



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**

**Canadian Nutrition Society
Annual Meeting
June 5, 2010**

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, projected total of 23,200 women will be diagnosed and 5,300 will die
- One in 9 women will develop during lifetime and one in 28 will die

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

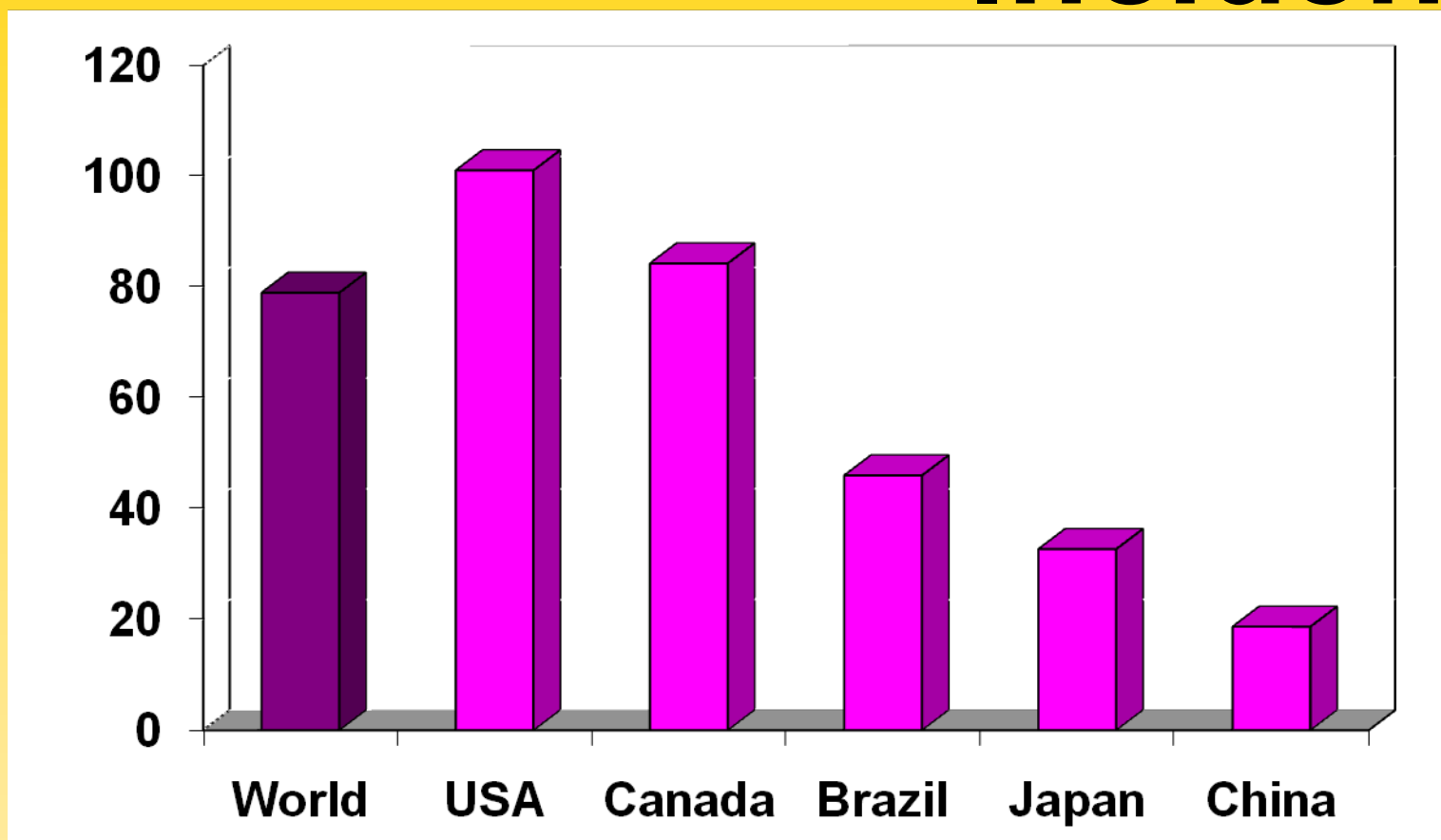
1,950 Leukemia

1,800 Kidney & renal pelvis

Canadian Cancer Society /National Cancer Institute of Canada, 2009.



Worldwide Breast Cancer Incidence



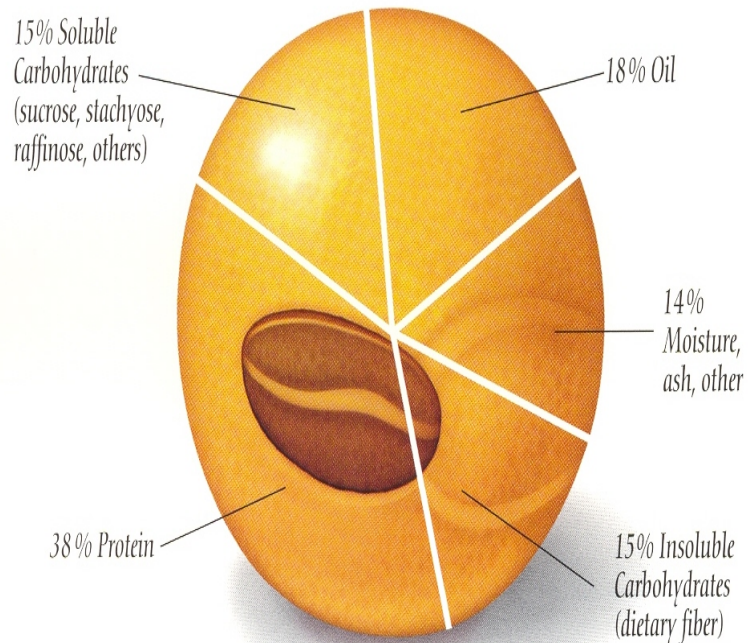
Source: J. Ferlay, F. Bray, P. Pisani and D.M. Parkin. **GLOBOCAN 2002**. Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5, version 2.0. IARC Press, Lyon, 2004.



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?



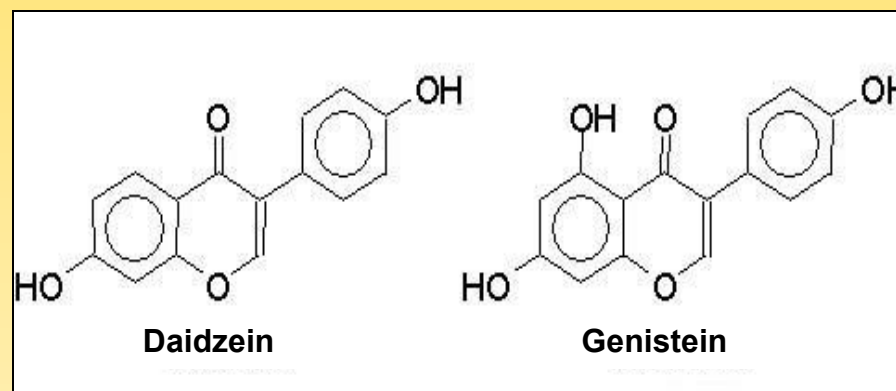
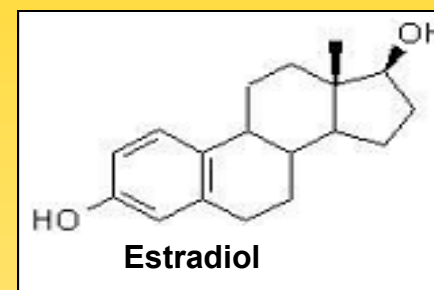
- Received scientific attention for its human health benefits
- Contains numerous constituents with potential to influence human health:
 - Protein; bioactive peptides
 - Isoflavones

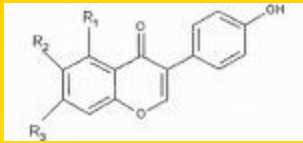
With respect to breast cancer, most attention has been paid to soy isoflavones



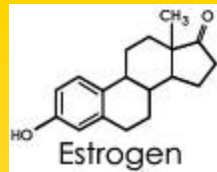
Soy Isoflavones

- 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



Estrogen

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



Soy Isoflavones and Breast Cancer **PREVENTION**



Breast Cancer PREVENTION

VOL 337: MAY 18, 1991

THE LANCET

EPIDEMIOLOGY

Dietary effects on breast-cancer risk in Singapore

H. P. LEE L. GOURLEY S. W. DUFFY J. ESTÈVE J. LEE
N. E. DAY

- First case-control study to report an inverse association between soy and breast cancer
- 200 Singapore Chinese premenopausal cases and 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

| Reference | Number of Studies | Odds Ratio Soy Foods | Odds Ratio Soy Isoflavones |
|--------------------|--|----------------------|--|
| Trock et al., 2006 | 12 case-control 6 cohort | 0.86 (0.75-0.99) | ----- |
| Qin et al., 2006 | 14 case-control 7 cohort | 0.75 (0.59-0.95) | 0.81 (0.67-0.99) |
| Wu et al., 2008 | Asian studies: 7 case control 1 cohort | ----- | 0.88 (10 mg) (0.78-0.98) 0.71 (\geq 20 mg) (0.60-0.85) |
| Wu et al., 2008 | Western studies: 11 case control | ----- | NS |

Nutrition and Cancer, 61(6), 792–798
Copyright © 2009, Taylor & Francis Group, LLC
ISSN: 0163-5581 print / 1532-7914 online
DOI: 10.1080/01635580903285015

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

Lamartiniere et al. Genistein chemoprevention: timing and mechanisms of action in murine mammary and prostate.
J Nutr 2002;132:552S-558S

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

| Exposure period | Number of Tumors/Rat |
|---------------------------------|----------------------|
| No genistein | 8.9 |
| Prenatal genistein | 8.8 |
| Adult genistein (after tumors) | 8.2 |
| Prepubertal genistein | 4.3 |
| Prepubertal and adult genistein | 2.8 |

Breast Cancer PREVENTION

Age of Exposure; HUMAN Evidence

Shu et al. Soyfood intake during adolescence and subsequent risk of BC among Chinese women. CEBP. 2001;10: 483–8.

Wu et al. Adolescent and adult soy intake and risk of breast cancer in Asian–Americans. Carcinogenesis. 2002;23:1491–6

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.

Korde et al. Childhood soy intake and breast cancer risk in Asian-American women. CEBP. 2009;18:1050-9.

Breast Cancer PREVENTION

Age of Exposure; HUMAN Evidence

Wu et al. Adolescent and adult soy intake and risk of breast cancer in Asian–Americans. *Carcinogenesis*. 2002; 23:1491–96

- 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

| Soy Exposure Time Period | Odds Ratio (high vs low intake) | BC Risk Redn |
|--------------------------|---------------------------------|--------------|
| Adolescence only | 0.77 (0.51-1.10) | 23% |
| Adolescence and Adult | 0.53 (0.36-0.78) | 47% |

BC and Soy

Age of Exposure; HUMAN Evidence

Korde et al. Childhood soy intake and BC risk in Asian-American women. *Cancer Epidemiol Biomarkers Prev.* 2009;18;1-9.

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

| Soy Exposure Time Period | RR (95% CI) | BC Risk Redn |
|--------------------------|------------------|--------------|
| Childhood (5-11 yrs) | 0.40 (0.18-0.83) | 60% (p=0.03) |
| Adolescence (12-19 yrs) | 0.80 (0.59-1.08) | 20% (NS) |
| Adult (\geq 20 yrs) | 0.76 (0.56-1.03) | 24% (p=0.04) |

Dietary PATTERNS including SOY reduce breast cancer risk

Dietary patterns and breast cancer risk in Asian American women¹⁻³

Anna H Wu, Mimi C Yu, Chiu-Chen Tseng, Frank Z Stanczyk, 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

Lesley M Butler, Anna H Wu, Renwei Wang, Woon-Puay Koh, Jian-Min 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 ($<10 \mu\text{mol/L}$); physiologic
 - Isoflavones **stimulate** growth
 - Estrogen-dependent effects
 - At HIGH concentrations ($>10 \mu\text{mol/L}$); non-physiologic
 - Isoflavones **inhibit** growth
 - Estrogen-independent effects



Breast Cancer SAFETY

Helferich Animal Studies

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.

Physiological concentrations of dietary genistein dose-dependently stimulate growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in athymic nude mice. *Ju et al., J Nutr. 2001;131:2957-62.*

Soy processing influences growth of estrogen-dependent breast cancer tumors. *Allred et al., Carcinogenesis; 2004;25:1649-57.*

- 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

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

**Soy Isoflavones
NIPPLE ASPIRATE
FLUID**



Healthy PRE, POST (n=24)
TVP; 38 mg ISO
6 months
Estrogenic response
↑ **NAF**
Epithelial hyperplasia in 7/24 women
Petrakis et al., 1996



BC Patients (n=84)
Soy protein; 45 mg ISO
14 days
Estrogenic response
↑ **pS2**, ↓ **apoD**
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

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

Soy Isoflavones BREAST BIOPSIES

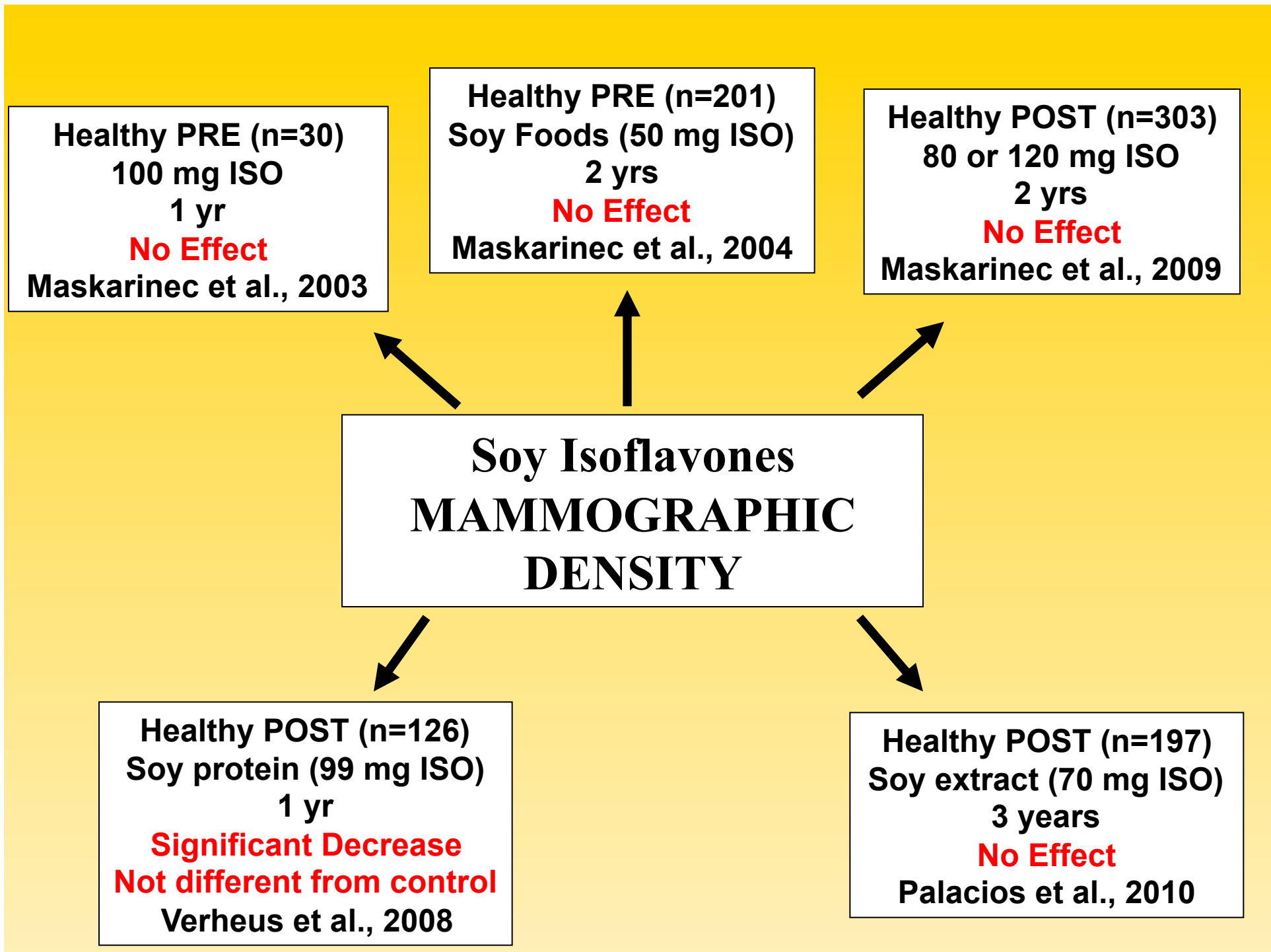
BC survivors (n=18)
100 mg ISO
11.7 months
No Effect
Ki67, ER, PR
Palomares et al., 2004 (abst)

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

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)



Breast Cancer SAFETY

Human Data; SURVIVAL, RECURRENCE

- 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, 4 prospective cohort studies have addressed soy isoflavones and breast cancer recurrence/survival

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

Soy Isoflavones
BREAST CANCER
RECURRENCE, SURVIVAL

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

Breast Cancer SAFETY

Human Data; SIDE EFFECTS

- Majority of intervention studies monitor adverse effects
- Opportunity to pool data to assess overall hormonal-related safety
- 1 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,^b Eva-Katrin Bentz, MD,^a Lukas A. Hefler, 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. Pornel, F. Vázquez†, L. Aubert‡, P. Chantre‡ and P. Marès***

Palacios Institute of Women's Health, Madrid, Spain; *Brussels Menopause Center, Brussels, Belgium; †Clínica 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

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 human studies show breast proliferation
- Remainder of studies in breast biopsies, mammographic density, survival, overall safety show no concerns