Soy and Cancer

Sense and Sensibility
The truth about soy and cancer

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Soy 2007

Jan. 14 Sydney - Shock! Horror!

Soy cancer alert

Clair Weaver

January 14, 2007 12:00am

CANCER patients are being warned to avoid foods rich in soy because they can accelerate the growth of tumours.

Cancer Council NSW will for the first time issue guidelines today warning about the dangers of high soy diets and soy supplements for cancer patients and those in remission. At particular risk are people suffering from hormone-dependent cancers including breast and prostate cancers, the two most common forms in Australia.

Cancer survivors are also being urged to avoid high doses of soy as they may be more vulnerable to a relapse.

Research has found that high consumption of soy products can also prevent the effectiveness of conventional medicines used to treat the disease.
Cancer patients warned to avoid soy products

Cancer patients are being urged to avoid soy food products due to fears they can cause tumours to grow faster.

The Cancer Council NSW will today issue guidelines warning of the dangers of consuming high amounts of soy products, a newspaper reports.

People with breast and prostate cancer - Australia's most common cancers - are most at risk as both forms of the disease are hormone dependent.

Research has found consuming high amounts of soy can limit the effectiveness of medicines used to treat the disease.
The truth is out there!

http://augmentinforce.50webs.com/ANTI%20SOY.htm
Why is this important?

- 74% - food and nutrition has a significant effect on the maintenance and improvement of their overall health.

- 33% - add particular foods or ingredients to their diet to improve or maintain health (27% in Australia).

- 59% - eat up to three foods specifically for functional health benefits.

USA survey data 1998; National Nutrition Survey, 1995
Why is this important?

• Cancer is the leading cause of death in Australia – 29.4% as the sole underlying cause, 40.6% as contributing cause

• Breast and prostate cancers are leading causes of mortality

ABS statistics 2005
The dietary origins of cancer

Initiation
Promotion
Progression

Chemicals
Obesity
Energy excess
Limited antioxidants
Saturated fats

Malignant Neoplasm (Cancer)
Why is this important?

- Diet is the single largest contributing factor
  - multifactorial in effect

<table>
<thead>
<tr>
<th>Factor</th>
<th>Best Estimate</th>
<th>Range of Acceptable Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>30</td>
<td>25-40</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>2-4</td>
</tr>
<tr>
<td>Diet</td>
<td>35</td>
<td>10-70</td>
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<tr>
<td>Food Additives</td>
<td>1</td>
<td>(-5**) -2</td>
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<tr>
<td>Reproductive/Sexual Behavior</td>
<td>7</td>
<td>1-13</td>
</tr>
<tr>
<td>Occupation</td>
<td>4</td>
<td>2-8</td>
</tr>
<tr>
<td>Pollution</td>
<td>2</td>
<td>1-5</td>
</tr>
<tr>
<td>Industrial Products</td>
<td>1</td>
<td>1-2</td>
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<tr>
<td>Medicines/Medical Products</td>
<td>1</td>
<td>0.5-3</td>
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<tr>
<td>Geophysical Factors</td>
<td>3</td>
<td>2-4</td>
</tr>
<tr>
<td>Infection</td>
<td>10</td>
<td>1-?</td>
</tr>
</tbody>
</table>

Doll and Peto (1981)
Why single out soy for attention?

- Soybeans contain chemicals known as **phytoestrogens**
- Natural plant substances
  - Three main classes
    - Isoflavones
    - Coumestans
    - Lignans
- Phytoestrogens plant relatives of the hormone oestrogen
  - They weakly mimic or modulate the hormone’s effects on some body tissues
- They have anti-carcinogenic properties
- But also due to the oestrogenic properties they can also promote cancer
Soy and cancer

How do we establish an evidence-based relationship between diet and cancer?

**Epidemiology**
- inverse relationship with nutrient intake
- incidence of site specific tumors varied with diet
- patterns between countries

**Clinical Studies**
- mainly retrospective
- used supplements
- equivocal findings

**Randomized Clinical Trials**
- large prospective underway
- biomarkers as endpoints

**Animal Studies**
- compelling but not generalizeable

**Cell Lines**
- elucidation of mechanisms
- evaluate genetic interactions

**Molecular Biology**
- confirmation of mechanisms
- demonstration of gene binding
What is the evidence - epidemiologic

- Populations with high soy food intake tend to have lower rates of breast, prostate, and colon cancer

Prostate cancer by country

Hsing et al. (2000) Int. J. Canc. 85: 60
Soy milk intake and prostate cancer

Adventists Health Study - 1 1976-1988
Epidemiologic evidence - 2

- Migrant populations (presumably adapting western diet) tend to develop cancer rates of adopted country

![Graph showing excretion of soy metabolites and prostate tissue characteristics](image)

Soy metabolites: Daidzein, Genistein
Prostate tissue characteristics: Caspase-3, Lipoxygenase

Marks et al. (2004) Urology 64: 765
Soy and Breast Cancer in Asian Americans

- Population-based case-control study (n=597 cases, 966 controls)
- Chinese-, Japanese-, Filipino-American women in Los Angeles, San Francisco, Oahu
- Age 20-55 years at diagnosis, 1983-1987
- First primary breast cancer
- FFQ: usual frequency of intake during adult life, 50 items common, 10 items specific to ethnic group
- Exposure: tofu (for Jap-Am tofu/miso/natto)

Wu et al, Cancer Epidemiol, Biomarkers, Prev, 1996
Soy and Breast Cancer in Asian Americans

![Graph showing decreased and increased risks by ethnicity and menopausal status]

- **Japanese**: Decreased risk, OR = 0.63
- **Chinese**: Decreased risk, OR = 0.79
- **Filipino**: Increased risk, OR = 1.26

*multi-adj OR per 1 category difference in tofu intake*

* Wu et al, Cancer Epidemiol, Biomarkers, Prev, 1996
Epidemiologic studies: meta-analysis

Association Between Soy and Breast Cancer Risk

OR or RR for high vs. low soy or isoflavone levels

* Premeno = premenopausal women, postmeno = postmenopausal women

Epidemiologic studies: meta-analysis

Association Between Soy and Breast Cancer Risk, by Population Subgroups

**Asian Women**
- Lee (postmeno) 1992
- Lee (premeno) 1992
- Hirose (postmeno) 1995
- Hirose (premeno) 1995
- Yuan (Tianjin) 1995
- Yuan (Shanghai) 1995
- Chi 1997
- Key (all women) 1999
- Dai 2001
- Yamamoto 2003

**Postmenopausal**
- Lee 1992
- Hirose 1995
- Wu 1996
- Greenshtein 1996
- Key 1999
- Shu 2001
- Horn-Ross 2001
- Den Tonkelaar 2001
- Wu 2002
- Yamamoto 2003

**Premenopausal**
- Lee 1992
- Hirose 1995
- Wu 1996
- Witte 1997
- Key 1999
- Shu 2001
- Horn-Ross 2001
- Wu 2002
- Yamamoto 2003
- Linseisen 2004

**All Premenopausal Studies**

**All Postmenopausal Studies**

OR or RR for high vs. low soy or isoflavone levels

* Premeno = premenopausal women, postmeno = postmenopausal women

# Case-control studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Phytoestrogen</th>
<th>Cancer</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pietinen</td>
<td>Finland</td>
<td>Lignans enterolactone</td>
<td>Breast</td>
<td>0.38 (0.18-0.77)</td>
</tr>
<tr>
<td>Ingram</td>
<td>Australia</td>
<td>Urinary equol</td>
<td>Breast</td>
<td>0.27 (0.10-0.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary enterolactone</td>
<td></td>
<td>1.1 (0.15-0.86)</td>
</tr>
<tr>
<td>Zheng</td>
<td>China</td>
<td>Total isoflavonoids</td>
<td>Breast</td>
<td>0.14 (0.02-0.88)</td>
</tr>
<tr>
<td>Sonoda</td>
<td>Japan</td>
<td>Total dietary soy</td>
<td>Prostate</td>
<td>0.53 (0.24-1.24)</td>
</tr>
</tbody>
</table>
Clinical studies – prostate cancer

“This work provides some evidence...that male populations who consume high phytoestrogen diets have a reduced risk of prostate cancer development and progression”

Dalais et al. (2004) Urology 64: 510
Epidemiologic studies & clinical trials

– Take home message

Soy foods are not harmful…

… and in fact maybe protective against cancer
Soy phytochemicals and tea bioactive components synergistically inhibit human prostate tumors in mice

Animal studies

• Genistein inhibits growth of a chemically induced mammary tumour in young rats

Lamartiniere et al. (1995) Carcinogenesis 16: 2833
Animal studies

- Genistein *promotes* mammary gland growth and mammary tumour growth in mice.

- Oh dear! But..

- Mice are nude, ovariectomised and athymic – humans are not!

Animal studies

Rats fed soy-based diets have increased preneoplastic lesions in liver

Battersby et al. (2006) APJCN 15: S106
Animal evidence

– Take home message

Soy phytoestrogens have been shown to reduce tumor growth but…

… under some experimental (not real life?) circumstances the opposite is observed.
Cell studies

- Genistein (and oestrogen) promotes growth of mammary tumour cells in vitro.
- Soy metabolites acting as phytoestrogens

Prepubertal exposure to E2 or genistein up-regulates Mammary BRCA1 mRNA expression.

Cell studies

– Take home message

Soy phytoestrogen genistein, like oestrogen, can promote tumor growth in the test tube but…

… it is very difficult to extrapolate results in a test tube to the whole human being. For example, we have an antioxidant system that may be promoted by soy as its metabolites are known antioxidants.
Conclusions

Soy and breast cancer:

• Cannot draw definitive conclusions on
  • Soy & breast cancer risk and
  • Soy & survival of breast cancer patients
• To establish that soy foods do not adversely affect the survival of breast cancer patients may not be possible
  • Long-term clinical trials with tumor recurrence or survival as endpoints – expensive & possibly unethical

Conclusions contd.

- Need further research to assess the potential of soy foods on breast cancer risk in high risk women
  - examine cancer risk markers (eg. cell proliferation, apoptosis)
  - assess safety and efficacy
  - use soy foods with a broad application

Soy and prostate cancer:

- Same conclusion in recent review:
  - “After reading this review ….. what will be evident at the conclusion of this manuscript is the need for future studies of the effects of soy in prostate cancer patients.”

Take home message

- The jury is still out
- We know that an Asian diet containing soy foods is not detrimental to health
- Increasing consumption of soy foods in Western diets?
  - We need to do more research
  - Must not consider cancer in isolation, other well recognised and established benefits of soy (Coronary Heart Disease) may well outweigh the possible adverse risk consequences for cancer development.
The future - nutrigenomics

Molecular Nutrition & Genomics

- Identification of dietary signals
- Identification of dietary sensors
- Identification of target genes
- Reconstruction of signaling pathways

Foods Nutrition

- Reconstruction of signaling pathways
- Measurement of stress signatures
- Identification of early biomarkers

Nutritional Systems Biology

- Identification of dietary signals
- Identification of dietary sensors
- Identification of target genes
- Reconstruction of signaling pathways

Small research groups
Small budgets

Large research consortia
Big money

Complexity
POSITION STATEMENT

Soy, Phyto-oestrogens and Cancer Prevention

Key Messages

Phyto-oestrogens are bioactive substances found in plant foods, with naturally occurring oestrogenic activity. Soy beans and other foods containing soy, such as tofu, tempeh and soy milk, are rich sources of phyto-oestrogens.

A high consumption of soy foods may lower the risk of breast and prostate cancers, but only a little.

There is no association between soy foods and the risk of other cancers, including bowel cancer.

While they may have a protective effect, there is also some evidence that phyto-oestrogens might stimulate the growth of existing hormone dependent cancers.

The Cancer Council supports the consumption of soy foods in the diet. This is consistent with Cancer Council recommendations and national dietary guidelines to eat a diet high in plant based foods.

The Cancer Council does not recommend or support the use of supplements such as soy protein isolates or isoflavone capsules for healthy men and women to prevent cancer.

The Cancer Council does not recommend or support the use of supplements for breast cancer survivors. There is evidence to suggest that women with existing breast cancer or past breast cancer should be cautious in consuming large quantities of soy foods or phyto-oestrogen supplements.
Oh, soy! Don't take scary headlines at face value

It was enough to make Sydneysiders spill their soy lattes as they read the Sunday papers – the recent tabloid headline that shrieked 'Soy cancer warning. High soy diets no good for cancer'. It was a shining example of the kind of journalism that distorts nutrition information and gets us all confused.

The real story that had originated from the Cancer Council NSW, was much tamer. Soy, it turned out, didn't cause cancer. The Cancer Council NSW had never suggested we should all avoid soy foods. Instead they say they don't support the use of soy supplements for cancer survivors because there's a lack of evidence that they help. The advice for women having treatment for breast cancer with tamoxifen was that it was unclear if a diet high in the plant hormones which soy foods contain could interfere with the treatment.