Biological factors involved in mediating the effects of soy foods on breast cancer survivors

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Soy contains estrogenic ingredients

Genistein

17-β estradiol

**Genistein in soy:**

- Has a chemical structure similar to that of ovarian estrogen [estradiol (E2)]
- Binds and activates the estrogen receptors (ER-α and ER-β) in the breast
Genistein and activation of ER-α and ER-β

- **Genistein**: the relative binding affinity (relative to E2 = 100%) of genistein is higher to ER-β (36-87%) than to ER-α (4-5%).

- **Genistein’s action via ER-α and ER-β**: genistein dose (300 nM) relevant to Asian soy intake activates both ER-α and ER-β similarly to E2.

Physiological doses of genistein mimic the actions of estradiol on the activation of the estrogen receptors.

Saji S et al. Cancer Chemother Pharmacol. 2005
Chang et al., Mol. Endo. 2008
Dietary soy exposure activates estrogen response element (ERE) in mouse mammary gland

Ovax ERE luc mice:
• fed isocaloric diets supplemented with soy (140 ppm genistein), flaxseed, rye or wheat (obtained from local supermarket in Finland) for 2 days
• ERE luc expression was determined.

Dietary soy exposure activated ERE in mouse liver and mammary gland

Penttinen et al. 2009
Breast cancer cells: genistein induces cell proliferation \textit{in vitro} and \textit{in vivo}

Helferich et al., 2000:
Genistein stimulates proliferation of human breast cancer cells in culture.

Helferich et al. 2001:
Dietary exposure to genistein increases the growth of human breast cancer cells in ovariectomized athymic mice.
E+P HRT increases breast cancer risk

**Risks**  ~ 5 y from start of study

- 29% Increase CHD (Coronary Heart Disease)
- 41% Increase Stroke
- 113% Increase Pulmonary Emboli
- 26% Increase Breast Cancer

**Benefits**

- (Hip) Fracture Reduction
- Fewer Colorectal Cancers

STOPPED Early, Clear Harm!!!

STOPPED 3.3 yrs early
* had 0.4 more yrs of data

*Adapted from: Writing Group for the Women’s Health Initiative. JAMA 2002;288:321-333
Soy intake during childhood reduces life-time breast cancer risk.

Soy intake limited to pregnancy increases female offspring’s later breast cancer risk.

Soy intake starting in adult life may not reduce breast cancer risk.

Life-time soy intake reduces breast cancer risk and risk of recurrence.

It is not known whether it is safe to start consuming soy after breast cancer diagnosis.
Breast cancer deaths vary in different countries (2008 estimate)

Average soy (isoflavone) intake

Europe: 0.5-0.7 mg/day
USA: 1-6 mg/day
Asia: 20-50 mg/day
Soy intake is high among Asian women: high soy intake prevents recurrence of breast cancer risk?

Difference in composition of soy products

Traditional soy foods

- Edamame are green, immature soybeans
- Mature soybeans
- Soymilk is made from soybeans
- Tofu is made from soymilk

Western soy products

- Western soy products
- made mainly of soy protein isolate and concentrate, not whole soybeans
- SOYJOY made of whole soybeans
Biological changes induced by genistein that may affect breast cancer growth

Inhibits NFkB, suppressing inflammatory & cancer inducing pathway

Up-regulates tumor suppressor genes:
- • BRCA1
- • PTEN
- • Caveolin-1

- these genes protect normal cells from cancer initiation

Is a potent tyrosine kinase inhibitor:
- • down-regulates Her2 in breast tumors, and perhaps other oncogenes

Epigenetically regulates gene expression
- Genistein may function to induce histone deacetylation or DNA methylation (both result suppression of gene expression)
Are tumors different in soy consumers than in non-consumers?
Breast cancers are not all the same

- Based on their biology, breast cancers are divided to different categories
  - luminal A, luminal B, HER2 and basal/triple negative.

Sandhu et al. (2010) LabMedicine, 41, 364-372

<table>
<thead>
<tr>
<th>Subtype</th>
<th>These tumors tend to be*</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER+ and/or PR+, HER2-, low Ki67</td>
<td>42-59%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>ER+ and/or PR+, HER2+ (or HER2- with high Ki67)</td>
<td>6-19%</td>
</tr>
<tr>
<td>Triple negative/basal-like</td>
<td>ER-, PR-, HER2-, cytokeratin 5/6 + and/or HER1+</td>
<td>14-20%</td>
</tr>
<tr>
<td>HER2+</td>
<td>ER-, PR-, HER2-</td>
<td>7-12%</td>
</tr>
</tbody>
</table>
Each breast cancer is different

- Gene expression patterns, obtained using mRNA microarrays, also separate the tumors into the four categories.
- Each category has different prognosis.
Basal-like and luminal B breast tumors are least common in young Asian women

<table>
<thead>
<tr>
<th>Population</th>
<th>Luminal A (%)</th>
<th>Luminal B (%)</th>
<th>HER+/ER- (%)</th>
<th>Basal-like (%)</th>
<th>Unclassified (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-AA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenop</td>
<td>51</td>
<td>18</td>
<td>6</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Postmenop</td>
<td>58</td>
<td>16</td>
<td>6</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenop</td>
<td>67A</td>
<td>10A</td>
<td>10</td>
<td>9A</td>
<td>4</td>
</tr>
<tr>
<td>Postmenop</td>
<td>57</td>
<td>8B</td>
<td>14</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenop</td>
<td>36B</td>
<td>9A</td>
<td>9</td>
<td>39B</td>
<td>6</td>
</tr>
<tr>
<td>Postmenop</td>
<td>59</td>
<td>16</td>
<td>7</td>
<td>14</td>
<td>4</td>
</tr>
</tbody>
</table>

α = indicative of low risk of recurrence, b = indicative of high risk of recurrence

Molecular subtypes of breast cancer in different populations

Lin et al CEBP 2009; 18: 1807-14
Pubertal genistein exposure alters biology of mammary tumors in adulthood

Mammary tumors in mice fed genistein before puberty are less malignant and have lower mitotic index.

Mammary tumors in mice fed genistein before puberty contain significantly reduced levels of ER-α, PgR and HER-2.

Mammary tumors are less aggressive in mice that consumed genistein before puberty than in “non-consumer” mice.

It is not known whether it is safe to start consuming soy after breast cancer diagnosis.

Genistein exposure at puberty induces a permanent epigenetic imprint and alters response to adult genistein exposure?
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