

# SOY

# & HEALTH



**Researchers  
Investigate the  
Breast Cancer  
Protection  
of Soy**

## **Soy Intake and Breast Cancer Risk**

### Introduction

Much of the early enthusiasm about the health benefits of soy had to do with its potential role in reducing breast cancer risk. This area of research continues to be actively investigated and often provides potentially exciting results. Ironically, however, there is also concern that soy consumption could be detrimental to women with estrogen-sensitive breast cancer, or to women at high risk of developing breast cancer.<sup>1</sup> The relationship between soy intake and breast cancer risk is undoubtedly one of the most confusing areas of soy research today.

### Background

The low breast cancer mortality rates among soyfood-consuming populations (five to sevenfold less than in the U.S.) such as the Japanese, in combination with data showing that weak estrogens can function as antiestrogens, prompted initial speculation that soy might reduce breast cancer risk. Greater lifelong exposure to estrogen is associated with increased breast cancer risk; this is why earlier age at menses, later age at menopause<sup>2</sup> and hormone replacement therapy usage<sup>3</sup> are considered to be risk factors for breast cancer development. Since estrogen increases breast cancer risk, certain antiestrogens such as the drug tamoxifen, can decrease risk. The first animal study showing that genistein (the main isoflavone in soybeans) possessed antiestrogenic activity was published in 1966.<sup>4</sup>

Although no definitive evidence states that soy exerts antiestrogenic effects in humans, soy was shown to counter the stimulatory effects of estrogen on mammary cell proliferation in monkeys.<sup>5</sup> Furthermore, during the past ten years, research has identified several different mechanisms by which soy could exert antiestrogenic effects. These include: 1) competing with estrogen for binding to the estrogen receptor, 2) down-regulating estrogen receptors, 3) increasing serum levels of sex hormone binding globulin (SHBG)<sup>6</sup> and 4) favorably altering estrogen metabolism.<sup>7,8</sup>

Despite the plethora of possible antiestrogenic mechanisms, arguably, the most excitement over the anticancer effects of soy is based on the ability of genistein to inhibit the activity of key enzymes and to influence cellular molecules, such as transforming growth factor beta, that lead to the inhibition of cancer cell growth.<sup>9,10</sup>

11,12,13

### Animal Studies

Studies examining the effects of soy/isoflavones on the development of mammary (breast) cancer in adult animals are somewhat inconsistent. Although studies generally show that the addition of soy to a standard laboratory diet does not significantly inhibit tumor incidence (percentage of animals in the group with tumors), in most cases, soy consumption does inhibit tumor multiplicity (number of tumors per animal) by 25

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percent to 50 percent.<sup>14,15,16</sup>

Furthermore, one recent study found that miso (fermented soy paste) acted synergistically with the breast cancer drug tamoxifen, to inhibit the development of mammary tumors in rats.<sup>17</sup> The study found that the combination of miso and tamoxifen inhibited the growth of existing mammary tumors, whereas tamoxifen by itself was ineffective.

There has been particular interest in research showing that genistein exposure for just a few days very early in life reduces mammary cancer development later in life by as much as 50 percent.<sup>18</sup>

### Epidemiology

Somewhat surprisingly, given the low breast cancer mortality rates in Asia, epidemiological studies (case-control and prospective cohort studies) conducted in Asia provide little support for the notion that the adult consumption of soy reduces postmenopausal breast cancer risk. However, modest support exists for protective effects against premenopausal breast cancer.<sup>19</sup> Interestingly, in agreement with the animal data, one recent study in Asia found that 13 to 15 year old girls who consumed soy were less likely to develop breast cancer later in life in comparison to girls who did not consume soy.<sup>20</sup>

A few studies conducted among Western populations have found that soy consumption, using urinary excretion of isoflavones as a measure of intake, is protective,<sup>21,22</sup> but soy intake in these studies was so minimal that the relevance of these findings is unclear.<sup>23</sup>

### Possible Contraindications

#### In Vitro Studies

At physiologic concentrations (levels likely found in humans), genistein stimulates the growth of estrogen-receptor positive (ER+) breast cancer cells (cells whose growth is stimulated by estrogen) in vitro.<sup>24</sup> Genistein does not stimulate the growth of estrogen-receptor negative (ER-) breast cancer cells, and at high concentrations genistein inhibits the growth of all types of cancer (prostate, colon, skin, ER+ and ER- breast cancer cells, etc.) cells.

The proposed explanation for these observations is that at low concentrations, genistein acts like an estrogen to stimulate the growth of ER+ breast cancer cells, but not ER- cells. However, at higher concentrations, non-hormonal properties of genistein come into play, which result in the growth of both types of breast cancer cells. In any event, because in vitro cell systems may be lacking important regulators of cell growth, the relevance of all data from in vitro models to humans is unclear.



#### Animal Studies

The bulk of studies show that soy at least modestly inhibits mammary tumorigenesis in adult animals. However, one study shows that, when immune deficient (athymic) mice with ovaries removed to stop estrogen production were implanted with ER+ breast cancer cells and given genistein, tumor growth was stimulated in comparison to mice not given genistein.<sup>24</sup> Soy protein isolate also had this effect, though both the effects of genistein and the isolate were much less than that of estrogen. However, this model, which is purported to mimic postmenopausal women, has been roundly criticized on methodological grounds. In addition, postmenopausal women have at least some circulating estrogen. Furthermore, a similarly designed experiment, in which mice were not ovariectomized (thus serum estrogen levels were high), demonstrated that genistein actually inhibited, rather than stimulated, tumor growth.<sup>25</sup>

### Human Studies

Two human studies have prompted concerns about women with ER+ breast cancer consuming soy. The first found that daily consumption of 38 g soy protein over a four-month period was associated with an increase in breast nipple fluid aspirate secretion -- previous epidemiological research suggests this may be a risk factor for breast cancer -- and breast cell hyperplasia (cell proliferation, typically viewed as a marker for cancer risk).<sup>26</sup> The authors of this pilot study concluded that soy appears to exert estrogenic effects on breast tissue. However, this study had serious methodological flaws including lack of a control group. Fluid secretion also continued to increase in women even after soy feeding was discontinued.

The second study looked at the effects of feeding 60 g of textured vegetable protein for two weeks on breast cell proliferation, a possible marker for cancer risk. A preliminary analysis of this study based on biopsies from only half of the subjects indicated soy consumption markedly increased breast cell proliferation. However, in the final analysis, which included all 84 subjects, no such effect on breast cell proliferation was noted.<sup>27</sup>

However, soy did appear to exert a weak estrogenic effect on breast tissue, because biopsies indicated that two proteins found in breast cells were affected by soy in the same way they are affected by estrogen, although to a lesser extent. The authors concluded that soy had a weak estrogenic effect on breast tissue, but also that the long term implications of this effect were unclear because soy did not increase cell proliferation. Also, the study was only two weeks in duration. Many of the proposed mechanisms for the antiestrogenic effects of soy likely take longer than two weeks to become evident.

### Lessons from Observational Studies of Hormone Replacement Therapy

Oncologists have been reluctant to recommend estrogen for their ER+ breast cancer patients because of studies suggesting that hormone replacement therapy (HRT) increases breast cancer risk. However, not only is this view being challenged because of conflicting data about the relationship between HRT and breast cancer risk, but also because two large epidemiological studies suggest that estrogen may not even be the culprit.

Women who have an intact uterus take estrogen plus another hormone, progesterone, because estrogen by itself greatly increases the risk of endometrial cancer, while estrogen plus progesterone does not increase risk or does so only slightly. Recent data indicate that estrogen taken by itself only very weakly increases breast cancer risk, whereas the combination of estrogen plus progesterone may increase breast cancer risk two to three fold over the course of a women's lifetime.<sup>28, 29, 30, 31</sup> These observations suggest that soy is unlikely to increase breast cancer risk because, although soy/isoflavones may have weak estrogenic activity, soy has no progesterone activity.

### Conclusions

The evidence that soy consumption reduces breast cancer risk in adult women is inconclusive. Epidemiological studies provide relatively little support for protective effects whereas animal studies are modestly encouraging. Several human studies show that soy favorably alters estrogen metabolism and may make estrogen less available to the tissues -- effects that should be protective against breast cancer.

Results from one animal model (overiectomized, athymic mice) and two human studies raise some concerns that soy could be contraindicated for ER+ breast cancer patients. However, the implications of these findings are unclear. Importantly, recent observational data suggests that the hormone progesterone, not estrogen, is responsible for the increased breast cancer risk seen in women using HRT.

Nevertheless, because more research is needed, prudence would dictate some caution in the amount of soy and isoflavones consumed by ER+ breast cancer patients. Until further data is available, a reasonable recommendation for ER+ breast cancer patients would be to consume soy as part of an overall healthy diet, perhaps three to four times per week.

On the whole, the evidence suggests that consuming moderate amounts of soy is much more likely to be of overall benefit to health rather than harmful, both in terms of breast cancer risk and other chronic diseases.

1. Affenito SG, Kerstetter J. Position of the American Dietetic Association and Dietitians of Canada: women's health and nutrition. *J Am Diet Assoc* 1999; 99:738-51.
2. Morabia A, Costanza MC. International variability in ages at menarche, first livebirth, and menopause. World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives [published erratum appears in *Am J Epidemiol* 1999 Sep 1;150(5):546]. *Am J Epidemiol* 1998; 148:1195-205.
3. Pike MC, Ross RK. Progestins and menopause: epidemiological studies of risks of endometrial and breast cancer. *Steroids* 2000; 65:659-64.
4. Folman Y, Pope GS. The interaction in the immature mouse of potent oestrogens with coumestrol, genistein and other utero-vaginitrophic compounds of low potency. *J Endocrinol* 1966; 34:215-25.
5. Foth D, Cline JM. Effects of mammalian and plant estrogens on mammary glands and uteri of macaques. *Am J Clin Nutr* 1998; 68:1413S-1417S.
6. Pino AM, Valladares LE, Palma MA, Mancilla AM, Yanez M, Albala C. Dietary isoflavones affect sex hormone-binding globulin levels in postmenopausal women. *J Clin Endocrinol Metab* 2000; 85:2797-800.
7. Lu LJ, Cree M, Josyula S, Nagamani M, Grady JJ, Anderson KE. Increased urinary excretion of 2-hydroxyestrone but not 16 $\alpha$ -hydroxyestrone in premenopausal women during a soya diet containing isoflavones. *Cancer Res* 2000; 60:1299-305.
8. Xu X, Duncan AM, Wangen KE, Kurzer MS. Soy consumption alters endogenous estrogen metabolism in postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2000; 9:781-6.
9. Constantinou A, Huberman E. Genistein as an inducer of tumor cell differentiation: possible mechanisms of action. *Proc Soc Exp Biol Med* 1995; 208:109-15.
10. Arora A, Valcic S, Cornejo S, Nair MG, Timmermann BN, Liebler DC. Reactions of Genistein with alkylperoxyl radicals. *Chem Res Toxicol* 2000; 13:638-45.
11. Arora A, Nair MG, Strasburg GM. Antioxidant activities of isoflavones and their biological metabolites in a liposomal system. *Arch Biochem Biophys* 1998; 356:133-41.
12. Fotsis T, Pepper MS, Montesano R, et al. Phytoestrogens and inhibition of angiogenesis. *Baillieres Clin Endocrinol Metab* 1998; 12:649-66.
13. Iishi H, Tatsuta M, Baba M, Yano H, Sakai N, Akedo H. Genistein attenuates peritoneal metastasis of azoxymethane-induced intestinal adenocarcinomas in Wistar rats. *Int J Cancer* 2000; 86:416-20.
14. Gotoh T, Yamada K, Yin H, Ito A, Kataoka T, Dohi K. Chemoprevention of N-nitroso-N-methylurea-induced rat mammary carcinogenesis by soy foods or biochanin A. *Jpn J Cancer Res* 1998; 89:137-42.
15. Barnes S, Grubbs C, Setchell KD, Carlson J. Soybeans inhibit mammary tumors in models of breast cancer. *Prog Clin Biol Res* 1990; 347:239-53.
16. Hakkak R, Korourian S, Shelnett SR, Lensing S, Ronis MJ, Badger TM. Diets containing whey proteins or soy protein isolate protect against 7,12-dimethylbenz(a)anthracene-induced mammary tumors in female rats. *Cancer Epidemiol Biomarkers Prev* 2000; 9:113-7.
17. Gotoh T, Yamada K, Ito A, Yin H, Kataoka T, Dohi K. Chemoprevention of N-nitroso-N-methylurea-induced rat mammary cancer by miso and tamoxifen, alone and in combination. *Jpn J Cancer Res* 1998; 89:487-95.
18. Lamartiniere CA. Protection against breast cancer with genistein: a component of soy. *Am J Clin Nutr* 2000; 71:1705S-7S; discussion 1708S-9S.
19. Trock B, Butler W, Clarke R, Hilakivi-Clarke L. Meta-analysis of soy intake and breast cancer risk. *J Nutr* 2000; 130:690S-691S.
20. Shu XO, Jin F, Qi D, et al. Adolescent soy food intake and other dietary habits. *Proc Am Assoc Cancer Res* 2000; 41:94 (abstract 602).
21. Ingram D, Sanders K, Kolybaba M, Lopez D. Case-control study of phyto-oestrogens and breast cancer. *Lancet* 1997; 350:990-4.

22. Murkies A, Dalais FS, Briganti EM, et al. Phytoestrogens and breast cancer in postmenopausal women: a case control study. *Menopause* 2000; 7:289-96.
23. Messina M, Barnes S, Setchell KD. Phyto-oestrogens and breast cancer [comment]. *Lancet* 1997; 350:971-2.
24. Hsieh CY, Santell RC, Haslam SZ, Helferich WG. Estrogenic effects of genistein on the growth of estrogen receptor- positive human breast cancer (MCF-7) cells in vitro and in vivo [published erratum appears in *Cancer Res* 1999 Mar 15;59(6):1388]. *Cancer Res* 1998; 58:3833-8.
25. Shao ZM, Wu J, Shen ZZ, Barsky SH. Genistein exerts multiple suppressive effects on human breast carcinoma cells. *Cancer Res* 1998; 58:4851-7.
26. Petrakis NL, Barnes S, King EB, et al. Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 1996; 5:785-94.
27. Hargreaves DF, Potten CS, Harding C, et al. Two-week dietary soy supplementation has an estrogenic effect on normal premenopausal breast. *J Clin Endocrinol Metab* 1999; 84:4017-24.
28. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Estrogen-progestin replacement and risk of breast cancer. *JAMA* 2000; 284:691-4.
29. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000; 283:485-91.
30. Pike MC, Ross RK. RESPONSE: re: effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000; 92:1951-2.
31. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000; 92:328-32.