (N=154), Recurrence (N=132)
# Soy Intake and Recurrence and Overall Death

**Table 2:** Adjusted association between soy isoflavones and recurrence of breast cancer or death in 248 premenopausal and 276 postmenopausal patients (total n = 524)

<table>
<thead>
<tr>
<th>Soy isoflavones, mg/d</th>
<th>Cases of recurrence</th>
<th>Cases of recurrence, adjusted HR* (95% CI)</th>
<th>Deaths</th>
<th>Deaths, adjusted HR* (95% CI)</th>
<th>Risk of recurrence, adjusted HR* (95% CI)</th>
<th>Deaths</th>
<th>Deaths, adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15.2</td>
<td>29/68</td>
<td>1.00</td>
<td>21/58</td>
<td>1.00</td>
<td>25/64</td>
<td>1.00</td>
<td>18/64</td>
</tr>
<tr>
<td>15.3–25.4</td>
<td>24/63</td>
<td>0.96 (0.62–1.46)</td>
<td>19/63</td>
<td>0.95 (0.76–1.56)</td>
<td>23/69</td>
<td>0.74 (0.64–0.96)</td>
<td>20/69</td>
</tr>
<tr>
<td>25.5–42.3</td>
<td>20/58</td>
<td>0.86 (0.56–1.47)</td>
<td>17/58</td>
<td>0.92 (0.59–1.43)</td>
<td>23/72</td>
<td>0.72 (0.58–0.92)</td>
<td>21/72</td>
</tr>
<tr>
<td>&gt; 42.3</td>
<td>21/59</td>
<td>0.88 (0.61–1.23)</td>
<td>19/59</td>
<td>1.05 (0.78–1.71)</td>
<td>20/71</td>
<td>0.67 (0.54–0.85)</td>
<td>19/71</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.46</td>
<td>0.87</td>
<td>0.02</td>
<td>0.76</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, HR = hazard ratio.

*Adjusted for age at diagnosis, TNM stage, estrogen and progesterone receptor status, chemotherapy and radiotherapy. Values of HR > 1 indicate increased risk.

Xang et al. 2010
Kang et al. Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy, 2010

<table>
<thead>
<tr>
<th>Factor</th>
<th>n/N</th>
<th>Comparison</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PR status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+/PR+</td>
<td>59/176</td>
<td>Q2 v. Q1</td>
<td>0.76 (0.58–0.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q3 v. Q1</td>
<td>0.72 (0.55–0.87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q4 v. Q1</td>
<td>0.66 (0.49–0.86)</td>
</tr>
<tr>
<td>ER+/PR−</td>
<td>21/62</td>
<td>Q2 v. Q1</td>
<td>1.21 (0.80–1.72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q3 v. Q1</td>
<td>1.04 (0.82–1.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q4 v. Q1</td>
<td>1.12 (0.81–1.66)</td>
</tr>
<tr>
<td>ER−/PR+</td>
<td>11/38</td>
<td>Q2 v. Q1</td>
<td>1.07 (0.85–1.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q3 v. Q1</td>
<td>1.10 (0.79–1.62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q4 v. Q1</td>
<td>1.05 (0.74–1.61)</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>64/190</td>
<td>Q2 v. Q1</td>
<td>1.23 (0.78–1.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q3 v. Q1</td>
<td>1.13 (0.79–1.71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q4 v. Q1</td>
<td>1.06 (0.76–1.67)</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>27/86</td>
<td>Q2 v. Q1</td>
<td>0.72 (0.56–0.92)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q3 v. Q1</td>
<td>0.71 (0.54–0.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q4 v. Q1</td>
<td>0.65 (0.47–0.85)</td>
</tr>
</tbody>
</table>

Figure 1: Forest plot of adjusted hazard ratios (HRs) for the effect of intake of soy isoflavones on recurrence among postmenopausal patients with breast cancer, stratified by estrogen and progesterone receptor status and endocrine therapy. CI = confidence interval, ER = estrogen receptor, PR = progesterone receptor, Q1 to Q4 = quartiles according to intake of soy isoflavones, where Q1 is < 15.2 mg/day and Q4 is > 42.3 mg/day.

Xang et al. 2010
9515 Cases (SBCSS, LACE and WHEL)
- Soy Intake assessed by questionnaire-
  mean time 14.5 months post diagnosis
- Mean Follow-up 7.4 years
- Mean isoflavone/day-( range 2.6-45.9)
- Deaths( N=1171) , Recurrence (N=1348)
HRs for Isoflavone Intake in Association with All-Cause Mortality, Breast Cancer-Specific Mortality, and Breast Cancer Recurrence (After Breast Cancer Pooling Project)

<table>
<thead>
<tr>
<th>Hazard Ratios</th>
<th>Isoflavones mg/day ≤4.0</th>
<th>Isoflavones mg/day 4.0-10.0</th>
<th>Isoflavones mg/day ≥10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>1</td>
<td>1</td>
<td>0.75</td>
</tr>
<tr>
<td>Breast Cancer-Specific Mortality</td>
<td>1</td>
<td>1.09</td>
<td>0.82</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>1</td>
<td>1.04</td>
<td>0.87</td>
</tr>
</tbody>
</table>
## Summary of the Epidemiological Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Recurrence</th>
<th>Overall Death</th>
<th>Menopause Status</th>
<th>ER Status</th>
<th>Tamoxifen Effect</th>
<th>Time of Measure</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boypati 2005</td>
<td>n/a</td>
<td>No assoc</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Usual intake 5 years prior to diagnosis</td>
<td>Chinese</td>
</tr>
<tr>
<td>Fink 2007</td>
<td>n/a</td>
<td>Decreased risk</td>
<td>Post only</td>
<td>n/a</td>
<td>n/a</td>
<td>1 year pre-diagnosis</td>
<td>Western</td>
</tr>
<tr>
<td>Guha 2009</td>
<td>Decreased risk</td>
<td>n/a</td>
<td>Post only</td>
<td>ER+ only</td>
<td>Decreased risk in Tam only</td>
<td>Post- Dx</td>
<td>Western</td>
</tr>
<tr>
<td>Shu 2009</td>
<td>Decreased risk</td>
<td>Decreased risk</td>
<td>Pre &amp;Post</td>
<td>ER+ / ER-</td>
<td>Decreased risk in Tam only</td>
<td>Post -Dx</td>
<td>Chinese</td>
</tr>
<tr>
<td>Kang 2010</td>
<td>Decreased risk</td>
<td>No assoc</td>
<td>Post only</td>
<td>Studied ER or PR+ only</td>
<td>Decreased risk in Aromatase only Tam no benefits.</td>
<td>Post -Dx</td>
<td>Chinese</td>
</tr>
<tr>
<td>Caan 2011</td>
<td>No assoc</td>
<td>Decreased risk</td>
<td>Post only</td>
<td>ER+ only</td>
<td>Decreased risk in Tam only</td>
<td>Post-Dx</td>
<td>Western</td>
</tr>
<tr>
<td>Nechuta (pooled) 2011</td>
<td>Decreased risk</td>
<td>Non - significant decreased risk</td>
<td>Post only</td>
<td>ER- and ER + Tam users</td>
<td>Decreased risk in Tam only</td>
<td>Post-Dx</td>
<td>Chinese &amp; US</td>
</tr>
</tbody>
</table>
Important Clinical Questions

Is soy harmful for women with breast cancer: In all 7 Epi studies done, no evidence of harm

Is soy beneficial for women with breast cancer: 6 out of 7 Epi studies demonstrate some type of benefit

Does soy negate the benefits of Tamoxifen: In 4 out 5 studies benefits in Tam only, 1 study no effect in Tam but benefit in aromatase inhibitor
Important Clinical Questions

Do effects vary by:

Populations: Surprisingly effects sizes are similar across populations and generally range between 25-35% reduction.

Estrogen status: In Western populations effects are seen in ER+ only, but in Asians, effects seen in ER-, perhaps due to larger dose (anticarcinogenic properties) or type of soy eaten.

Menopausal status: Effects are predominantly seen in Postmenopausal women – perhaps due to lower levels of endogenous estrogens.

When soy intake is started: No epi data is currently available to study this but no differences by country would support that time of initiation may not matter.

Do results reflect a healthy survivor bias? In US, we are seeing similar results to China where this is unlikely to be the case since soy is commonly consumed by all.
Additional Evidence Supporting Soy and Adjuvant Therapy

- A study among Asian-American women with breast cancer found no evidence that soy intake adversely affected levels of circulating tamoxifen.

- Soy protein isolates in combination with tamoxifen were found to be more effective than tamoxifen alone in preventing chemically-induced rat mammary cancers.

- Isoflavones may also prevent the formation of carcinogenic metabolites of tamoxifen via inhibition of the cytochrome P450 enzymes, making this synergistic interaction a more effective therapy for breast cancer survivors.

- Genistein increased growth inhibitory effects of Herceptin in HER2 overexpressing cells
Summary of the Evidence of Soy for the Breast Cancer Survivor

- In Vitro and Animal data conflicting

- Human clinical data generally supportive of safety, not benefit

- Epidemiological data fully supportive of safety, even in combo with tamoxifen or aromatase inhibitors and is quite suggestive of benefit
Clinicians have several possible options

- Routinely prohibit soy from the diet of breast cancer patients- Current science does not support this option

- Based on the lack of harm and the benefits reported in the epidemiologic studies, recommend that breast cancer patients begin eating whole soyfoods to treat breast cancer - Existing data are not sufficiently strong to justify this recommendation.

- Adopt a stance of permitting use in patients who want to begin eating reasonable amounts of soyfoods or for whom soyfoods already represent a normal part of their diet. Data support this option and it is one that is consistent with the position of the American Cancer Society
Policy Recommendations from ACS for the Breast Cancer Survivor

2005 - Up to 3 servings a day of traditional soy foods unlikely to be Harmful (typical Asian Intake)

2010 - Women with breast cancer can take in moderate amounts of soy foods

2005 and 2010. Avoid concentrated sources of soy such as soy-containing pills or powders, or supplements containing high amounts of isoflavones.
Questions?