Soy Isoflavones and Breast Cancer
A Review of the Evidence

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March 9, 2011

Presentation Outline

- Breast cancer basics
  - Statistics, risk factors, role of estrogen
- Soy isoflavones basics
  - Definitions, metabolism
- Soy isoflavones and breast cancer
  - Prevention
    - Meta-analyses
    - Age of exposure
    - Dietary Patterns
  - Safety
    - Cell culture
    - Animal studies
    - Human studies
- Summary Notes
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

<table>
<thead>
<tr>
<th>22,700 Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>10,700 Lung</td>
</tr>
<tr>
<td>9,900 Colon &amp; rectum</td>
</tr>
<tr>
<td>4,400 Uterine corpus</td>
</tr>
<tr>
<td>3,700 Thyroid</td>
</tr>
<tr>
<td>3,300 Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>2,500 Ovary</td>
</tr>
<tr>
<td>2,300 Melanoma of skin</td>
</tr>
<tr>
<td>1,950 Leukemia</td>
</tr>
<tr>
<td>1,800 Kidney &amp; renal pelvis</td>
</tr>
</tbody>
</table>

Canadian Cancer Society/National Cancer Institute of Canada, 2009.
Worldwide Breast Cancer Incidence

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 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 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.
Isoflavones as SERMS

- May better characterize isoflavone effects
- Preferentially bind to ER-beta
  - ER agonist in some tissues
  - ER antagonist in other tissues
- Similar to tamoxifen, raloxifene


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 (nmol) and breast (pmol) biopsies demonstrated exposure levels of isoflavones that have biological relevance

Bioavailability is key to realization of health effects of phytochemicals
Isoflavones and Breast Cancer Observational Studies

- Relate BC incidence to isoflavone intake
  - monitor BC RATES or study BC CASES
  - quantify soy and/or isoflavone intake
  - generate RR or OR

- Advantages:
  - large sample size
  - generate hypotheses and rationalize further study

- Disadvantages:
  - cannot conclude cause and effect
  - not specifically designed to study role of soy
  - narrow range of isoflavone intake (exposure range)
  - assessment of soy crude and incomplete

Breast Cancer PREVENTION

- First case-control 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)
  - Soy protein: OR=0.43 (0.23, 0.79)
- Prompted further interest in soy and breast cancer
## Breast Cancer PREVENTION Meta-Analyses

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Studies</th>
<th>Odds Ratio Soy Foods</th>
<th>Odds Ratio Soy Isoflavones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trock et al., 2006</td>
<td>12 case-control</td>
<td>0.86 (0.75-0.99)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>6 cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qin et al., 2006</td>
<td>14 case-control</td>
<td>0.75 (0.59-0.95)</td>
<td>0.81 (0.67-0.99)</td>
</tr>
<tr>
<td></td>
<td>7 cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu et al., 2008</td>
<td>Asian studies:</td>
<td>-----</td>
<td>0.88 (10mg) (0.78-0.98)</td>
</tr>
<tr>
<td></td>
<td>7 case control</td>
<td></td>
<td>0.71 (&gt;20 mg) (0.60-0.85)</td>
</tr>
<tr>
<td></td>
<td>1 cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu et al., 2008</td>
<td>Western studies:</td>
<td>-----</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>11 case control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Review

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
- Overall RR=0.89 (0.79-0.99) for BC incidence
- Protection only in ASIAN studies (RR=0.76; 0.65-0.86)
- Not in WESTERN studies (RR=0.97; 0.87-1.06)
Soy Isoflavones and BC
Plasma Isoflavones

- Plasma isoflavones overcome limitations in dietary assessment
- 24,226 women, Japan Public Health Center-based prospective study
- 10.6 years follow-up
- Plasma genistein significantly inversely associated with BC risk; OR=0.34 (0.16-0.74)
- Plasma daidzein not associated

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 # tumours 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>
</tr>
</tbody>
</table>

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 women\(^1-3\)
Anna H Wu, Mimi C Yu, Chia-Chen Tseng, Frank Z Stanczak, 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 women\(^1-3\)
Lesley M Butler, Anna H Wu, Renwei Wang, Woon-Passy Koh, Jian-Ming Yuan, and Mimi C Yu  
AJCN 2010;91:1013-9

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

Soy Isoflavones and Breast Cancer  
SAFETY
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
Helferich Mouse Model Notes

- OVX athymic mouse model
  - Lack of immune function could eliminate possible mechanism for genistein to reduce tumour incidence
    - Enhanced immune function resulting from genistein treatment correlated with reduced mammary tumours (Guo et al. Carcinogenesis; 2007;28:2560-6).
  - Complete lack of ovarian function does not mimic a postmenopausal women
    - OVX mice cannot produce ANY estrogen
    - ANY estrogenic stimulus (no matter how weak) would stimulate this hypo-estrogenic environment

- Isoflavone dose
  - Genistein dose of 750ppm often used greatly exceeds dietary intake
    - Japanese intake 15-20 mg genistein/day equates to 40 ppm
    - Even greater difference when isoflavones are expressed on a caloric basis to adjust for differences in metabolism
      - 30 g mouse: 405 mg iso per 1800 kcal
      - Humans: 25-50 mg iso per 1800 kcal

- MCF-7 xenoplants
  - Fully transformed tumors highly sensitive to estrogen’s growth stimulatory effects
  - Unclear how this reflects tumours in BC patients
Breast Cancer SAFETY
Human Data; NIPPLE ASPIRATE FLUID

- Proteins in nipple aspirate fluid are estrogen-regulated (Harding et al., 2006)
  - apoD (or GCDFP-24), pS2
- Serves as a feasible biomarker to reflect estrogen action on the breast

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### Soy Isoflavones

**NIPPLE ASPIRATE FLUID**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Duration</th>
<th>Estrogenic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy PRE, POST (n=24)</td>
<td>TVP; 38 mg ISO</td>
<td>6 months</td>
<td>↑ NAF, Epithelial hyperplasia in 7/24 women</td>
</tr>
<tr>
<td>BC Patients (n=84)</td>
<td>Soy protein; 45 mg ISO</td>
<td>14 days</td>
<td>↑ pS2, ↓ apoD</td>
</tr>
</tbody>
</table>

Petrakis et al., 1996
Hargreaves et al., 1999
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

**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 patients (n=17)**
120 mg ISO
22 days
No Effect
p53, ER, PR
Sartippour et al., 2004

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

- Healthy PRE (n=30)
  - 100 mg ISO
  - 1 yr
  - No Effect
  - Maskarinec et al., 2003

- Healthy PRE (n=201)
  - Soy Foods (50 mg ISO)
  - 2 yrs
  - No Effect
  - Maskarinec et al., 2004

- Healthy POST (n=80 or 120 mg ISO)
  - 2 yrs
  - No Effect
  - Maskarinec et al., 2009

- Healthy POST (n=126)
  - Soy protein (99 mg ISO)
  - 1 yr
  - Significant Decrease
  - Not different from control
  - Verheus et al., 2008

- Healthy POST (n=197)
  - Soy extract (70 mg ISO)
  - 3 years
  - No Effect
  - Palacios et al., 2010
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 and a meta-analysis have examined soy isoflavones and breast cancer recurrence/survival

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**Soy Isoflavones**

**BREAST CANCER RECURRENTE, SURVIVAL**

**Breast Cancer SAFETY**

**Human Data; SURVIVAL, RECURRENCE**

- BC survivors (n=1459)
  - 5.2-year follow-up
  - HR=1.06 (0.79-1.42)
  - Survival
  - Boyapati et al., 2005

- BC survivors (n=1210)
  - 5-year follow-up
  - HR=0.87 (0.54-1.41)
  - Survival
  - HR=0.52 (0.33-0.82)
  - All-cause mortality
  - Fink et al., 2007

- BC survivors (n=1954)
  - 6.3-year follow-up
  - HR=0.48 (0.21-0.79)
  - Recurrence
  - (postmen. tamoxifen users)
  - Guha et al., 2009

- BC survivors (n=5042)
  - 3.9-year follow-up
  - HR=0.68 (0.54-0.87)
  - Recurrence
  - (not dependent on tamoxifen use)
  - Shu et al., 2009
Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies

Jia-Yi Dong • Li-Qiang Qin

- Combined data from 4 studies that related soy isoflavone intake to recurrence of breast cancer
- No significant heterogeneity among studies
- Combined 9656 breast cancer cases and 1226 recurrences
- Combined RR=0.84 (0.70-0.99) comparing highest to lowest isoflavone intake
- Supports a significant inverse association between risk of breast cancer recurrence and soy isoflavone consumption

Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy

Xinmei Kang MD PhD, Qingyuan Zhang MD PhD, Shuhuai Wang MD, Xu Huang MD, Shi Jin MD

- Followed 524 breast cancer patients who had undergone surgery for breast cancer and were receiving adjuvant endocrine therapy (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: death rate (30.1%) was not significantly related to soy isoflavones; HR=1.05 (0.78-1.71; >42.3mg compared to <15.2 mg/day)
Soy Food Consumption and Breast Cancer Prognosis
Betty J. Caan, Loki Natarajan, Barbara A. Parker, et al.

- 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

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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, Georg Freese, MD, Georg Heinze, PhD, Eva-Katrin Bentz, MD, Lukas A. Heffer, MD, Johannes C. Huber, MD, PhD

- 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. Porel*, F. Vázquez†, L. Aubert‡, P. Chantré§ and P. Marion**

Palacios Institute of Women’s Health, Madrid, Spain; *Brussels Menopause Center, Brussels, Belgium; †Clinica CEOGA, Lugo, Spain; ‡Laboratoires 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
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 soy foods or for whom soy foods already represent a normal part of their diet (mainly vegetarian and patients of Asian ethnicity).”

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

Soy Isoflavones and Breast Cancer Summary Notes

Breast Cancer **PREVENTION**
- Biological plausibility for soy isoflavones to be involved in breast cancer
- Meta-analyses show positive results but inconsistencies exist
- Age of exposure issue is important

Breast Cancer **SAFETY**
- Cell culture and animal data raise concern
- Two uncontrolled human studies show breast proliferation
- Studies of breast biopsies, mammographic density, survival, recurrence, overall safety show no concerns