Soy Foods and Breast Cancer:
Do Soy Isoflavones Reduce Primary Breast Cancer Risk?

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Introduction

The hypothesis that consuming soy-containing foods may lower breast cancer risk comes from the observation of substantially lower breast cancer incidence rates in Asian countries where soy consumption is high relative to Western countries where soy consumption is low. The fact that after a couple of generations Asian immigrants assume their host country's higher rate of breast cancer argues for an environmental cause that correlates with acculturation: the possibility that risk increases when traditional Asian foods such as soy are no longer consumed.[7] However, epidemiologic studies are inconsistent in their conclusions. In the laboratory, soy food consumption has been attributed both to breast cancer risk reduction and increased risk.[1] This paper is an analysis of those studies.

A search of the World Wide Web and health magazines reveals a confounding litany of claims that soy consumption both *reduces* and *increases* breast cancer risk. With such contradictory opinions circulating in the media, it is no surprise that general consumers are confused about the efficacy of soy as a functional food for breast cancer protection. Several large food companies have taken advantage of the media attention to market new, convenient soy products, such as breakfast cereals and energy bars. Some have even acquired soy food manufacturers,[2] which will likely result in the introduction of new soy products that further ensure soy's mainstream presence in the Western marketplace.

Soy phytoestrogens, or isoflavones, are the biologic premise upon which the theory of soy's risk reduction potential is based. Americans consume soy isoflavones primarily from the following sources: traditional Asian foods such as tofu, tempeh, natto and miso; popular

soymilks; soy flour added to products and, recently, as soy protein powders. Extracted isoflavones are also marketed in numerous forms as dietary supplements, regulated under the Dietary Supplement Heath and Education Act.[3]

It has been shown that isoflavones may have different mechanisms for primary versus secondary prevention.[7] Several studies suggest that isoflavones can stimulate existing breast tumor growth and act as a tamoxifen antagonist in women with breast cancer. It is therefore suggested that women with a history of breast cancer use soy products cautiously, especially at high concentrations.[4,5] For this reason, this paper will only consider soy for its primary cancer protective effects and will not address the significance of soy for women who already have a breast cancer history.

Phytoestrogens

Phytoestrogens are secondary plant components that show structural similarity to mammalian estrogens and, therefore, are able to bind to mammalian estrogen receptors. The diverse biological activity of phytoestrogens is due in part to their ability to act estrogenically as estrogen agonists and anti-estrogenically as antagonists. As estrogen agonists, phytoestrogens mimic endogenous estrogens and cause estrogenic effects. As estrogen antagonists, they may block or alter estrogen receptors (ER+) and prevent estrogenic activity, causing anti-estrogenic effects.[6] This dual role becomes particularly significant in medical conditions unique to women.

Phytoestrogens are found in several foods such as soy, flax, whole grain breads, herbs and vegetables. Four different families of phenolic compounds produced by plants are considered phytoestrogens: isoflavonoids, lignans, coumestans and stilbenes. Different classes of phytoestrogens and diverse compounds within each class affect the estrogen-mediated

response in different ways.[6] This paper's focus is on the *in vivo* studies of the soy phytoestrogens, the isoflavones.

Isoflavones

Soy isoflavones might help reduce cancer risk because they lower lifetime exposure to natural estrogens by competing for receptor sites or changing the way the body breaks them down. The major isoflavones found in soy are the glycones genistin (~60%) and daidzin (~25%). These molecules are called glycones because they have a glucose molecule attached to them and occur in high concentrations almost exclusively as glycosidic conjugate forms in most soy-protein products.[7] (Note that most articles on soy isoflavones incorrectly state that soy contains the aglycone form of the isoflavone and this paper uses that de facto nomenclature.) The glycone isoflavones provided in the diet from soy products undergo enzymatic transformations in the gut to the functional molecules, such as genistein and daidzein, known as aglycones because the glucose moiety is removed. Genistein (4' 5, 7-trihydroxyisoflavone) and daidzein (4', 7-dihydroxyisoflavone) differ by one hydroxyl group (-OH) on the A ring of the isoflavone structure. Also contained in soy are the aglycone isoflavones biochanin A and formononetin. Biochanin A is metabolized to genistein, and formononetin may be converted to daidzein once ingested. Within the lumen of the GI tract, bacteria have the enzymatic capability of metabolically modifying the aglycones isoflavones to other structures, such as the conversion of daidzein to equol. The structures of the isoflavones have some similarity to estradiol. [8]

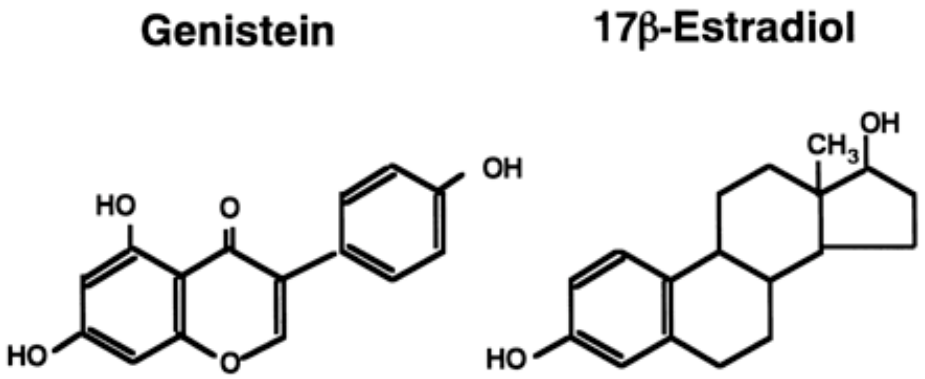

Figure 1

Mechanism of Action

Both genomic and non-genomic mechanisms have been proposed to explain phytoestrogenic effects on breast cancer tissue. Frequent consumption of isoflavones may competitively inhibit 17ß-estradiol at the estrogen receptor binding sites, thereby decreasing the availability of 17ß-estradiol and its metabolites in hormone-sensitive tissues.[8] Isoflavones are able to interact with enzymes and receptors. Due to their stable structure and low molecular weight they can pass through cell membranes.[9] These interactions allow them to: bind to the ERs[9]; induce specific estrogen-responsive gene products[10]; stimulate ER+ breast cancer cell growth[10]; interfere with steroid hormone metabolism or action[9] and alter ER structure and affect transcription[6].

Non-genomic effects that don't involve the ERs include:[11] induction of cancer cell differentiation; inhibition of tyrosine kinase and DNA topoisomerase activity; suppression of angiogenesis and acting as an antioxidant.

The different activities and the bioavailability of phytoestrogens vary depending on such factors as the form of administration, dosage, individual metabolism and ingestion of other pharmacological substances.[11]

Materials and Methods

Studies for this review were initially identified via Pub Med using the search string "*("Breast Neoplasms/diet therapy"[MeSH] OR "Breast Neoplasms/prevention and control"[MeSH] OR "Breast Neoplasms/therapy"[MeSH]) AND "Isoflavones"[MeSH])*". The search turned up 175 matches, 27 of which were used in this paper. Other articles were found following threads of references and citations in the identified papers. The articles were obtained in the following ways: 8 articles were ordered from the University of New Haven's ILL (Inter-library loan) program; 13 were obtained through EBSCOHost and Ovid; and 24 were either free-full text via Pub Med or obtained via personal online journal subscriptions.

Of the identified articles the large majority of randomized control trial (RCT) studies were conducted on animals. Many animal *in vivo* experiments were conducted providing both positive and negative correlation with breast cancer risk, just as human *in vivo* studies have shown.[12] However, what is applicable to animals may not be representative of human metabolism.[12] Therefore animal studies are not reviewed herein; however, they are briefly discussed to correlate with the human data.

In vitro observations may not be relevant to humans because they tend to use supraphysiological levels of genistein or isoflavone mixtures—possibly 10 to 1,000 times higher than physiological levels—and provide isoflavones without other soy components.[37] It is clear that *in vitro* data should be interpreted with caution when applied to human health, as it should be used primarily to help determine the biological actions of individual phytochemicals. Therefore, the majority of studies reviewed in this paper are human epidemiological studies or case-control examining soy isoflavone consumption, excretion, hormonal changes and mammographic densities related to risk.

Studies Concluding Definitive Protective Effect

Loss of Traditional Japanese Foods Leads to Increased Risk- 1978

In a frequently cited 1978 study showing a correlation between the American diet and breast cancer, the diets of 6,860 Japanese couples living in Hawaii were analyzed[13]. Of this pool, 86 women were diagnosed with breast cancer. Since it was assumed that individual couples shared similar diets, the diets of the husbands of the women with breast cancer were compared to the diets of the other husbands. The study determined that the couples with breast cancer consumed less traditional Japanese soy foods, such as miso, and more American foods. This was one of the first studies to identify a possible correlation between diet and breast cancer.

Soy Intake Inverse to Incidence - 1991

A landmark 1991 case-controlled retrospective study focused on the soy intake of 200 Singapore women with confirmed breast cancer and 420 controls age range 28-83 years old.[14] This was the first study to identify soy's protective effects. A Food Frequency Questionnaire (FFQ) assessed the intakes of 90 selected nutrients and foods a year prior to the interview. Researchers reported high intakes of animal proteins and red meat were associated with an increased risk, while a higher consumption of soy foods was associated with a decreased risk. In premenopausal women, an inverse relationship was found between the risk of breast cancer and the intake of soy proteins and total soy products. The women who consumed the most soy foods (approximately 2.0 times that standard soy portion or >55g) were approximately 70% less likely to get breast cancer than those who consumed little or no soy foods (<20g). The study concluded that soy products may protect against breast cancer in premenopausal women, OR .30(0.1,0.6). However, in postmenopausal women, a statistically significant relationship did not exist among the dietary variables and breast cancer.

Since the study relied on dietary recall it involved incomplete reporting. It also did not account for the possibility that women who eat healthier may also lead healthier lifestyles that can contribute to a reduced cancer risk—an oversight common to other studies. However, the study did use women from the same culture in the same city, which minimizes the confounding variables.

Tofu Intake in Asian Americans Decreases Risk – 1996

In 1996, Wu et al., set out to determine why Asian-Americans have a lower incidence of breast cancer than American Caucasians, but a considerably higher rate than those in Asia. [15] The researchers conducted a population based case control study among 597 recently diagnosed Chinese-American, Japanese-American and Filipino-American women and 966 population-based controls age 30-55 years old. The study used a 90-item FFQ with approximately 50 common items to all 3 groups and approximately 10 items unique to each group. For example, only the Japanese immigrants were asked about natto and miso consumption. After adjustment for age, ethnicity and study area, intake of tofu was more than twice as high among Asian-American women born in Asia, with an upper intake of 8g/day compared to those born in the US with an upper intake of 4g/day. Among immigrants, intake of tofu decreased with years of residence in the United States, dropping from a median of 4g/day for less than 7 years to a median of 2g/day for greater than 7 years. Overall tofu consumption ranged from about 2g/day for the low intake group to 9g/day for the high intake group. Risk of breast cancer decreased with increasing frequency of tofu intake after adjustment for age, study area, ethnicity and migration history; the adjusted OR associated with each additional serving per week was 0.85 (95% CI = 0.74-0.99). The protective effect of high tofu intake was observed in pre- and postmenopausal women. This

association remained after adjustment for selected dietary factors and menstrual and reproductive factors.

However, this study was not designed specifically to investigate the role of soy intake. Therefore the assessment of soy intake may be incomplete and it is possible that soy intake is a marker of other protective aspects of Asian diet and/or Asian lifestyle. Another drawback is that this study does not take into account other variables, such as the possibility of newer American generations eating more American processed foods, which have recently been linked to increased cancer risk.

Urinary Phytoestrogens Output Suggests Protective Role - 1997

An often-referenced Australian retrospective case-control study published in the *Lancet* determined that the metabolites of soy phytoestrogens provided a risk reduction.[16] This study consisted of 144 pairs of recently diagnosed breast cancer patients (ages 30–84) and a matched control. A 72h urine collection and blood sample were collected before cancer treatment began as well as a similar collection for the controls. An FFQ was used to match urine output to stated food intake. This study aimed to determine if breast cancer patients have a lower urinary output of phytoestrogens as compared with matched controls. It found that equol, the metabolite of daidzein, provided benefit, and the study concluded that there is a substantial risk reduction in women with a high intake of phytoestrogens equol (from daidzein) (OR 0.27 95% CI 0.10-0.69) as well as enterolactone, a metabolite from lignans in flax.

The strength of this study is that it did not rely solely on an FFQ, but rather correlated urinary output with the questionnaire, which also indicates bioavailability. However, it was limited in that the researchers failed to study genistein and therefore did not confirm that the 72h urinary output was complete, nor did it provide urinary biomarkers. The assumption regarding

equol output being a marker of intake was refuted in a study three years later[28] and was questioned in a study two years prior by Hutchins et al.[35] Therefore this study may be dubious since the premise regarding equol as a marker has been refuted[17] and the failure to measure genistein. However, the study is included because of its historical importance indicating that there may be individual differences in soy metabolism.

Isoflavone Urinary Excretion Inverse to Incidence - 1999

One Shanghai Breast Cancer sub-study[18] measured the isoflavone urinary excretion similar to the above study. It concluded that high intakes of soy food might reduce breast cancer risks. The study recruited 1459 newly diagnosed women aged 25 to 64 and 1556 age-matched controls from August 1996 to March 1998. All participants were interviewed face to face with a detail questionnaire determining demographics, detailed health history, and substance abuse in addition to a FFQ. Blood and urine samples were collected from all participants in the morning before any meals. This sub-study measured total urinary excretion of total isoflavonoids, daidzein, genistein, glycitein, equol, *O*-desmethylangolensin (O-DMA) and Phenols in 60 case-control pairs, in which all case measurements were before cancer therapy. The FFQ was used to correlate results. The results showed that women newly diagnosed with breast cancer excreted substantially lower level of urinary isoflavones than controls. The total isoflavonoids were significantly lower (p =.04), as was glycitein (p < .01) in breast cancer subjects. However, other isoflavones such as daidzein and genistein were not significant. The adjusted odds ratio for breast cancer was 0.14 (0.02–0.88) for women whose urinary excretion of both phenol and total isoflavonoids was in the upper 50% compared with those in the lower 50%. The authors conclude that this study supports the hypothesis that a high intake of soy foods may reduce the risk of breast cancer.

The strength of this study's results is that the findings were remarkably consistent internally, therefore probably not due by chance even with the small sample size. The weakness is that the urine samples reflect only recent (24-96h) consumption; therefore one urine sample may not provide accurate results. Although urine samples from subjects were collected as soon a possible after initial diagnosis, it is possible that dietary changes as a result of diagnosis can confound the results.

Adolescent Intake Inverse to Risk - 2001

In May 2001, an important study was published that associated adolescent soy food intake with incidence of breast cancer in later life.[19] (This was another sub-study from the Shanghai Breast Cancer study.) In addition to the standard Shanghai study data (1459 newly diagnosed women aged 25 to 64 and 1556 age-matched controls) 372 biological case mothers and 439 control mothers under 45yo were approached to obtain their daughter's dietary intake from 13-15yo, as well as *in utero* and early life experiences. Dietary intake during adolescence was ascertained using a brief interview FFQ of 17 raw food items including three categories of soy foods: tofu, soymilk, and other soy products. Breast cancer cases reported a lower soyfood intake than controls during adolescence. The mean soy protein intake per day was 6.45 and 7.23 grams/day respectively, for cases and controls (p=.002). After adjustment for a variety of other risk factors, adolescent soy food intake was inversely associated with risk, with ORs of 0.75 (0.60–0.93), 0.69 (0.55–0.87), 0.69 (0.55–0.86), and 0.51 (0.40–0.65), respectively, from the lowest to highest quintiles of total soy food intake. However, there was not a consistent trend of decreasing risk with increasing amounts consumed. The inverse association was observed for each of the soy foods examined and existed for both pre- and postmenopausal women. Adolescent soy food intakes reported by participants' mothers were also inversely associated

with breast cancer risk, with an OR of 0.35 (0.21–0.60) for women in the highest soy food intake group. Adjustment for usual adult soy food intake did not change the soy food associations. The authors concluded the substantial difference in breast cancer incidence between Asian and Caucasian women and increasing breast cancer incidence among Asian-Americans may be partly explained by soyfood intake during adolescence.

The study's strengths are the number of subjects and the fact that Chinese are a population with a large soy intake. However a major concern may be the accuracy of adolescent intake, although the interviewers were blinded to the study and soy was not publicized as anti-cancer at the time of the study.

Isoflavones Increase Menstrual Length - 2002

A double-blinded RCT study of 67 premenopausal cancer-free women, ages 25-55 yo, determined that isoflavone supplementation produces favorable change in steroid hormones and menstrual cycle length.[20] The mitotic rate for breast tissue is almost fourfold greater during the luteal phase than during the follicular phase; therefore if soy isoflavones can increase the length of the follicular phase, they may be able to reduce the risk of breast cancer. Thirty-four women were instructed to consume 40 mg of genistein per day, while a randomized control group of thirty-three women consumed a placebo milk-protein for a 12-week period. Changes in their anthropometric, nutritional, and hormonal biomarkers from early follicular phase were analyzed at baseline and post-intervention. Participants were instructed to monitor their cycle length and luteal hormone surge using a commercial kit to provide qualitative information regarding ovulation and length of follicular phase. They completed a daily Symptoms Monitor to document days of cycle and nutritional symptoms for digestive issues. Results showed a moderate, but non-significant decreases in free estradiol and estrone, and an increase in sex

hormone-binding globulin (SHBG). However, menstrual cycle length was increased by 3.52 days (p=.04), and the follicular phase of the cycle was extended by 1.46 (p=.08) days. The authors concluded that the results support the hypothesis that soy consumption may alter circulating ovarian steroid hormone concentrations in premenopausal women and increase menstrual cycle length. An increase in menstrual cycle length would reduce the number of menstrual cycles during a lifetime, thereby reducing the total number of times the breast is exposed to estrogen. In addition, women will spend more days in the increased follicular cycle, when proliferation is at its lowest. The menstrual cycle of women from Western populations ranges from 26 days to 29 days, whereas the average cycle length for Japanese women and other Asian women is longer. This may account, in part, for the lower risk of breast carcinoma in populations that consume soy in their daily diet. This study demonstrates that daily soy consumption can lead to statistically significant changes in menstrual cycles, even in Western women.

An experimental randomized double-blinded RCT is the gold standard, therefore this study is held in high regard among researchers. However the study was short (12 weeks) and administered a concentrated amount of only one isoflavone (genistein) normally not found in food, as food would have a mixture of isoflavones. It did not take into consideration side-effects and long-term considerations. Improvements on this study would include lengthening it through many menstrual cycles with a washout period and administering whole forms of soy food, not just genistein.

Adolescent Intake in Asian-Americans Reduces Risk - 2002

A similar study as above conducted by Wu, again in the late 1990's, concluded that high soy intake during childhood by Asian-Americans (Chinese, Japanese, Filipino) is associated with

reduced breast cancer risks and that risks may be further reduced by adult intake.[21] This retrospective case-control study of 501 Asian women between 25-74yo at the time of breast cancer diagnosis and 594 age-matched controls was carried out in the Los Angeles area. In-person interviews were conducted for dietary intake during the year prior to diagnosis. Soy intake in adult life was estimated based on the intake pattern of 14 soy-rich foods and an adolescent (12-18yo) soy assessment was based on interviewee recall. After considering all potential cofounders and risk factor adjustments, subjects who were high-soy consumers during adolescence and as adults showed the lowest risk (OR=0.53, 95% CI=0.36–0.78) compared with those who were low consumers during both time periods. Risk of breast cancer was intermediate among subjects who were high-soy consumers during adolescence and low-soy consumers during adult life (OR=0.77, 95% CI=0.51–1.10). The median isoflavone intake was approximately 12 mg/day and the greatest risk reduction was most apparent among individuals in the highest quartile of intake.

This is another an important study linking the importance of adolescent intake to decrease risk. The study's strength is that it looked at 3 different Asian groups. However the study size was small and the adolescent intake may be biased, as soy intake may be associated with a healthier lifestyle image.

Total Isoflavone Intake Reduces Risk 2003

A study in Japan from 1990-1999, of 21,852 women aged 40-59yo reported that frequent miso soup and isoflavone consumption was associated with a reduced risk of breast cancer.[22] A questionnaire was used at the study's start with 38 questions concerning food consumption. Two questions focused on soy and isoflavone consumption, specifically miso soup and the consumption of any soy food. Only 179 of the 21,852 subjects were diagnosed with breast

cancer after 1993. The study reported that there was no significant effect when tofu consumption alone was calculated, but total calculated isoflavones from soy food and miso soup had an inverse effect. The highest quartile of isoflavone intake (25.3mg/day) had an OR of 0.46 (95% CI = 0.25 to 0.84), and the inverse association was strongest in postmenopausal women. The highest incidence (99.2/100 000) of breast cancer in the present study was observed among women in the lowest quartile of isoflavone consumption (6.9mg/day).

The large numbers of women and the length of this prospective study (10 years) are convincing. Being a prospective study it was free from recall bias, which gives it an advantage. The results gave a significantly strong inverse correlation when postmenopausal women were considered separately and the lowest quartile considered as a whole. However, there were only 179 cases of breast cancer which may be too small a sample to base results on. Furthermore, the questionnaire did not differentiate between different soy foods and it only had an item for miso soup and soy foods. A newer FFQ[23] would better differentiate between various soy foods and might highlight fermented foods (miso, tempeh, natto) in particular.

Phytoestrogen Intake of Premenopausal Germans 2004

A German population-based case control study evaluating the association between dietary intakes of various phytoestrogens (daidzein, genistein, formononetin, biochanin A) and premenopausal breast cancer risk suggested an important role of daidzein and genistein in reducing risk.[24] A Risk Factor Questionnaire and FFQ were collected from 278 premenopausal cases and 666 age-matched controls. The adjusted values showed that genistein (OR 0.62 (0.40-0.95)) and daidzein (OR0.47 (0.29-0.74)) have a protective effect on hormone receptor positive (ER+) breast tumors. However the results were largely unexpected because the intakes are extremely low (160 μg/day) for a German population in comparison to an Asian population (20

mg/day). In correlating with *in vitro* studies the authors conclude that soy offers a protective mechanism against hormone-dependent breast cancer via phytoestrogen's effects on the generation, transport and removal of endogenous steroid hormones in premenopausal women.

The strength of the study is that it looked at multiple phytoestrogens, in addition to formononetin and biochanin A, the precursors to daidzein and genistein. This suggests that the precursors may not get converted to their biologically active components. However the study suffered from the same limitations as other retrospective studies with a FFQ: The isoflavonoid intake was calculated based on the FFQ and is subject to errors in phytochemical estimation as well as food recall errors and biases.

Studies Concluding Non Definitive Protective Effect

No Correlation Between Dietary Soy and Risk - 1995

A study published in the mid-nineties that looked at diet and breast cancer correlation in Shanghai and Tianjin, China found no association between soy protein and breast cancer risk for pre- and post-menopausal women.[25] It used an interviewer-administered lifetime history FFQ with 834-breast cancer cases aged 25-64 and appropriate matched (1:1) controls. Cases and controls were similar in their consumption of soy protein, measured either in absolute levels or as percentages of total protein. After adjustments they found an inverse association with fiber, carotene and vitamin C and risk. However, there was no association with soy protein or soy as a percentage of total protein.

The study's claimed strengths are that the women's food was probably accurate because of political food rationing at the time. However with any observational retrospective study there is the inherit weakness of historical data and information bias offered by the subjects.

Isoflavones Have Weak Hormonal Effect - 1999

Duncan et al[26] in a randomized cross-over study investigated the hypothesis that soy isoflavones are responsible for changes in hormone action and thereby associated with a reduced cancer risk. Subjects consumed their habitual diets but were provided with instructions to minimize phytoestrogen consumption. They were supplemented with one of three soy protein powders (low, medium, hi isoflavonoids) in a randomized cross-over within 3 diet periods each consisting of three menstrual cycles plus 9 days. The three soy powders provided 0.15 ± 0.01 (control), 1.01 ± 0.04 (low-iso), and 2.01 ± 0.03 (high-iso) mg total isoflavones/kg BW·day (10 ± 1.1, 64 ± 9.2, and 128 ± 16 mg isoflavones/day, respectively). Complete 24h urine collections were collected daily during menstrual cycle 3 of each diet period. Fasting blood was drawn every other day of cycle 2 during each diet period. An optional endometrial biopsy was performed once during menstrual cycle 3 of each period. Various plasma hormones and urine LH were used to measure hormonal effect. In contrast to the findings by Kumar[20], the results of this study suggests that effects on plasma hormones and the menstrual cycle are not likely to be the primary mechanisms by which isoflavones may prevent cancer in premenopausal women.

Although this isn't the only study to examine the hormonal effects of soy consumption on women it is the first to report with three isoflavone doses in a cross-over design. However, there may be potential flaws in the study design as they are using a soy isolate. Soy isolate may have missing phytochemicals and not have as great a hormonal effect. Compliance that all subjects took the appropriate dosage three times a day for a period of 12 months is questionable. Overall it is a strong study in that it is one of the few RCTs and the dosage of isoflavones is based on BMI, also it is over three menstrual cycles.

No Protective Effect For Women Exposed to Radiation – 1999

The association between soy foods and breast cancer risk was investigated in a prospective study of 34,759 women in Hiroshima and Nagasaki, Japan.[27] Women completed FFQ in 1969/70 and/or in 1979-81 and were followed for incidence of breast cancer until 1993. Of the total women studied, 11,067 completed both FFQ surveys. The FFQ considered miso soup and tofu along with meats, fish, dairy, rice, vegetables, pickled vegetables, sea vegetables and teas. There were 427 cases of primary breast cancer. The risk after adjustments was not significantly associated with tofu or miso intake. Interestingly relatively high consumption of tofu was associated with a small increase in risk whereas a high consumption of miso was associated with a small decrease in risk. The only significant dietary associations were a decrease in risk with increased consumption of dried fish and pickled vegetables. Interestingly risk was not significantly associated with the use of hormone compounds, smoking or alcohol consumption. Risk was associated with well-established risk factors, including, age, age at menarche, age at menopause, age at first birth and BMI. This was true of pre- and post-menopausal women.

The study provides an interesting look at the effects of soy in an area with a very high rate of cancer. The strength of this study lies in its prospective nature, however since these women were exposed to radiation the results may not apply to the general population. However the FFQ did not include portion sizes, all major soy foods and was not validated, so it wasn't possible to estimate the intake of soy isoflavones.

Urinary Equol Doesn't Correlate with Intake - 2000

Duncan et al[28] used data from their previous study[26] of 14 premenopausal women to conclude that the urinary excretion of equol does not correlate with isoflavone intake, but rather is a hormonal difference between people, known as "equol excretors" and "non- excretors". They

showed that urinary daidzein and genistein increased as isoflavone intake increased in all women, yet urinary equol only increased in equol-excretors (n=5)(p=.003) while remaining constant in equol-non-excretors (n=9)(p=.22). This was the first study to report that equol excretors and non-excretors show different plasma hormone profiles. Interestingly equol-excretors tended to have longer cycles, although non-significant. The results suggest that the inverse association between equol excretion and breast cancer risk may not be correctly attributable to only differences in isoflavone intake as suggested by Ingram *et al*.[16], but rather a person's ability to produce equol

The strength of this study is that it was the first to provide *in vivo* evidence that equol excretion is not a function of isoflavone intake. It suggests that perhaps there is individuality in risk factors based on the GIs ability to produce equol. However, number of subjects is small, so a larger study should be carried out with various types of fermented soy foods and soy supplements to test this important hypothesis.

No Correlation Between Urinary Phytoestrogens and Risk in Postmenopausal Women - 2001

A 10-y prospective cohort case-controlled Dutch sub-study on the urinary levels of genistein in postmenopausal women did not show any association between urinary phytoestrogens and risk.[29] Over the course of 10 years there were 88 breast cancer cases selected and 268 controls selected from a cohort of postmenopausal (50-64 yo) participating in a breast cancer screening. Five urinary samples over a 10-year period were collected. Higher urinary genistein excretion was weakly and non-significantly (p=.60) associated with a reduced breast cancer risk where the upper tier of genistein excretion was 90*u*mol/mol in controls as compared to 27 *u*mol/mol in subjects. Therefore researchers were not able to confirm only a weak association for post-menopausal women.

The study's strengths were that it was a prospective study and a homogeneous population of post-menopausal women. However dietary phytoestrogen intake may have been too low to account for any protective effect as Dutch do not typically have a high isoflavone intake; therefore there was no measurable change and clearer associations may be present in populations with a large phytoestrogen exposure. Similar to the Shanghai study[18] one fault is that urinary levels reflect the intake levels of soy foods over the previous 24-96h period, therefore recent past consumption might not reflect typical consumptions especially since there were only five samples in the course of 10 years.

Soy Isoflavones Show No Protective Effect for non-Asian Women– 2001

Bay Area researchers examined the effects on breast cancer risk of seven specific phytoestrogenic compounds by using a newly developed nutrient database for assessing phytoestrogen intake from a wide variety of foods.[30] The subjects were 1,272 non-Asian US women aged 35-79 years, who were diagnosed with breast cancer between 1995 and 1998. They were compared with 1,610 controls selected from the general population via random digit dialing. Usual intake of the phytoestrogen classes, isoflavones, coumestans, and lignans were assessed via an interviewed FFQ. The isoflavones measured were genistein, daidzein, formononetin, and biochanin A. The soy foods items were tofu, soymilk, miso soup and foods with added soy flour. The highest quartile of consumption in this population was approximately 3mg isoflavones/day. Neither total isoflavone intake nor phytoestrogen intake were inversely associated with breast cancer risk. This includes pre- and postmenopausal women and for women in each ethnic group. However they did find a significant decrease in breast cancer risk associated with soymilk, although only 3% of cases and 5% of controls consumed the beverage.

The study's strong point is its phytoestrogen calculations were based on a more accurate database and thus if the interviewees answered truthfully, then phytoestrogen calculations were accurate. However the phytoestrogen intake equated to less than one serving of tofu per week, therefore the intake may be too low to exhibit any effect.

Isoflavone Intake Not Related to Risk - 2004

A prospective Dutch cohort study of the European Prospective Investigation into Cancer And Nutrition (EPIC) concluded that phytoestrogens include the soy isoflavones daidzein and genistein are not significantly related to breast cancer risk.[31] This study collected data on 15,555 healthy women aged 49-70yo with 280 diagnoses of breast cancer during follow-up. At recruitment, each participant filled out a self-administered FFQ regarding habitual intake of 178 food items during the preceding year. The FFQ was not specifically designed to estimate foods that contain high amount of estrogens such as soy since these foods aren't frequently consumed in The Netherlands. It did measure phytoestrogens from Western society foods such as grains, fruits, nuts, seeds and alcoholic beverages. Isoflavone and other phytoestrogen intake were estimated based on the FFQ results. The estimated intake for soy products was 4.9mg/day in the highest quartile. The results showed a non-significant trend and no protective effects of isoflavones or phytoestrogens against breast cancer.

The strengths of the study in terms of evaluating soy's protective role in breast cancer include careful development of a database for the isoflavone content of various foods; prospectively collected dietary data at the study's inception; and comprehensive ascertainment of cases. However this study had remarkably low isoflavone intakes, median isoflavone intake was just 0.37 mg/d; even among women in the fourth quartile. The isoflavone intake of Dutch women is considerably less than the 50 mg/d typically consumed by Japanese women. Diet was

considered only over the past year and not over the subject's lifetimes. Given the large population and prospective nature this study might have shown different results in a population that consumes moderate amounts of soy foods.

Isoflavone Intervention Doesn't Change Mammographic Density - 2004

Women with dense tissue in more than 60-75% of the breast are at four to six times greater risk of breast cancer than those with no densities.[33] A recent RCT studied 220 premenopausal women to examine the effects of soy foods and lifetime soy intake on mammographic densities.[32] Women randomized to the intervention group consumed a mean of ~58mg isoflavones/day approximating the daily intake of women in Asian countries, whereas the control group consumed ~5mg isoflavones/day. The nutritional intervention consisted of a choice of 2 daily servings of soy. A serving was defined as the amount of food that contains 25 mg of isoflavones and corresponded to 180 g soymilk, 126 g tofu, a 58 g soy protein bar, 31 g soy protein powder, or 23 g roasted soy nuts. The control women consumed their usual diet; they were asked not to increase their previous low soy intake. Compliance was excellent as evidenced by a self-reported dietary intake form and unannounced 24-h urine tests for biomarkers of isoflavone intake. Mammograms were obtained at baseline and follow-up. At the end of the 2-y intervention period, there were no significant differences in any mammographic characteristics that could be attributed to the dietary intervention. Researchers also administered a lifetime soy questionnaire and found that in contrary to other studies associating a risk reduction with adolescent isoflavone intake that Caucasian subjects who consumed soy throughout their lives had breasts that were 28% more dense compared with women who consumed less soy.

This study has several strengths including the randomized trial with sufficient time for a biological response in target tissues. However it was conducted on healthy premenopausal

women and it has been shown that breast density is different in postmenopausal women. It does not look at women with a strong family history of breast cancer or consider the heritability aspects of mammographic density.[33] It also fails to consider cyclic mammographic density changes and having the subjects undergo the exam during the follicular phase.[34]

Studies Showing Definitive Chemoprevention Effect							
Study	**Design & Location**	**Sample**	**Purpose**	**Data Collection**	**Results**	**Study's Strengths**	**Study's Limitations**
Lee et al[14] 1991	Observational matched case-controlled	Singapore Chinese women in situ breast cancer (n=200) case controls (n=420)	What are the dietary effects on breast cancer in Singapore women?	FFQ , Measured food items and nutrients(vitamins, minerals) calculated from food recall 1 year normal dietary intake	Soya products may protect pre-menopausal women against breast cancer. (p=.02). High intake (>55g/day) led to a 70% risk reduction over low intake (<20g day)	Women were from the same cultural background.	Did not specifically focus on soy. Dietary recall could be biased. People that eat healthier may have healthier lifestyles that could influence health.
Wu et al.[15] 1996	Observational case-controlled Los Angelas, San Francisco, Hawaii	Asian American women dx w/breast cancer n=597	Why do Asian-American women have a higher rate of breast cancer than in Asia	FFQ of normal dietary intake. Measured food substances tofu, meats, fish, etc. 90 food items	High tofu intake showed a significant inverse relationship to breast cancer in both pre- and post-menopausal.	Used controls, variety of Asian populations.	Study wasn't focused on soy so may be incomplete only looking at tofu. Tofu intake may correlate with other lifestyle choices not accounted for.
Ingram et al [16] 1997	Retrospective case-controlled Perth, Australia 1992-94	Australian women (30-84yo) In situ breast cancer (n=144). Control chosen from electoral roll.(n=144)	Does urinary phytoestrogens correlate with reduced risk?	Questionnaire normal dietary intake, 72 h urine sample measuring urine metabolites Daidzein, genistein, equol via mass spectrometry	Substantial risk reduction in women with a high intake of phytoestrogens equol (from daidzein) (OR 0.27 95% CI 0.10-0.69) Insignificant for daidzein.	Did not rely on an FFQ, but used urinary output confirmed with FFQ.	72h urine sample may not be complete. Failure to measure genistein, Equol metabolite is hormonal dependent.[28]
Zheng et al [18] 1999	Observational case-controlled 1997 18-month period, Shanghai Breast Cancer Sub-Study. Shanghai, China	Newly diagnosed breast cancer 25-64yo. (n=60) Aged and menopausal status matched controls	Do women with breast cancer excrete fewer isoflavonoids compared to controls?	Questionnaire for diet hx, health hx, demographics. Urine sample measuring urinary total isoflavonoids, genistein, daidzein, equol, glycitein, phenols	Urinary excretions of total isoflavonoids were significant lower in breast cancer cases than controls. They interpolate the high intake of soy food may reduce breast cancer. Median intake of 33mg isoflavones/day	Measured all major isoflavone metabolites. Results showed strong correlation with each other.	Urinary output a reflection of recent diet (24-96h) not long-term. Small sample size.
Shu XO et al, [19] 2001	Retrospective match case-control 1997 18-month period, Shanghai Breast Cancer Sub-Study. Shanghai, China	Newly dx breast cancer subject(n=1459) age-matched controls n=1556 n=296 mothers of subjects under 45yo. N=359 controls	Does adolescent soy intake (13-15yo) influence breast cancer risk?	FFQ (various soy foods), Dietary recall from childhood. Case mothers interview about daughters adolescent nutrition	Adolescent soy intake has an inverse relationship with breast cancer risk for both pre- and post-menopausal. Median intake of 33mg isoflavones per day.	Large number of subjects. Correlated mothers data with daughters	Dietary recall is subject to errors and bias may result in adolescent intake.

Studies Showing Definitive Chemoprevention Effect							
Study	**Design & Location**	**Sample**	**Purpose**	**Data Collection**	**Results**	**Study's Strengths**	**Study's Limitations**
Kumar et al[20] 2002	Experimental Intervention double-blinded RCT 12 weeks, Tampa FL Administered 40mg/day genistein	Premenopausal women in Florida Subjects(n=34) Controls(n=34)	Determine if Genistein administration causes changes in steroid hormones and menstrual cycle length.	Blood serum hormones, estrone, estradiol, SHBG at baseline and studies end. Participants monitored cycle length, diet intake, symptoms	Cycle length increased by 3.52 days (p=.04) and follicular phase increased by 1.46 days(p=.08). Moderate decrease in serum-free estradiol and estrone.	Double-blinded RCT	Short term, isoflavone intake was extremely high in genistein alone. No long-term effects considered. .
Wu et al [21] 2002	Retrospective case control Los Angelas, 1995-98	Asian-American recently dx breast cancer(n=501) control (n=594)	Does adolescent soy intake (12-18yo) influence breast cancer risk?	Dietary intake interview of previous year, adult life and adolescent life. Soy intake estimated based on intake pattern of 14 foods rich in soy. adolescent intake measure on intake of tofu.	High-soy consumers during adolescence and adults showed lowest risk (OR=0.53, 95% CI=0.36–0.78) Intermediate risk for high consumers during adolescence and low consumers during adult life (OR=0.77, 95% CI=0.51–1.10) Median isoflavone intake 12mg/day.	Considered adolescent variables. FFQ based on 14 soy foods instead of just a few.	Estimation of adolescent soy intake crude, based on tofu alone, possible measurement errors and biases. Soy intake can be related to other lifestyle confounding variables.
Yamamoto et al. [22] 2003	Prospective cohort Japan 1990-99	Japanese women 10-year period. (n=21,852) From 1993-1999 179 women diagnosed	Relationship between miso soup and soy foods and risk	Dietary recall soy intake questionnaire from previous year, & adolescence. Estimation of isoflavone, soy, miso intake	Total calculated isoflavones from soy food and miso soup had an inverse effect. OR of 0.46 (95% CI = 0.25 to 0.84), strongest association in postmenopausal women.	Prospective study so no recall bias. Estimation of isoflavone by validated questionnaire.	Only a small number of cancer diagnoses. (n=179) Questionnaire did not differentiate between soy foods.
Linseisen et al[24] 2004	Retrospective case-controlled. Southern Germany, 1992-1995	Premenopausal German women, < 50 yo. *In situ* breast cancer n=278 cases, 666 age-matched controls	Does the consumption of phytoestrogens reduce risk?	FFQ prior year to Dx (cases) or entering study (controls), Risk factor Questionnaire. Phytoestrogen intake estimated based on FFQ	Protective effect of genistein and daidzein on ER+ tumors for premenopausal women. ORs 0.62 (0.40-0.95) and 0.47 (0.29-0.74)	Measured several types of phytoestrogens, looked at isoflavonoids and lignans.	FFQ so suffers from bias and recall errors.

Studies Showing No or Non-Definitive Effect							
Study	**Design & Location**	**Sample**	**Purpose**	**Data Collection**	**Results**	**Study's Strengths**	**Study's Limitations**
Yuan et al[25] 1995	Observational case-controlled Shanghai &Tianjin, China.	Pre and Postmenopausal women with breast cancer (n=834) and case matched controls.	Determine connection between diet and breast cancer in Shanghai & Tianjin	Interviewer-administered FFQ of typical diet history	No association with soy protein or soy as percentage of total protein in pre and postmenopausal women.	Food rationing likely made recall excellent.	Inherit weaknesses of Observational studies. Possible insufficient number of soy items on intake.
Duncan et al [26] 1999	Experimental Randomized cross-over	Healthy premenopausal women n=14 Administered 3 different dosages of isoflavones for each menstrual cycle Otherwise normal dietary intake but limiting phytoestrogens	Are soy isoflavones responsible for hormonal changes assoc with decreased risk?	24h urine samples daily during menstrual cycle 3 samples each diet period, optional endometrial biopsies. Fasting blood cycle 2 Plasma measured for various plasma hormones. Urine measure for LH. Control, lo, med, and high levels of isoflavones administered/day.	No significant effects of isoflavone consumption on lengths of the follicular phase, luteal phase, or total menstrual cycle.	Experimental RCT design. Isoflavone intake based on BMI.	Lack of whole food, other phytochemicals may have an effect. Compliance. Small sample size.
Key et al[27] 1999	Prospective cohort Hiroshima and Nagasaki Radiation Effects Research Study 1969-1973	34,759 women present at time of bombings.	Is there an association between soy foods and breast cancer risk?	FFQ 19 foods miso soup, tofu of entire life.	No Significant correlation between tofu or miso intake and risk. Risk associated with well-established factors: menarche age, first birth age, BMI.	Prospective study and over a long period of time.	Women were exposed to radiation so may not apply to general population. FFQ not validated. Could not estimate isoflavone intake, no portion sized.
Horn-Ross et al. [30] 2001	Retrospective case-controlled Bay Area Cancer Study 1995-1998	Non-Asian women. Breast cancer cases (n=1,326) controls (n=1,675) matched on age-ethnicity 35-79yo.	Phytoestrogen consumption and breast-cancer risk in multiethnic populations	Interview FFQ based on previous 7-year history. Random digit dialing of controls.	Phytoestrogens appear to have little effect on breast cancer risk at the levels commonly consumed by non-Asian US women: an average intake equivalent to less than one serving of tofu per week. Pre- and Post-menopausal.	Multiethnic population, large number of women.	Accuracy of food recall and random digit dialing of controls may not give truthful answers.

Studies Showing No or Non-Definitive Effect							
Study	**Design & Location**	**Sample**	**Purpose**	**Data Collection**	**Results**	**Study's Strengths**	**Study's Limitations**
Tonkelaar et al[29] 2001	Prospective Case-controlled Netherlands, 1974-85	Postmenopausal women in Netherlands Cases (n=88) Controls (n=268)	Determine if urinary genistein and enterolactone are associated with breast cancer risk	5 Urinary collections over an 11 year period measuring urinary genistein	No conclusive association between urinary genistein and breast cancer risk	Prospective study. Homogeneous postmenopausal population	Low levels of genistein were detected so intake may be too low. No FFQ to correlate diet with urine output. Only 5 urine samples in 10 years.
Keinan-Boker et al. [31] 2004	Cohort prospective. Utrecht, Netherlands 1993-2001	Cancer free Dutch women (n=15,555) . 280(1.8%) newly Dx during follow-up. Most subjects (n=11,655, 74.9%) were postmenopausal at enrollment.	Relationship between dietary isoflavone intake and breast cancer.	EPIC general questionnaire, anthropometric measurements, and FFQ of 178 food items the previous year. Phytoestrogen intake estimated based on FFQ	No protective effect of isoflavones or phytoestrogens against breast cancer.	Prospective collected dietary data, detailed validated FFQ,	Low isoflavone intake (0.37mg/day). Majority of population was postmenopausal. Only looks at diet of 1 year, not over lifetime.
2004 Maskarinec et al[32]	Experimental Intervention RCT Oahu,Hawaii	Premenopausal Intervention (n=109) 2 servings of soy/day. (~50mg isoflavones/day) Control (n=111)	Determine relationship between soy intake and mammographic densities	Mammograms densities at baseline and 2 years. Confirmed soy intake by urinary isoflavone excretions. Lifetime Isoflavone intake measured by FFQ	No changes in % of densities over 2-year period of intervention. Soy consumption early in life influences density.	RCT, High compliance self-selection of soy foods. Urinary biomarkers to test compliance. Low dropout, 2 year duration	Did not take cycle into account for mammograms. Other confounding variables not adjusted. FFQ not validated.

Discussion

The above studies present several conflicting viewpoints that need to be analyzed in order to clarify soy's potential role as a functional food for the prevention of breast cancer. There are many confounding variables for which it is difficult to adjust as presented below.

Bioavailability of Whole Foods vs. Supplements

It has been shown that there is a significant difference in urinary isoflavonoid recovery between fermented and non-fermented soybean products.[35] The Hutchins study[35] concluded that daidzein and genistein are significantly more bioavailable in a fermented soy product than an unfermented product, thus exerting more of an estrogenic effect. Asians typically use fermented soybean products (tempeh, miso, natto), while American's are adding large amount of non-fermented products such as soymilk, tofu, soy flour and soy supplements.[3] It is important to recognize that most epidemiologic studies that examined the relationship between soy intake and health outcomes involved Asian populations. Therefore these studies evaluated the intake of traditional soy foods[13,14,15,18,19,21,22] such as tofu or soy milk, which are derived from whole or dehulled soybeans. In contrast, few animal or human intervention studies have involved whole soy foods. Instead, soy concentrates, soy isolates, isolated isoflavone mixtures, supplements or pure genistein are generally used.[20,26, 32,41,36] Soy supplements have a tremendous range of isoflavone concentrations depending on how they are processed. The differences among products are due in part to the species of soybeans, the variance in growing and storage conditions, and the multitude of food processing techniques.

The scientific community must accurately understand the chemical composition of soy products and their synergistic interactions before making research conclusions.[37] Many commercial soy isoflavone supplements are made from the soy germ. Those soy isoflavone

supplements do not contain the same isoflavone profile as that obtained from the consumption of soy foods that are produced primarily from the whole or the dehulled soybean. This difference leads to markedly different plasma isoflavone profiles.[38] An analysis of 33 phytoestrogen supplements and extracts revealed considerable differences in the isoflavone content from that claimed by the manufacturers. Plasma concentrations of isoflavones demonstrate marked qualitative and quantitative differences depending on the type of supplement ingested.[38]

The most conclusive studies associating an inverse risk with intake are the epidemiological studies with FFQ about whole soy products, not supplements.[13,14,15,18,19,21,22] Thus, a major distinction usually occurs between the population-based association studies of soy food intake and health outcomes of most experimental research that is based on use of isolated fractions of the soybean. Interestingly, the Yamamoto study[22] showed an inverse relationship for miso and total calculated isoflavones, yet not for tofu, a non-fermented food. Why the association between intake of tofu and breast cancer is different than the association between intake of miso soup and breast cancer is unclear. One possibility involves the chemical structure of isoflavones and the method of cooking. Isoflavone glucoside is altered easily during extraction, processing and cooking. The hot aqueous extraction used to produce tofu results in the formation of β-glucoside conjugates[39]. Fermentation to produce miso and natto forms aglucones[40]. Although the total isoflavones in food are not affected under usual cooking conditions, high temperatures cause an increase in aglucones and a decrease in total isoflavones. Because aglucones are more potent and more rapidly absorbed than β-glucoside conjugates, fermented products such as miso soup and natto may have more anticarcinogenic effects than glucoside conjugates.[40]

Therefore, the Duncan study [26] concluding that soy protein powder did not alter plasma hormone levels may only be true for protein powder, not fermented soy foods such as tempeh, miso and natto. Similarly, the Maskarinec RCT study[32] used unfermented soy products and powder supplements and did not find an inverse relationship with mammographic densities. However, mammographic densities were influenced when they examined lifetime soy epidemiologic data. Yet RCT findings take precedence over epidemiologic findings in the research community, therefore this study bears weight. More studies similar to Maskarinec's need to be conducted using traditional fermented soy products rather than isolated compounds or improperly prepared foods.

Adolescent Exposure

Response to estrogens during puberty seems to provide the most convincing data for soy's protective effect. Two epidemiological studies discussed in this review showed a strong inverse correlation between adolescent intake and incidence.[19,21] Asian women who had consumed tofu during adolescence but not in adult life still had a lowered incidence of breast cancer compared with those who never consumed tofu or only did so in adult life. Perhaps this is where the real protective effect of soy comes into play, when developing mammary glands are exposed to the isoflavones. Although animal studies were not reviewed here, experimental studies on rats corroborate these findings. Treatment of rats given a combination of 17ß-estradiol and progesterone just before puberty led to a 90% reduction in mammary tumors induced by the carcinogen N-methyl-N-nitrosourea.[41] Another study showed that rats exposed to dietary levels of genistein after they are only a few days old have a lower incidence of adult mammary tumors by 50% when injected by a carcinogen, whereas genistein only administered during adult life has no affect on mammary tumors in rats.[36]

These studies indicate that isoflavones may affect important physiological and biochemical events that occur during puberty. A study of identical twins showed that the first twin to menstruate is 5 times as likely to get breast cancer than the twin who menstruates later[42]. Kumar[20] reported an increase in cycle length by administering genistein. Could it also be possible that adolescent soy intake provides the anti-estrogenic effect to delay menarche? Thus, dietary exposure to isoflavones at critical times in development strongly indicates an inverse relationship for the development of breast cancer later in life.

However, an association between adolescent soy intake and a reduction of risk does not mean we should load up young girls with soy. In fact, soy-infant formulas can present their own problems such as an increased risk of developing peanut allergies[43] in addition to other hormonal effects.[44]

Equol Producers

Equol is exclusively a product of intestinal bacterial metabolism of daidzein. It possesses approximately 0.2% of the estrogenic activity of 17*B*-estradiol, but is excreted in amounts 10 to 1,000 times higher than the endogenous estrogens, depending on the diet. However, equol is not produced in all healthy adults in response to a dietary challenge with soy or daidzein.[17] The Hutchin's[35] study, which was published 5 years before Duncan,[28] showed that equol urinary output does not change in some individuals (in this study of 17 men) even when given more isoflavones. Of course this impacts the conclusion of Ingram et al[16] in their Australian study that high equol intake correlates with high daidzein intake. About 30-50% of the adult population do not excrete equol in urine when challenged daily with soy foods, even when daidzein alone is administered. It is theorized that adding probiotics or prebiotics may increase equol production.[35] Perhaps it is equol that is the most important isoflavone in disease prevention, with soy's benefit

provided to those who are "equol excretors." Those who are not "equol excretors" may not benefit by adding soy to their diet. This theory correlates well with the traditional Asian diet. Since the diet contains many probiotics in the form of fermented foods (miso, pickles, etc.), perhaps a larger percentage of Asian populations are "equol excretors." Further research studies similar to Duncan's[28] needs to be carried out with a larger population, the administration of fermented soy products and supplementation of probiotics to determine if equol excretion will increase with the administration of beneficial bacteria.

Dosage Response

How much soy is needed to determine a quantifiable change? The Kumar study[20] administered 40mg of genistein per day and showed a significant change in menstrual length. Intake of soy among the Asian-American women in the Wu et al. Los Angeles study (12mg isoflavones/day)[21] appears comparable with that consumed by Chinese women in the Wu et al. Singapore study that found estrone decreases with increased isoflavone intake.[45] In the Singapore study the highest levels of isoflavone intake corresponded with the lowest plasma estrone levels. In the Los Angeles study the lowest risk was found in those who were high consumers during adolescents and as adults. Similarly, in the Shanghai[19] study a reduction in risk was observed between those in the lowest decile of soy intake and those not in the lowest decile of intake. However, intake was considerably lower than that in Shanghai (33 mg isoflavones/day). In the Yamamoto Japanese study[22] the lowest quartile of isoflavone intake (6.9 mg isoflavones/day) had the highest incidence rate. The significantly lower soy intake among non-Asians in the Horn-Ross study[30] (3.2 mg isoflavone/day) may explain, in part, the null association reported in this large study. Similarly in the Keinan-Boker Dutch study[31] the median intake was just 0.7mg/day, which is less than 1 serving of tofu per month. It would

appear that at these dosages there would not be enough isoflavones to induce a quantifiable response. However, the Linseisen German study[24] had less than 1mg isoflavone/day and found a protective effect for premenopausal ER+ tumors. It is surprising that a protective effect was found with this low a dosage.

In the Japanese[22] study the highest quartile of intake was 25.3mg isoflavones/day, and this study had the strongest inverse relationship to risk. In contrast, the Duncan[26] experimental study used varying dosages of isoflavones (64–128 mg) and found no changes in hormones. One might expect a certain amount of isoflavone, or a certain ratio of various isoflavones needed to induce an effect. Perhaps an individual plateau level may exist providing no additional benefit above a certain threshold of soy intake. Traditional soy foods have an isoflavone (mg) to protein (g) ratio of approximately 3.5:1. Therefore, consuming 15 g soy protein will result in consuming approximately 50 mg isoflavones.[2] However, there is insufficient data to suggest a portion size based on weight or BMI. These amounts of soy protein and isoflavones are roughly equivalent to two servings of traditional soy foods and may be the quantities needed to realize a potential benefit.

Lifestyle Differences

Soy foods, which are generally perceived as healthful, are not a traditional part of Western diets. Therefore, higher soy consumption may reflect an overall healthier lifestyle that is not easily identified or controlled in studies. Similarly, in Asian countries, soy intake may be a marker of a less sedentary lifestyle and more traditional diet—low fat, low in red meat, high in green tea. Therefore, it is inconclusive if soy or the other components of the traditional Asian diet and lifestyle are most influential in reducing risk.

Conclusion

Consumption of properly prepared fermented soy foods (miso, natto, tempeh) during adolescence appears to provide a chemoprotective effect later in life. Furthermore, sustained soy intake throughout life, both during adolescence and adulthood, may offer the most beneficial effects. However, there is no concrete evidence to suggest that soy or isoflavone consumption only during adult life is protective against breast cancer, although it may provide benefit to some women. The daily isoflavone dosage may factor into the protective effect as well with approximately 15g or two servings of traditional soy foods needed to offer any health benefit. Since intestinal bacteria produce equol adding fermented foods and probiotics to ones diet may realize better phytoestrogen benefits. Therefore, recommendations are for adults that enjoy soy to continue doing so at the suggested servings. For pre-pubescent and adolescent girls adding a couple of traditional soy food servings per day along with fermented foods and/or probiotics may reduce breast cancer risk later in life.

To understand the relationship between soy consumption, lifestyle differences, dosages, individuality and breast cancer, more research is necessary, particularly RCTs. The RCTs need to take into account "equol producers" to determine what, if any, dietary changes can increase equol production. Furthermore, research is needed on soy supplementation to evaluate its effectiveness and safety before it can be recommended as an addition to traditional soy foods.

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