

# Comments for Your Consideration on the Soy Controversy

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**The word phytoestrogen means “plant estrogen.” There is currently a wave of confusion surrounding the phytoestrogens in soy. Despite their being named phytoestrogens, the soy isoflavones genistein and diadzein are NOT true estrogens. In fact, their potency has been estimated as 500-1000 times weaker than human estrogen [Leffers et al., 2001]. The binding affinity of phytoestrogens to the alpha estrogen receptor is 1,000-10,000-fold lower compared to endogenous estrogen (estradiol) [Schmitt et al., 2001].**

Consider the following analogy: The estrogen receptor is like a keyhole in a locked door, and estrogen is the key that opens that door and “turns on” growth-promoting effects in the cell. However, among dozens of keys, you might find some that fit into the keyhole but do not work to turn the lock and open the door. This analogy appears to describe phytoestrogens quite well: they are like keys that fit into the lock, but generally do not open the door or “turn on” the estrogenic effect. The capacity of soy compounds to dock on the estrogen receptor prevents human estrogens and xenoestrogens (environmental chemicals that act as highly potent estrogens) from binding to the receptor and promoting growth [Huber 2000]! This last point is very important, because a primary benefit of soy phytoestrogen are their ability to COMPETE with estrogen and xenoestrogens. Epidemiological studies have reported that the risk of developing breast cancer is reduced 5- to 10-fold in women who regularly consume soy foods [Wu et al., 1998; Fournier et al., 1998; Stevens 1997; Messina & Barnes 1991]. When women in Asian countries develop breast cancer, their prognosis no less favorable than in Western countries: yet their diet contains abundant soy.

By the way, it's interesting to note that, while soy foods have been “singled out” for attention, dozens of other common foods are rich in phyto-

estrogens, including all legumes (black beans, lentils, peas, kidney beans, pinto beans, etc.), wheat and whole grains, nuts, seeds (especially flax seeds), spinach, cabbage, sprouts, apples, celery, parsley, kudzu, red clover, licorice, thyme, oregano, turmeric, hops, and many other herbs/spices [Humfrey 1998; Zava et al., 1998]. Nature has provided these foods as a “checks and balances” system to help regulate the effects of estrogen in mammals and humans. Even if you choose to avoid soy, it's nearly impossible to eat a healthy diet that completely avoids phytoestrogens. So let's take a closer look at the research that has been done to date on these compounds.

One of the reasons for the controversy surrounding soy phyto- estrogens is the poor quality of the many research studies that have been done. During the past decade, there have been more than 155 published articles in the medical literature on the topic of soy phytoestrogens and breast cancer, including more than 85 in vitro (test tube) studies, 21 animal (in vivo) studies and a dozen human studies. The vast majority of these studies have reported that genistein inhibits the proliferation of cancer cells [Boik 2001:252; Peterson & Barnes 1991]. However, a small minority of

studies have found that very low concentrations of soy genistein may stimulate the proliferation of estrogen-dependent cancer cells under certain conditions. However, every one of these studies suffers from poor design or flawed research methodology, as summarized below.

## Flawed Research on Soy, Estrogen & Breast Cancer

**Type of Soy**  
 Use of GMO Soy Many commercially produced soy products are genetically modified (called GMO soy), and the effects of these products cannot be attributed solely to the phytoestrogens as the effects of genetically-modified foods have not yet been examined in research studies. A recent study in the journal Carcinogenesis found that while whole-soy food did not stimulate the growth of

### Sources of Isoflavones

(Milligrams per 100-gram or 3-ounce edible portion)

Description	Genistein	Daidzein	Total Isoflavones
Soy flour (full-fat, roasted)	99	99	199
Soy flour (full-fat, raw)	96	71	178
Soy flour (textured)	79	60	149
Soy flour (defatted)	71	57	131
Soynut, roasted	66	52	128
Soybeans, raw	65	35	119
Instant Soy Beverage, powder	62	40	110
Soy protein, powder (isolate)	60	34	97
Miso soup mix, dry	35	25	60
Yuba (soymilk skin), cooked	33	18	51
Tempeh, cooked	32	20	53
Natto (boiled, fermented soybeans)	29	22	58
Edamame (boiled soy bean)	28	27	55
Miso	25	16	43
Tempeh burger	20	6	29
Tofu, soft	18	12	31
Tofu, MORI-NU brand, firm	16	11	28
Tofu, nigari/calcium sulfate prepared	13	9	25
Tofu “yogurt”	9	6	16
Soy “hot dog”	8	3	15
Soy “bacon” (meatless)	7	3	12
Soymilk, 8 ounces	6	4	10
Soy noodles	4	1	8
Soy cheese, mozzarella	4	1	8
Soy cheese, cheddar	2	2	7
Shoyu	1	1	2
Soy sauce	0	0	0

Source: USDA, Iowa State University Database on Isoflavone Content of Foods, 1999

breast cancer in animals, highly refined and processed soy isolates was problematic [Allred et al., 2004].

**Use of Unfermented Soy** The isoflavones in soy are highest and most bioavailable in fermented soy foods (e.g., miso, tempeh), which is how soy foods are predominately eaten in Asian countries, where the risk of breast cancer is very low. Yet many studies have tested unfermented soy products.

**Use of Isolated Genistein** Soy products contain several isoflavones (genistein, genistin, diadzein, diadzin, dihydrodaidzin, dihydr-ogenistin, formononetin, and glycyetin) [Hosny & Rosazza 2002]. These constituents act synergistically [Willard & Frawley 1998], yet the many studies on "soy" have tested only genistein alone. In a telling experiment, researchers fed female mice with experimental breast cancers diets providing whole soy or isolated genistein. Genistein reduced the volume of breast tumors by 40%, whereas whole soy food—providing the same dose of genistein, together with other soy isoflavones—reduced tumor volume by 90% [Hewitt & Singletary 2003].

In addition, when eating a healthy diet, we consume dozens of phytoestrogenic compounds from other foods, and these interact with soy constituents. Several nutrients have been shown to offer a synergistic effect increasing the action of genistein against breast cancer cells, including quercetin [Shen & Weber 1997], curcumin [Verma et al., 1997], and fish oil EPA [Nakagawa et al., 2000]. For a fair evaluation, soy compounds should be studied not in isolation, but in relation to a healthy diet and all the vitamins, minerals and phytonutrients it provides.

#### Metabolism Differences in Rodents vs. Humans

In humans, phytoestrogens are short lived compounds, remaining in the body for just hours (in contrast, environmental xenoestrogens are long-lived, and may persist in human tissue for decades). Rodents lack an enzyme needed to help break down and remove phytoestrogens. This persistence alters the physiological effects of phytoestrogens in rat and mouse studies.

#### Dose of Soy

**Non-Physiological Dose Concentrations** The physiological level of soy in human plasma is likely to be approximately 1-5 $\mu$ mol [Lu et al., 2000a; Barnes et al., 1996; Barnes 1995]. Because isoflavones accumulate in breast and reproductive tissues, the target tissues achieve concentrations perhaps up to 10-30 $\mu$ mol in those consuming high-soy diets. Yet some studies have used amounts far below (1 nMol) or substantially greater than this (90 $\mu$ mol). Studies examining physiologic doses of 5-30 $\mu$ Mol show that genistein strongly inhibits cancer cell proliferation [Zava & Duwe 1997]. Several studies have used doses of soy genistein profoundly exceeding doses achievable in humans. For example, several studies have reported a potential proliferating effect of soy extracts at 90mg/kg in rats or mice who have had their ovaries removed [Charland et al., 1998; Hsieh et al., 1998; Allred et al., 1999]. The human equivalent dose of genistein would be about 870mg/day [Boik 2001:254]. You'd need to eat 40 servings of tofu daily to get this dose. Other studies have demonstrated a bi-phasic response, with low doses (1 nMol to 1  $\mu$ Mol) of soy stimulated cancer cell growth but higher doses (10-40 $\mu$ Mol) inhibiting it [Dampier et al., 2001; Miodini et al., 1999; Wang & Kurzer 1998, 1997; Wang et al., 1996]. If you are eating two or more serving of soy foods daily, your intake will be 30-50mg/day, achieving an average physiological level of 2-5 $\mu$ Mol.

#### Duration and Timing of Exposure

Some studies have shown a differential effect for exposure

to soy before versus after menopause.

#### Effects of Soy in Pre-Menopausal Women (or those taking HRT):

At the Moffitt Cancer Center in Southern Florida, researchers fed a group of 68 premenopausal women soy isoflavone supplements (40mg genistein daily) or placebo over a 12-week period. Women taking soy experienced > 50% decrease in levels of estradiol and estrone; and also showed an increase in the levels of sex hormone binding globulin (SHBG, a protein that binds to estrogen and limits its availability to the body's tissues) [Kumar et al., 2002]. In addition, women consuming soy in this study had their menstrual cycle length increase by 3.5 days due to prolonged time after ovulation to menses (an effect which decreases a women's lifetime exposure to estrogen and thereby her risk of breast cancer) [Kumar et al., 2002]. An earlier study also reported beneficial results. Feeding women 60 grams of soy protein daily (providing 45 mg isoflavones) offered beneficial effects with respect to risk factors for breast cancer—prolonged time after ovulation to menstruation and suppressed mid-cycle surges of luteinizing hormone and follicle stimulating hormone [Cassidy et al., 1994].

A study conducted in Hawaii by Dr. Gertraud Maskarinec reported much smaller hormone modulating effects (that did not reach statistical significance) for soy intake in 34 premenopausal women over a 1-year period [Maskarinec et al., 2002]. Unlike the studies described above, however, this study used high dose soy intake (100mg isoflavones per day). It is interesting to note that no harmful effects were reported in this study.

Yet another study examined the effects a soy protein powder providing various amounts of soy isoflavones—low (10mg), moderate (64mg) or high intake (128mg) in 14 premenopausal women over a 3-month period. Small favorable alterations on hormone levels were reported: decreased luteinizing hormone (LH) and follicle stimulating hormone (FSH) in the low soy diet and decreased estrone (E1) levels in the high soy diet [Duncan et al., 1999]. Biopsies of endometrial tissue from the women demonstrated no estrogenic effect on this estrogen-sensitive tissue.

Overall, these human studies on premenopausal women suggest a favorable effect of soy on hormonal parameters associated with breast cancer.

#### Effects of Soy Post-Menopausal Women:

Because phytoestrogens act most favorably when they can compete with estrogen, and because it has been assumed that menopause is associated with a loss of estrogen (based on blood or plasma levels), many researchers have assumed that soy may fail to offer a protective effect in post-menopausal women and may even produce an estrogenic effect. A study that examined the effects of soy consumption (38 grams soy protein daily providing 38mg genistein for 1 year) found no stimulatory effect in post-menopausal women [Petrakis et al., 1996].

However, is estrogen actually absent after menopause? Studies examining tissue levels suggest estrogen is actually higher in breast tissue at this time in a women's life [Bland 2001]. In actuality, post-menopausal estrogen levels are elevated due to three factors:

- (a) manufacture of estrogen in fat cells by the enzyme aromatase,
- (b) exposure to dietary estrogens in commercially-raised meat and dairy products;

(c) bioaccumulation of xenoestrogens in breast and other fatty tissues from lifelong exposure to plastics, pesticides, solvents and other environmental chemicals.

If you are post-menopausal, carry 10+ pounds extra weight, eat commercially produced meat and dairy products, live in an agricultural area (pesticide exposure), have average exposure to solvents, plastics, and other xenoestrogens, it is reasonable to assume your total estrogen environment is high and phytoestrogens would likely be protective for you. Interestingly, post-menopausal women with breast cancer have lower plasma levels of soy isoflavones genistein and diadzein than are found in healthy controls [Murkies et al., 2000].

On the other hand, if you are an underweight, vegan (no meat or dairy consumption) post-menopausal woman who has taken precautions in life to avoid xenoestrogen exposure (no guarantee), you may have low estrogen levels after menopause, and it might be prudent for you to avoid soy consumption.

#### Brief Exposure Time

Some studies have shown that with short duration exposure (say, 1-2 weeks), soy can produce an estrogenic effect such as increasing breast tissue density [McMichael-Phillips et al., 1998]. One study looked at the effects of soy consumption on breast markers in premenopausal women eating 60 grams soy (45mg isoflavones) over a short 2-week period. The results suggested a weak estrogenic response on breast tissue (though there was no cell proliferation effect detected) [Hargreaves et al., 1999]. However, studies that have re-examined the effect with continued dosing show ablation of this short-term effect. Recently conducted year-long studies indicate that isoflavone supplements do not affect breast tissue density in premenopausal women, and may decrease density in post-menopausal women [Messina & Loprinzi 2001]. (In contrast, hormone replacement therapy increases breast density and increases risk of breast cancer.) In addition, an in vitro study that demonstrated a growth promoting effect for soy during brief exposure showed that, with prolonged exposure, genistein resulted in a decrease response of estrogen receptors to stimulation by estradiol [Wang et al., 1996].

#### Late Exposure Time

It appears that the strongest cancer preventing effects of soy may be achieved when exposure is timed during puberty (or earlier) [Aldercreutz et al., 2002; Lamartiniere et al., 1998, 1995; Barnes 1997]. Animals exposed to genistein prior to or during puberty experience a longer latency period before developing carcinogen-induced mammary tumors and have fewer tumors [Jin & MacDonald 2002; Murrill et al., 1996; Barnes 1997]. Studies of Asian women suggest that those who consume a traditional diet high in soy products have a low incidence of breast cancer, but that among emigrants to the U.S. the second generation—but not the first—loses this protection, suggesting early exposure to soybean foods protects against later development of breast cancer [Lamartiniere 2000]. Early exposure to soy isoflavones promotes maturity (differentiation) of breast tissue, and appears to alter the endocrine system in ways that reduce breast cell proliferation in vivo [Lamartiniere et al., 1995]. While this finding is of little relevance for your current situation, it does suggest that your pre-pubertal and adolescent female relatives (who are increased risk for breast cancer due to family history of the disease) should consider adding soy products to their diet!

#### Inactive Compound Tested

**Bowel Conversion** When humans eat soy foods, our digestive process alters the phytoestrogens they contain.

Specifically, the healthy bacteria in our intestines metabolize isoflavones, converting them into activated compounds [Mizunuma et al., 2002; Stoll 1997]. The soy isoflavone biochanin A is converted to genistein, and diadzein is converted to equol. Some studies have failed to use these active constituents, which are the actual compounds found in human tissues. Of note: if your intestinal tract is devoid of healthy bacteria (such as during the 2 months following antibiotic or chemotherapy treatment), you may fail to obtain the benefits of soy. Taking a probiotic supplement to replace these healthy bacteria is recommended.

**Metabolism to Active Constituents** Metabolism of genistein and other soy compounds within the body (and in tumor tissue) may be responsible for their anti-cancer effects. Particularly, hydroxylation and methylation of phytoestrogens has been shown to correlate to the growth inhibitory effects against breast cancer cells [Peterson et al., 1998]. If you are deficient in vitamins B12, B6, folic acid and/or trimethylglycine (as demonstrated by a homocysteine lab test result > 8), you may have difficulty metabolizing soy phytoestrogens to their beneficial compounds.

#### Competitive Environment

**Inhibiting Effects of Estrogen & Xenoestrogens** In real life, we humans are exposed to estrogen from several sources: (a) the estrogen our body produces, (b) dietary sources (meat & dairy products), and (c) a daily dose of "chemical soup" from the environment, including many xenoestrogens. So we are most interested in the effects of soy and other phytoestrogens in a competitive environment (e.g., when phyto-estrogens compete against all other sources of estrogen). While many test tube studies have shown the potential for soy phytoestrogens to stimulate breast cancer growth in the absence of estrogen, studies carried out in the presence of estrogen (or other growth factors) have shown phytoestrogens to inhibit growth of human breast cancer cell lines [Peterson & Barnes 1996]. In animal studies, with the complete absence of estrogen (e.g., rats with ovaries removed and living in controlled lab environments), soy can produce a pro-estrogen effect, even stimulate the growth of breast cancer cells [Ju et al., 2001; Allred et al., 2001; Hsieh et al., 1998]. (Note: genistein does not have an estrogen-like effect in rats with intact ovaries.) However, when estrogen is added back into the mix, soy phytoestrogens have been shown to block the growth promoting effects of estrogen on breast cancer cells [Messina & Loprinzi 2001; Shao et al., 2000; Barnes 1997; Sathyamoorthy & Wang 1997]. In summary, studies that have tested soy with the presence of estrogen have all shown competitive inhibition: soy phytoestrogens inhibit breast cancer cell growth when estrogen or xenoestrogens are present in the medium (an environment that closely resembles human conditions).

In a very well designed study done by researchers in Japan, the proliferation of human breast cancer cells were tested with concomitant exposure to (1) pharmaceutical estrogens, like DES and tamoxifen, (2) xenoestrogens, and (3) phytoestrogens. While very low (nanomolar) concentrations of estrogens and xenoestrogens strongly promoting the growth of the cancer cells, the addition of phytoestrogens inhibited the proliferation-stimulating activity of xenoestrogens [Han et al., 2002, 2001].

Researchers at Tufts University School of Medicine in Boston conducted a similar research study in which soy phytoestrogens were tested in comparison with xenoestrogens. When soy compounds were tested (at doses < 10 $\mu$ Mol) in the absence of environmental chemicals, they enhanced the growth of breast cancer cells. In the presence

of xenoestrogens, soy isoflavones (at doses = 25-30 $\mu$ Mol) were able to inhibit the xenoestrogen-induced proliferation breast cancer cells [Verma & Goldin 1998].

These two studies demonstrate a strong protective effect of soy phytoestrogens against the proliferation-inducing effect of xenoestrogens. This finding is of particular concern when considering that separate research has shown women with breast cancer have levels of phytoestrogens (as measured by urinary excretion) that are 50-65% lower than healthy women [Dai et al., 2002; Zheng et al., 1999]. This finding suggests that a possible contributor to the development of breast cancer is low levels of isoflavones with their xenoestrogen-inhibiting effects. In a case-control study published in the journal *Lancet*, it was found that the women with breast cancer had significantly lower intake of phytoestrogens (as reported on questionnaires and measured in urine samples) than healthy women [Ingram et al., 1997].

#### Xenoestrogen Contamination

Some of the studies which have reported estrogenic effects for soy were done using plastic test tubes or petri dishes. Even some types of glass test tubes have hidden plastics added to reduce breakage. Plasticizers are known xenoestrogens with very potent estrogenic actions. Researchers may have inadvertently attributed observed effects to soy which were actually caused by xenoestrogens.

#### Inappropriate Endpoint

What constitutes "estrogenic effect" Research studies have defined "estrogenic effect" very differently, and sometimes inappropriately. Some studies have concluded soy has an estrogenic effect merely because it "binds" to estrogen receptors, without demonstrating that it actually promotes an estrogenic effect. (i.e., just because the key fits into the lock doesn't mean it will open the door). Better studies have endpoints like proliferation of ER+ breast cancer cells or increase of downstream products of estrogen stimulation (e.g. S2 protein or TGF-beta).

#### Failure to Consider Type of Estrogen Receptors

Recently it has been discovered that there are 2 types of estrogen receptors: type I (or alpha) receptors, and type II estrogen binding sites (Type II EBS, or beta receptors). One of the checks the body has against breast cancer is a protective compound made from flax lignans called methyl-p-hydroxyphenyllactate (MeHPLA for short). When MeHPLA binds to Type II EBS, the growth of estrogen-responsive cells is regulated (slowed). Unfortunately, levels of this regulatory compound, MeHPLA, are decreased in breast cancer due to an enzyme (esterase) that breaks MeHPLA down. The result is that Type II EBS are made available docking by estrogen (or xenoestrogens), with their growth promoting effects. Genistein has been shown to act synergistically with inhibitors of

### OTHER EFFECTS OF SOY AGAINST CANCER

Soy isoflavones also possess many other anti-cancer actions unrelated to their phytoestrogenic properties [Po et al., 2002; Messina & Loprinzi 2001; Shao & Shen 2000; Shao et al., 1998a]. Some research has shown genistein exerts multiple suppressive effects on both ER+ AND ER- breast cancers [Shao et al., 2000, 1998; Stoll 1997], and that these effects are independent of estrogen-mediated pathways [Shao et al., 1998a]. For example: in ER-negative breast cancer cell lines, genistein sharply inhibits tumor growth and promotes cell death (apoptosis) [Shao et al., 1998a; Wang & Kurzer 1997].

- Arrest the cell cycle (cytostasis) Genistein induces cell cycle arrest, halting the growth of both ER+ and ER- breast cancer cells in vitro at doses achievable in humans—10 $\mu$ Mol [Balabhadrapathruni et al., 2000; Cappelletti et al., 2000; Fioravanti et al., 1998; Pagliacci et al., 1994]. The other soy isoflavones (diadzein and biochanin A) also show similar effects in arresting breast cancer cell cycle in vitro [Ying et al., 2002].

- Promote differentiation In animal studies, genistein increases cell differentiation in breast tissue [Lamartiniere et al., 2002; Barnes 1995]. Dr. Andreas Constantinou at the University of Illinois, Chicago, has demonstrated that soy genistein induces differentiation in both ER+ and ER- human breast cancer cells [Constantinou et al., 1998b].

- Induce programmed cell death (apoptosis) Genistein induces apoptosis (programmed cell death) in breast cancer cells in vitro at doses achievable in humans—10-25 $\mu$ Mol [Leung & Wang 2000; Li et al., 1999; Fioravanti et al., 1998; Constantinou et al., 1998a; Shao et al., 1998b; Pagliacci et al., 1994]. Researchers at the Strang Cancer Research Laboratory have confirmed the apoptosis inducing effects of soy in human breast cancer cells expressing the HER-2/neu oncogene [Katdare et al., 2002].

- Modify gene expression Genistein has a direct effect on gene expression, down-regulating cancer-promoting genes called oncogenes (like Her2neu) and increasing tumor suppressor genes (like p53 and p21) [Li et al., 1999; Constantinou et al., 1998]

- Inhibit insulin-promoted growth Genistein blocks the promotional effect of insulin on breast cancer cell growth [Pagliacci et al., 1994].

- Inhibit growth-promoting enzymes Genistein is a potent inhibitor of tyrosine protein kinase, an enzyme that promotes cancer [Shao et al., 2000; Barnes et al., 2000; Clark et al., 1996]. Tyrosine kinase enzymes are found throughout the body, and are involved in many cellular functions, including growth and differentiation. Tyrosine kinase inhibitors can inhibit the proliferation of breast cancer cells. Soy compounds also inhibit another tumor-promoting enzyme, called topoisomerase II [Constantinou et al., 1998; Kim et al., 1998]

- Anti-angiogenesis Genistein is a potent inhibitor of angiogenesis in vitro [Fotsis et al., 1998] and in vivo [Shao & Shen 2000; Shao et al., 1998b], decreasing levels of vascular endothelial growth factor (VEGF) and transforming growth factor-beta1 (TGF- $\beta$ 1).

- Inhibit invasion and metastasis Genistein exhibited at 50% inhibition of the invasion of highly metastatic breast cancer cells in vitro at low concentrations (1 $\mu$ Mol), and at higher concentrations (37 $\mu$ Mol) achieved nearly complete inhibition of invasion [Scholar & Toews 1994]. Genistein inhibits metastasis in vivo in both ER+ and ER- breast cancers [Wietrzyk et al., 2000; Shao & Shen 2000; Shao et al., 1998b, 1998c]. Polish researchers surgically resected mammary tumors then treated mice with genistein, cyclophosphamide chemotherapy or combination. In untreated mice, 100% of tumors recurred. In mice treated with genistein or cyclophosphamide, the recurrence rate dropped to 40% [Wietrzyk et al., 2000]. Genistein's ability to reduce invasion of cancer may be due to its ability to inhibit MMP (matrix metalloproteinase) enzymes [Shao et al., 1998b].

this esterase enzyme [Attalla et al., 1997].

Phytoestrogens have shown a preference for binding Type II receptors, and they compete with estrogen for these ER sites [Boue et al., 2003; Morito et al., 2001; Aldercreutz et al., 1992].

In a brilliantly designed study completed by researchers at the University of California, San Francisco, the effects of phytoestrogens and estrogens were compared on both alpha and beta estrogen receptors. Whereas estrogen triggered a response when binding with either alpha or beta receptors, soy phytoestrogens at physiological levels selectively bind to ER-beta and promote repression of estrogen activation [An et al., 2001]. This study demonstrated that phytoestrogens act as SERMs that elicit distinct clinical effects from estrogens.

Additional research confirms the molecular properties of genistein on human breast cancer cells in vitro are comparable to the Selective Estrogen Receptor Modulators (SERMs) raloxifene and faslodex [Diel et al., 2001]

#### Failure to Consider Systemic Effects of Soy: Looking Beyond Estrogen Receptors

Narrow focus on the relationship between genistein and estrogen receptors in test tube studies has overlooked several beneficial effects of soy (and flax) phytoestrogens following human consumption.

- Decrease circulating estrogen and progesterone levels A study using very high dose soy (100-200mg isoflavones per day) in premenopausal women on a controlled diet. This diet reduced circulating levels of estradiol by 25% and progesterone by 45% [Lu et al., 2000a].
- Increase SHBG in vivo Eating soy products raises a protein in the bloodstream called Sex Hormone Binding Globulin (SHBG). SHBG binds estrogen and reduces its availability to the tissues. Human studies have shown that in women the level of SHBG increases with increased dietary intake of phytoestrogens [Aldercreutz et al., 1992].
- Increased conversion of estrogen to weaker forms Genistein in small concentrations (100nMol) has been shown to increase the conversion of estradiol (strong form of estrogen) to estrone (E1, weaker form of estrogen) [Brueggemeier et al., 2001].
- Altered ratio of 2OHE to 16OHE Research on both pre- and post-menopausal women confirms that isoflavones from soy (genistein and diadzein) alter the ratio between estrogen metabolites, enhancing the production of favorable 2-OH estrogens and/or decreasing the production of 16-OH estrogens [Lu et al., 2000b; Xu et al., 2000, 1998; Aldercreutz et al., 1992]. Animal studies with fermented soy extract, genistein and diadzein also show reduced levels of 16OH-estrogens [Kishida et al., 2000].
- Disrupting metabolism of endogenous estrogen and xenoestrogens Phytoestrogens inhibit enzymes that are involved in the generation and removal of endogenous (made in body) hormones. Particularly, phytoestrogens inhibit sulphotransferase enzymes which attach a sulfate group to both estrogen and to a variety of environmental chemicals (including carcinogens). Circulating estrogen-sulfate is the major source of estrogen in post-menopausal breast tumors. Sulfation is a key step in the activation of many pro-carcinogens. Hence, the inhibition of sulfotransferase enzymes by soy phytoestrogens may have a beneficial protective effect on the susceptibility to breast cancer [Kirk et al., 2001].
- Inhibition of xenoestrogen-induced BrCa proliferation (described above)

## Summary & Conclusion on Soy

What is needed is a well-designed human study that takes into account the many factors detailed above. No such study has yet been done, so there is at this point not a definitive answer to the many questions about soy: "Should women with breast cancer eat soy and/or take genistein supplements?" Whom does soy most benefit? What amounts should be consumed? When should it be avoided? What types of soy are best? Consider the information in this handout carefully so that you can make an informed decision, and feel free to share this information with your doctor.

Certainly, more human data is needed, but in light of the current evidence, moderate dietary intake of soy—two or more servings of soy foods daily (providing 30-60mg of isoflavones)—appears reasonable for most women with a history of breast cancer. You can maximize soy's beneficial effect by choosing fermented soy foods (natto, miso, tempeh) and ensuring adequate levels of healthy intestinal bacteria (acidophilus and bifidus) which are needed to convert the phytoestrogens to their active forms. On the other hand, with many questions as yet unanswered, it seems prudent to avoid the use of high-dose isolated genistein supplements or refined/processed soy powder or pills. Because some research shows possible estrogen-like response with very small amounts of soy, it also seems wise if you are going to eat soy to have a consistent moderate intake (2+ servings daily) rather than a small, inconsistent or irregular intake.

### Quotes on Soy & Breast Cancer from Key Researchers:

"Special sessions at the symposium on breast cancer did much to alleviate concerns that soy could have detrimental effects in this area." Mark Messina et al., Fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease, Nov 4-7, 2001, San Diego.

"No negative effects of soy on breast cancer have been observed." Herman Aldercreutz:  
Phytoestrogens and breast cancer, J Steroid Biochem Mol Biol, Dec 2002.

"These compounds show cytostatic activity for both ER-positive and negative human mammary cancer cell lines, and also inhibit the growth and progress of the rat mammary cancer model [in vivo]." Dr. Brian Stoll: Eating to Beat Breast Cancer: Potential Role for Soy Supplements, Lancet, 1997.

"If breast cancer patients enjoy soy products, it seems reasonable for them to continue to use them." Mark J. Messina & C.L. Loprinzi: Soy for Breast Cancer Survivors: A Critical Review of the Literature, Journal of Nutrition, 2001.

*References available upon request.*