Soy Isoflavones and Breast Cancer
A Review of the Evidence

Alison M. Duncan, Ph.D., R.D.
Associate Professor
Dept. of Human Health and Nutritional Sciences
University of Guelph

Community Cancer Support Network
Alberta Health Services
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Presentation Outline

- FACTS on Breast Cancer
  - Statistics, risk factors, role of estrogen
- FACTS on Isoflavones
  - Definitions, metabolism
- Soy Isoflavones and Breast Cancer: What does the research reveal about:
  - Breast Cancer Prevention
  - Breast Cancer Survival and Recurrence
- What is Recommended by Professionals
Breast Cancer Statistics

- Most frequent cancer for Canadian women
- In 2010, projections were for 23,200 diagnoses and 5,300 deaths
- One in 9 women will develop during lifetime and one in 28 will die

Canadian Cancer Society, 2010.

Canadian Cancer Cases (2008)

Females
81,700

22,700 Breast
10,700 Lung
9,900 Colon & rectum
4,400 Uterine corpus
3,700 Thyroid
3,300 Non-Hodgkin lymphoma
2,500 Ovary
2,300 Melanoma of skin
1,950 Leukemia
1,800 Kidney & renal pelvis

Canadian Cancer Society /National Cancer Institute of Canada, 2009.
Global differences in Breast Cancer incidence rates
- Significantly lower in Asian countries compared with Western countries (Pisani et al., 1999)
Worldwide Breast Cancer: Does Lifestyle Contribute?

- Breast cancer rates are low in Asians (Pisani/99)
- Asians who migrate to the United States have:
  - Breast cancer rates that approach that of non-Asian women born in the United States (Zeigler/93)
  - Suggests that lifestyle factors contribute to the international variation in breast cancer rates
- A dietary factor clearly separating Asian countries from the rest of the world is **SOY**
  - Asians consume significantly greater amounts of soy when compared to their Western counterparts

What is Soy?

- Received scientific attention for its human health benefits
- Contains numerous constituents with potential to influence human health:
  - Protein; bioactive peptides
  - Isoflavones

*With respect to breast cancer, most attention has been paid to soy isoflavones*
Soy Foods are Nutritious

- Soy foods are an excellent addition to a healthy diet that focuses on variety and moderation.
- Soy foods are part of Canada’s Food Guide to Healthy Eating.
- Key nutritional attributes:
  - Protein quality
  - Micronutrients
  - Omega-3 fatty acids

Soy Isoflavones

- Class of phytoestrogens
- Structurally similar to human estrogen:
  - binds weakly to the estrogen receptor
- Soy is richest dietary source
- Specific isoflavones:
  - Daidzein
  - Genistein
  - Glycitein
Isoflavone Metabolism

Isoflavone Glycosides

- Food enzymes
- Stomach acid
- Intestinal Bacteria

 Isoflavones

- Intestinal Bacteria

 Isoflavone Metabolites

✓ food
✓ intestine, blood
✓ urine, bile

Soy Isoflavone Resources

- USDA-Iowa State University Database

- Soy Foods Association of North America:
  [http://www.soys.org](http://www.soys.org)
Soy Isoflavones and Estrogen

- Isoflavones are weakly estrogenic, up to 1000x less potent than estrogen.
- Isoflavones can circulate at levels up to 1000x higher than endogenous estrogens in premenopausal women.
- Considered biologically relevant with potential to contribute to risk of diseases with estrogenic-related etiology.

Breast Cancer and Estrogen

- Numerous breast cancer risk factors relate to estrogen exposure:
  - Age of menarche
  - Age of menopause
  - Parity
  - Lactation
  - Age (pre- vs post-menopausal)
- Rationalizes research examining factors that can mitigate estrogen exposure.
Isoflavones are bioavailable and can reach the breast tissue

Healthy women consumed soy milk, soy supplement or control for 5 days before breast reduction surgery

Blood and breast samples showed isoflavones levels that can produce health effects

Bioavailability is key to realization of health effects of phytochemicals

Soy Isoflavones and Breast Cancer PREVENTION
**Breast Cancer PREVENTION**

- First study to report an inverse association between soy and breast cancer
- 200 Singapore Chinese premenopausal cases, 420 controls
- Reported on various dietary factors, highlighted soy
  - Soy foods: OR=0.44 (0.24, 0.81); **56% risk reduction**
  - Soy protein: OR=0.43 (0.23, 0.79); **57% risk reduction**
- Prompted further interest in soy and breast cancer

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Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies

Jia-Yi Dong • Li-Qiang Qin

- Most recent, 14 studies combined to look at overall relationship between soy isoflavones and breast cancer
- Overall RR=0.89 (0.79-0.99) for BC incidence which means **11% reduction in risk** with isoflavone intake
- Protection only in ASIAN studies (RR=0.76; 0.65-0.86) which means **24% reduction in risk**
  - Isoflavone intakes around 30-40 mg/day
- Not in WESTERN studies (RR=0.97; 0.87-1.06)
Early Intake Appears to Be the Key to the Proposed Protective Effects of Soy Intake Against Breast Cancer

Mark Messina
Loma Linda University, Loma Linda, California, and Nutrition Matters, Inc., Port Townsend, Washington, USA

Leena Hilakivi-Clarke
Georgetown University Medical Center, Washington, DC, USA

- Age of exposure is an exciting hypothesis that may explain the inconsistencies among soy isoflavone, breast cancer studies
- Early life events contribute toward breast cancer risk
- Supported by animal experiments
- Supported by human epidemiological studies

Breast Cancer PREVENTION
Age of Exposure


- Evaluated effect of genistein consumption during pre-natal, pre-puberty and adulthood on # tumors following DMBA-induced BC in rats

<table>
<thead>
<tr>
<th>Exposure period</th>
<th>Number of Tumors/Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>No genistein</td>
<td>8.9</td>
</tr>
<tr>
<td>Prenatal genistein</td>
<td>8.8</td>
</tr>
<tr>
<td>Adult genistein (after tumors)</td>
<td>8.2</td>
</tr>
<tr>
<td>Prepubertal genistein</td>
<td>4.3</td>
</tr>
<tr>
<td>Prepubertal and adult genistein</td>
<td>2.8</td>
</tr>
</tbody>
</table>
Breast Cancer PREVENTION
Age of Exposure; HUMAN Evidence


Thanos et al. Adolescent dietary phytoestrogen intake and BC risk (Canada). Cancer Causes Control. 2006; 17:1253-61

Lee et al. Adolescent and adult soy food intake and breast cancer risk: results from the Shanghai Women’s Health Study. AJCN; 2009;89:1920-6.


Breast Cancer PREVENTION
Age of Exposure; HUMAN Evidence


- Case (n=501) control (n=594) study of Asian Americans living in Los Angeles county
- Soy intake during adolescence and adult life
- Median isoflavone intake 12 mg/d

<table>
<thead>
<tr>
<th>Soy Exposure Time Period</th>
<th>Odds Ratio (high vs low intake)</th>
<th>BC Risk Redn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescence only</td>
<td>0.77 (0.51-1.10)</td>
<td>23%</td>
</tr>
<tr>
<td>Adolescence and Adult</td>
<td>0.53 (0.36-0.78)</td>
<td>47%</td>
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BC and Soy
Age of Exposure; HUMAN Evidence


- 99 cases, 56 controls
- Interviewed mothers
- 2-12 servings versus <1 serving/week

<table>
<thead>
<tr>
<th>Soy Exposure Time Period</th>
<th>RR (95% CI)</th>
<th>BC Risk Redn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood (5-11 yrs)</td>
<td>0.40 (0.18-0.83)</td>
<td>60% (p=0.03)</td>
</tr>
<tr>
<td>Adolescence (12-19 yrs)</td>
<td>0.80 (0.59-1.08)</td>
<td>20% (NS)</td>
</tr>
<tr>
<td>Adult (≥ 20 yrs)</td>
<td>0.76 (0.56-1.03)</td>
<td>24% (p=0.04)</td>
</tr>
</tbody>
</table>

Dietary PATTERNS including SOY reduce breast cancer risk

Dietary patterns and breast cancer risk in Asian American women1–3
Anna H Wu, Min C Yu, Chia-Chen Tseng, Frank Z Sloneczk, and Malcolm C Pike. AJCN 2009;89:1145-54

- Case-control study of Asian American women in Los Angeles
- Vegetable/soy dietary pattern associated with a 31% reduction in breast cancer risk (RR=0.69; 0.52-0.91)

A vegetable-fruit-soy dietary pattern protects against breast cancer among postmenopausal Singapore Chinese women1–3

- Cohort study of 34,000 Singapore Chinese women
- Vegetable-fruit-soy dietary pattern associated with 30% reduction in breast cancer risk (HR=0.70; 0.51-0.95)
Soy Isoflavones and Breast Cancer

**SAFETY**

**Cell Culture Studies**

- MCF-7 estrogen-dependent breast cancer cells
  - At LOW concentrations (<10 µmol/L); physiologic
    - Isoflavones stimulate growth
    - Estrogen-dependent effects
  - At HIGH concentrations (>10 µmol/L); non-physiologic
    - Isoflavones inhibit growth
    - Estrogen-independent effects


Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose dependent manner. Allred et al., Cancer Res. 2001;61:5045-50.

Dietary genistin stimulates growth of estrogen-dependent breast cancer tumors similar to that observed with genistein. Allred et al., Carcinogenesis; 2001;10:1667-73.

Breast Cancer SAFETY
Helferich Animal Studies

- OVX, athymic mice, implanted with E-dependent MCF-7 cells
- When mice were fed soy or isoflavones in various forms:
  - Breast tumour growth increased
  - Often dose-dependent
  - Doses relevant to human intake

Can we extrapolate animal study results to humans?

- Provide important information to rationalize study in humans
- Important limitations of animal MODEL can limit direct relevance to humans
- In this case, the factors include:
  - Athymic, no immune system
  - OVX, no ovaries
  - Metabolism of isoflavones is different
  - Relevance of dose of isoflavones
  - Nature of MCF-7 cells implanted into animals
- Despite limitations, concerns warrant study in humans
Breast Cancer SAFETY
Human Data; BREAST BIOPSIES

- Breast tissue is highly regulated by estrogen
- Breast epithelial proliferation reflects estrogen exposure
- Ki67 is a common proliferation marker
- 4 human studies completed

Soy Isoflavones
BREAST BIOPSIES

BC patients (n=84)
Soy protein (45 mg ISO)
14 days
No Effect
Ki67, ER, PR
Hargreaves et al., 1999

Healthy (n=51)
60 mg ISO
12 weeks
No Effect
Ki67, ER, PR
Cheng et al., 2007

BC survivors (n=18)
100 mg ISO
11.7 months
No Effect
Ki67, ER, PR
Palomares et al., 2004 (abst)

BC patients (n=17)
120 mg ISO
22 days
No Effect
p53, ER, PR
Sartippour et al., 2004
Breast Cancer SAFETY
Human Data; MAMMOGRAPHIC DENSITY

- High mammographic density associated with increased breast cancer risk
  - Odds Ratio: 2.1 to 6.0 (highest vs lowest MD) (Boyd et al, CEBP;1998;7:1133-44)
- Mammographic density reflects current and past hormone exposure
  - increased with HRT use (Lundstrom/99)
  - decreased with HRT discontinuation (Lundstrom/99)
  - decreased with tamoxifen (Brisson/00)

### Soy Isoflavones

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Duration</th>
<th>Result</th>
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<tbody>
<tr>
<td>Healthy PRE (n=30)</td>
<td>Soy Foods (50 mg ISO)</td>
<td>1 yr</td>
<td>No Effect</td>
</tr>
<tr>
<td>Healthy PRE (n=201)</td>
<td>Soy Foods (50 mg ISO)</td>
<td>2 yrs</td>
<td>No Effect</td>
</tr>
<tr>
<td>Healthy PRE (n=30)</td>
<td>Soy Foods (100 mg ISO)</td>
<td>1 yr</td>
<td>No Effect</td>
</tr>
<tr>
<td>Healthy POST (n=126)</td>
<td>Soy protein (99 mg ISO)</td>
<td>1 yr</td>
<td>Significant Decrease Not different from control</td>
</tr>
<tr>
<td>Healthy POST (n=197)</td>
<td>Soy extract (70 mg ISO)</td>
<td>3 yrs</td>
<td>No Effect</td>
</tr>
<tr>
<td>Healthy POST (n=303)</td>
<td>80 or 120 mg ISO</td>
<td>2 yrs</td>
<td>No Effect</td>
</tr>
</tbody>
</table>

Maskarinec et al., 2003
Maskarinec et al., 2004
Verheus et al., 2008
Palacios et al., 2009
Breast cancer survivors are increasingly interested in CAM (Boon et al., 2007)

Concern about interaction of soy isoflavones with rate of recurrence, survival, interaction with tamoxifen therapy

To date, 6 prospective cohort studies have addressed soy isoflavones and breast cancer recurrence/survival

**Soy Isoflavones**

**BREAST CANCER RECURRENCE, SURVIVAL**

**BC survivors (n=1459)**
- 5.2-year follow-up
- HR=1.06 NO RELATION
  - Survival
  - Boyapati et al., 2005

**BC survivors (n=5042)**
- 3.9-year follow-up
- HR=0.68 (0.54-0.87) PROTECTIVE
  - Recurrence (not dependent on tamoxifen use)
  - Shu et al., 2009

**BC survivors (n=1210)**
- 5-year follow-up
- HR=0.52 (0.33-0.82)
  - Survival
  - Fink et al., 2007

**Soy Isoflavones**

**BREAST CANCER RECURRENCE, SURVIVAL**

**BC survivors (n=1954)**
- 6.3-year follow-up
- HR=0.48 (0.21-0.79) PROTECTIVE
  - Recurrence (postmen. tamoxifen users)
  - Guha et al., 2009
Combined data from 4 studies that related soy isoflavone intake to recurrence of breast cancer

Combined 9656 breast cancer cases and 1226 recurrences

Combined RR=0.84 (0.70-0.99) comparing highest to lowest isoflavone intake; **14% reduction in recurrence with isoflavone intake**

Supports a significant inverse association between risk of breast cancer recurrence and soy isoflavone consumption

Followed 524 breast cancer patients who had undergone surgery for breast cancer and were receiving an aromatase inhibitor for 5.1 years

Postmenopausal women: **breast cancer recurrence reduced by 33%** in women who consumed >42.3mg compared to <15.2 mg/day (HR=0.67; 0.54-0.85)

Premenopausal women: no relationship found
Just published Feb 25, 2011, used data from the Women’s Healthy Eating and Living Well Study

Total of 3088 breast cancer survivors followed for 7.3 years

As isoflavone intake increased, risk of death decreased

Highest level of isoflavone intake (<16.3 mg/day) associated with a 54% reduction in risk of death (not significant)

Appeared to be strongest in women who used tamoxifen

Breast Cancer SAFETY
Human Data; SIDE EFFECTS

- Majority of intervention studies monitor adverse effects
- Opportunity to pool data to assess overall hormonal-related safety
- Meta-analysis published in 2009
Side Effects of Phytoestrogens: A Meta-analysis of Randomized Trials

Clemens B. Tempfer, MD, a Georg Froese, MD, a Georg Heinze, PhD, a Eva-Katrin Bentz, MD, a Lukas A. Heffler, MD, a Johannes C. Huber, MD, PhD a

- Meta-analysis of 174 RCTs, n=9629 participants
- Overall side effect incidence
  - Phytoestrogen groups: 36.7%
  - Control groups: 38.8%
- No differences in hormone-related side effects
  - Endometrial hyperplasia, endometrial cancer, breast cancer

Long-term endometrial and breast safety of a specific, standardized soy extract

S. Palacios, B. Fornel *, F. Vázquez 1, L. Aubert 5, P. Chantré 5 and P. Maris * *

Palacios Institute of Women’s Health, Madrid, Spain; *Brussels Menopause Center, Brussels, Belgium; 1Clinica CEOGA, Lugo, Spain; 5Laboratoires Arkopharma, Carros Cedex, France; **CHU Caremeau, Service de Gynécologie Obstétrique, Nîmes Cedex, France

- 395 postmenopausal women consumed a soy isoflavone extract (70 mg/day) for 3 years
- Endometrial biopsy, transvaginal ultrasonography and mammography before and after 3 years
  - No cases of hyperplasia or cancer
  - 1 case of simple hyperplasia
  - No change in endometrial thickness
  - No change in mammographies
Soy Isoflavones and Breast Cancer

WHAT ARE PROFESSIONALS RECOMMENDING?

Women with breast cancer should take in only moderate amounts of soy foods as part of a healthy, plant-based diet. They should not ingest very high levels of soy in their diet or take concentrated sources of soy such as soy-containing pills or powders, or supplements containing high amounts of isoflavones.
For the breast cancer survivor, current research finds no special benefits or harmful effects when no more than 3 servings of soy are eaten per day as part of a healthy diet. This compares to the amounts eaten in most Asian diets. But higher doses of soy may have estrogen-like effects, and higher levels of estrogens can cause certain breast cancers to grow and spread. For this reason, it is best for breast cancer survivors to avoid the high doses that are found in more concentrated sources such as soy powders and isoflavone supplements.

American Institute for Cancer Research (AICR)

"Current research shows that it is safe to eat moderate amounts of soy foods (e.g., soymilk, tofu), up to two to three servings per day. As a precaution, women receiving anti-estrogen treatments such as tamoxifen, should minimize soy foods and avoid isoflavone supplements."

"Evidence still does not support adding soy to your diet hoping that it will help prevent breast cancer. But soy is a healthful food. It is low in saturated fat, high in nutrients, fiber and antioxidants."

"Women who are at high risk for breast cancer, take tamoxifen or aromatase inhibitor medications or have been diagnosed with estrogen receptor-positive (ER+) breast cancer may want to limit themselves to no more than a few servings per week. Supplements of soy components like soy protein or isoflavones haven’t been well researched and are not recommended."
**Canadian Cancer Society**

Nutritional Concerns for Breast Cancer

Phytoestrogens are natural chemicals from plants that act weakly like estrogen. They are found in foods such as soy and flaxseed. The debate around phytoestrogens is whether their estrogen-like quality increases the growth of breast cancer.

Not enough scientific study has been done to prove or disprove that soy might act in the same way as the body’s estrogens and increase the growth of breast cancer. And different studies tell us different things about soy and breast cancer coming back. Talk to your healthcare team about eating soy-based foods. Some doctors may recommend that people on hormonal therapy (such as tamoxifen) avoid soy because it may interfere with the therapy.

www.cancer.ca; March 2010

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**Dietitians of Canada**

www.dietitians.ca

“Breast cancer – To help prevent breast cancer, soy foods should be eaten starting during childhood or adolescence. Starting to eat soy products during adulthood, does not appear to prevent breast cancer. For breast cancer survivors, soy remains a healthy food to add protein, fibre and variety. **Soy supplements** in the form of pills, powders and isolated components of soy foods are not recommended.”

“Tofu, soybeans and other soy-based foods can be eaten as part of a healthy diet. However, **soy tablets are not recommended** until more research is available. Note that soy foods and soy tablets are not recommended for women who have breast cancer, who have a family history of breast cancer or who are taking certain medications for breast cancer.”

www.dietitians.ca
No consensus among research or clinical communities

…“Current data warrants a re-evaluation of the default prohibition against soy foods for breast cancer patients”

…”Clinicians can adopt a stance of permitting use in patients who want to begin eating soyfoods or for whom soyfoods already represent a normal part of their diet (mainly vegetarian and patients of Asian ethnicity).”

Data not sufficiently strong to justify the use of soyfoods in the treatment of breast cancer patients

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Soy Isoflavones and Breast Cancer
Take Home Messages

Breast Cancer PREVENTION

- Studies show that soy isoflavones either prevent or do not affect breast cancer risk
- Age of exposure issue is important

Breast Cancer SAFETY

- Studies in cells and animals raise concern that isoflavones can harm women with breast cancer, but this is not supported by studies in humans
- However, no cause and effect studies have been completed on actual recurrence or survival
- Prudent to avoid supplements
- Prudent to enjoy soy FOODS in moderation