SOY AND THE PREVENTION AND TREATMENT OF CHRONIC DISEASE:
A SHORT REVIEW OF THE LITERATURE

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INTRODUCTION

The soybean has long been embraced by Asian populations as a source of high quality protein from which can be made into a wide variety of foods. However, more recently, soyfoods have attracted widespread research attention in the West for their purported health benefits. Media coverage of this research has led to an improved consumer attitude toward soy and to skyrocketing soyfood sales, which have more than tripled in the United States within the past decade. In fact, a recent U.S. survey found that in 2000, 76% of consumers considered soy products healthy, up from 59% in 1998. Increasing numbers of consumers are incorporating soyfoods into their diet; in 2000, 27% of Americans reported using soy products at least once week. The entrance of mainstream food companies into the soyfood market has greatly increased consumer access to soyfoods such that currently about half of all soy products are now sold in large retail establishments rather than specialty stores.

Soybeans have a very different macronutrient composition from other legumes in that they are high in both protein and fat (approximately 40% on a caloric basis), contain relatively little carbohydrate and, partly for this reason, have a low glycemic index. Importantly, soybeans and fat-containing soyfoods are rich in both essential fatty acids, linoleic acid and α-linolenic acid. Although also high in several vitamin and minerals and an assortment of phytochemicals, the two components of soybeans thought to be primarily responsible for the hypothesized health benefits are the soy protein and isoflavones.

SOY PROTEIN QUALITY

When expressed on a caloric basis, the protein content of legumes is generally between 20% and 30% whereas soybeans are about 35% protein. Thus, whole soybeans and many traditional soyfoods, such as tofu (10 g/serving) and tempeh (14 g/serving), provide quite a bit of protein per serving. Furthermore, foods using soy isolates, concentrates, or flours as a base can provide as much as 15-20 g of soy protein per serving.

Soy protein typically has a protein digestibility corrected amino acid score (PDCAAS) above 0.9, which is similar to that of animal proteins. Assays based on the growth of laboratory rodents, such as the protein efficiency ratio, undervalue the quality of soy protein because rodents have a much higher requirement than humans for the sulfur amino acids (SAA), methionine and cysteine, which are the limiting amino acids in legume proteins such as soy. Formal recognition of the high quality of soy protein recently came in the form of a ruling by the U.S. Department of Agriculture allowing soy protein to replace 100% of animal protein in the National School Lunch Program. To qualify for complete substitution, a protein must have a PDCAAS that is at least 80% that of milk protein. Previously, substitution was limited to 30%.
RENAL FUNCTION

With the alarming rates of diabetes occurring throughout the world, the incidence of renal disease is expected to markedly increase since renal problems are a main complication of diabetes. The effects of dietary protein on renal function and disease have been the subject of much investigation. Because protein is metabolized by the kidneys, low-protein diets have generally been recommended for the prevention of kidney disease in high risk individuals and as a means of preventing further deterioration of the kidneys in those with existing disease. One comprehensive analysis of the relationship between protein intake and kidney function concluded that low-protein diets reduce the risk of death due to kidney failure in diabetic patients. However, patients have a very difficult time eating a low protein diet because the typical Western diet exceeds protein needs by about 50%. Fortunately, it appears that not all proteins have similar effects on the kidneys.

After a large protein meal, blood flow to the kidneys and kidney filtering increases as measured by the glomerular filtration rate (GFR). As early as 1990, researchers showed that in response to meat protein, blood flow increased about 20-30% whereas the same amount of soy protein has little effect on GFR or on the amount of blood flowing to the kidneys. Support for the benefits of soy also come from two recent studies that examined the impact of soy protein on kidney function in diabetic subjects. In one study from the University of Illinois, patients with diabetic nephropathy consumed in random order for eight weeks a cholesterol-lowering diet, but in which 50% of the total protein was derived from either casein (milk protein) or soy. Results showed that serum cholesterol and urinary protein excretion were reduced on the soy protein diet; the latter measure a direct indicator of improved kidney function. Similar results were reported from a study conducted by the University of Kentucky. This study involved 14 type I (insulin requiring) diabetic patients with an average age of 29 years. Over an eight-week period, GFR was significantly improved when subjects substituted 45-55 g of soy protein for animal protein in their diet. When subjects went back on their habitual diet, GFR was adversely affected. Also, as in the previous study, serum cholesterol levels were lowered. Lower serum cholesterol may be an additional advantage of soy protein since elevated cholesterol adversely affects renal function.

URINARY CALCIUM EXCRETION

Soy protein has been shown to decrease urinary calcium excretion when substituted for a similar amount of animal protein, such as meat and milk protein. The metabolism of the sulfur amino acids (SAA) in protein results in the production of hydrogen ions, which causes bone dissolution so that the buffering agents in bone can be utilized. Because soy protein has a relatively low SAA content and is more alkaline, soy protein has been shown to result in less urinary calcium excretion in comparison to the consumption of a similar amount of whey, and meat protein, and a casein-whey protein mix. Evidence suggests every gram of soy protein substituted for animal protein decreases urinary calcium excretion by 0.5-1.0 mg/day. Factors that increase calcium excretion will likely adversely affect bone health because net calcium absorption may be no more than 10%. Consequently, excretion of an extra 50 mg of calcium/day may require consuming as much as an additional 500 mg of calcium to compensate for this loss. As an aside, calcium bioavailability from soy is quite good and is similar to the absorption from dairy milk, despite being very high in phytate and oxalate, two components that inhibit calcium absorption. However, calcium
absorption from soymilk fortified with tricalcium phosphate is about 25% lower than from dairy milk.26

CHOLESTEROL REDUCTION

Research on the hypocholesterolemic effects of soy protein in humans dates back to the late 1960s27 but as recently as 1993, the American Heart Association (AHA) concluded that soy protein lowered serum cholesterol in animals but not humans.28 Their interpretation of the literature was criticized29 but it was not until 2000 that they reversed their position and recommended that subjects with elevated cholesterol incorporate soyfoods into their diet.30, 31 Formal recognition of the cholesterol-lowering properties of soy protein came one year earlier when in 1999, the U.S. Food and Drug Administration (FDA) approved a health claim for the cholesterol-lowering effects of soy protein and set 25 g/day as the target intake goal for cholesterol reduction.32 However, cross sectional studies and limited clinical research suggests fewer than 25 g soy protein is needed for cholesterol reduction.33-36 It is clear that the effects of soy protein are most pronounced in those with elevated serum cholesterol.37

ISOFLAVONES

Isoflavones are a subclass of a larger and more ubiquitous group of nutraceuticals called flavonoids. In comparison to most flavonoids however, isoflavones have a very limited distribution in the plant kingdom. The soybean is the only nutritionally relevant naturally occurring dietary source of isoflavones although isoflavones are now widely available in supplement form and are being used as food fortificants. The primary isoflavones in soyleans are genistein (4’  5, 7-trihydroxyisoflavone) and daidzein (4’, 7-dihydroxyisoflavone), and their respective fl-glycosides, genistin and daidzin. Typically, more genist(e)in exists in soybeans and soyfoods than daidz(e)in.38 There are also small amounts of a third isoflavone in soybeans, glycitein (7, 4’-dihydroxy-6-methoxyisoflavone) and its glycoside, glycitin. Isoflavones have a similar chemical structure to estrogen, so it is not surprising they bind to estrogen receptors and for this reason are considered to be phytoestrogens. Compared to 17β-estradiol however, isoflavones have a relatively low binding affinity for estrogen receptor alpha (ERβ) although their binding affinity for the recently discovered estrogen receptor, estrogen receptor beta (ERβ), is only slightly lower.39-41 But even the lower binding affinity for ERα suggests isoflavones hold the potential to exert physiological effects in vivo since serum isoflavone levels in people who eat soyfoods reach the low micromolar range, which is approximately 1,000 fold higher than endogenous estrogen levels.42

Of course, estrogen binding is only one factor that determines the effects of estrogen-receptor binding ligands in cells possessing estrogen receptors. The way in which the conformational change in the receptor that occurs in response to binding, which differs among ligands, affects the interaction between the receptor-ligand complex and coactivators and corepressors within cells, ultimately determines the overall effect.43 Consequently, each ligand needs to be evaluated individually when attempting to determine probable physiological effects. For this reason, it is more appropriate to refer to the estrogen-like properties of isoflavones rather than to their estrogenic properties, since isoflavones are different from estrogen. Furthermore, arguably, isoflavones are more accurately classified as selective estrogen receptor modulators (SERMs) such as the breast cancer drug tamoxifen and the osteoporosis drug raloxifene, rather than as phytoestrogens.43-45 Unlike estrogen, SERMs are tissue selective, having estrogen-like effects in some tissues.
but either no effects or antiestrogenic effects in other tissues.

The ideal SERM would seemingly have estrogen-like effects on the coronary vessels, skeletal system, and brain, but antiestrogenic effects on the breast and endometrium. Support for the SERM-like qualities of isoflavones include the observation that estrogen increases endometrial cell proliferation (and consequently endometrial cancer risk)\textsuperscript{46, 47} and serum triglyceride levels\textsuperscript{48} whereas isoflavone-rich soy protein\textsuperscript{49, 50} and isolated isoflavones\textsuperscript{51, 52} have no effect on endometrial cell proliferation and have either no effect or slightly decrease serum triglyceride levels.\textsuperscript{37, 53} The SERM-like qualities of isoflavones likely stems at least in part from their preferential binding to ER\textsubscript{\beta} and to their greater ability to trigger transcriptional activity when bound to ER\textsubscript{\beta} than to ER\textsubscript{\alpha}.\textsuperscript{54} However, isoflavones also have nonhormonal effects which may contribute to their physiological effects so even classifying isoflavones as SERMs is an incomplete characterization.\textsuperscript{55, 56}

**BREAST CANCER**

**Introduction**

Three early observations prompted research of the relationship between breast cancer risk and soy intake. One, the low breast cancer mortality rates among soyfood-consuming populations.\textsuperscript{57} Two, when added to a typical laboratory diet, soybeans inhibited the development of chemically induced mammary cancer.\textsuperscript{58} And three, the knowledge that weak estrogens can function as anti-estrogens.\textsuperscript{59} This latter finding is obviously important because greater lifelong exposure to estrogen is known to increase breast cancer risk. This is why earlier age at menarche, later age at menopause,\textsuperscript{60} and hormone replacement therapy,\textsuperscript{61} are considered to be risk factors for breast cancer.

Interestingly, the first animal study showing that genistein possessed antiestrogenic activity was published in 1966.\textsuperscript{62} There are multiple mechanisms by which isoflavones can exert antiestrogenic effects and several studies have shown that soy, and specifically isoflavones, can inhibit the effects of estrogen under certain experimental conditions.\textsuperscript{63} However, there are no definitive data that this is in fact the case in humans.\textsuperscript{64} In any event, as noted above soy also holds the potential to reduce cancer risk through non-hormonal mechanisms.

**Animal and Epidemiologic Studies**

Several studies have examined the effects of soy protein and isoflavones on the development of mammary cancer in adult animals. The data are somewhat inconsistent, but generally show that the addition of soy or isoflavones to a standard laboratory diet typically does not significantly inhibit tumor incidence (percentage of animals in the group with tumors) but in most cases, inhibits tumor multiplicity (number of tumors per animal) by 25%-50%.\textsuperscript{58, 65-68}

In any event, as noted above soy also holds the potential to reduce cancer risk through non-hormonal mechanisms.
soy does not contribute to the low breast cancer rates in soyfood-consuming countries. This is because a very intriguing body of evidence suggests consuming soyfoods early in life dramatically reduces the likelihood of developing breast cancer later in life.

**Early Soy Consumption**

There is considerable interest in the possible protective effects of early soy consumption on adult breast cancer risk. This hypothesis is particularly attractive because migration data from Japan\(^7\) and most recently Sweden,\(^7\)\(^2\),\(^7\)\(^3\) indicate early life events greatly influence the development of breast cancer in adults. That is, risk of breast cancer may largely depend upon influences that occur during the first 20 years of life. In support of this theory are the breast cancer rates among Japanese women who were exposed to radiation from the atomic explosion in 1945. Those women were ≤19 years of age experienced a 3.5 fold increased risk of developing breast cancer whereas those who were 20-39 years of age or ≤40 years of age experienced a 2.5 and 1.1 fold increased risk, respectively.\(^7\)\(^4\)

Research from the University of Alabama in the United States by Lamartiniere and colleagues has consistently shown genistein given orally or by injection for just brief periods during the perinatal and prepubertal periods reduces chemically induced rat mammary cancer by approximately 50\%.\(^7\)\(^5\) Furthermore, Lamartiniere et al have found that in their studies, genistein inhibits mammary cancer when given to adult animals only when also first given to rats when young. Recently, researchers from the University of Arkansas in the United States have confirmed the findings of Lamartiniere et al but in their research, soy protein, not genistein was fed to the rodents.\(^7\)\(^6\) It appears that soy stimulates mammary cell differentiation causing a decrease in the number of terminal end buds in the mammary glands.\(^7\)\(^5\) Terminal end buds are the anatomical structures within the mammary gland that are most sensitive to attack by carcinogens and thus most likely to be the site of tumor development. Consequently, reducing the number of terminal end buds should reduce cancer risk.

In support of the animal studies is a very important Chinese case-control study involving approximately 1500 cases and 1500 controls. In this study, women from Shanghai were asked about their soy consumption specifically during the teenage years (13-15 y). Shu et al found that those women who consumed on average approximately 11 g of soy protein per day during the teenage years were 50\% less likely to develop breast cancer as compared to women who rarely (<2 g soy protein/day) consumed soy as teenagers.\(^7\)\(^7\) Adult soy intake did not affect these results. This finding is quite impressive to be certain, especially considering that only approximately 300-400 ml soymilk or 100 g tofu each providing 11 g soy protein were reported consumed. Of course, additional epidemiologic confirmation is needed before definitive conclusions can be drawn.

**PROSTATE CANCER**

**Introduction**

The International Prostate Health Council, a European expert committee, recently concluded that isoflavones prevented latent prostate cancer from progressing to the more advanced forms of this disease.\(^7\)\(^8\) Thus, soy intake may help to explain why although Japanese men do develop prostate cancer, they rarely die from it.\(^5\)\(^7\),\(^7\)\(^9\) Preventing small prostate tumors often referred to as latent cancer, from progressing to the larger tumors which are capable of metastasizing and thus of becoming life-threatening, is the key to reducing prostate cancer mortality.

Since prostate cancer is a disease of older men (the average age of diagnosis is approximately
75 years) and prostate tumors are generally slow growing, if soy can even slightly slow the growth of prostate cancer and/or delay the onset of this disease, prostate cancer morbidity and mortality will be greatly decreased. Men will die with their cancer rather than of their cancer. Fortunately, since migration data suggest late life events influence prostate cancer development and progression, even older men who make the appropriate lifestyle changes should be able to significantly reduce their risk of dying of the disease.  

In support of the conclusion of International Prostate Health Council are intriguing in vitro, rodent, and human data. In vitro, genistein inhibits the growth of hormone-dependent and independent prostate cancer cells, and independent of growth effects, inhibits the metastatic potential of prostate cancer cells. Also, Geller et al have shown that in histoculture, genistein inhibits the growth of prostate tissue from humans with benign prostatic hyperplasia and prostate cancer.

Animal Studies
In severe combined immune-deficient mice implanted with androgen sensitive human prostate cancer cells, Zhou et al found that isolated isoflavones inhibited tumor growth in a dose-dependent manner. Also, Dalu et al found that genistein administration down-regulated epidermal growth factor receptor levels in the rat prostate despite rather low prostate genistein concentrations. This suggests, as noted by Zhou et al, that genistein may actually be more potent in vivo than in vitro, and therefore, that the rather high genistein concentrations required to inhibit the growth of prostate cancer cells in vitro may be relevant to humans consuming soy. Findings by Zhou et al agree with those of Mentor-Marcel et al who found that dietary genistein reduces the incidence of poorly differentiated prostatic adenocarcinoma in transgenic mice. Finally, Pollard et al have found in several studies that isoflavone-rich soy protein inhibits both spontaneously formed and chemically-induced prostate cancer in Lobund-Wistar rats in comparison to soy protein low in, or nearly devoid of, isoflavones.

Epidemiologic and Clinical Studies
The epidemiological data on soy intake and prostate cancer risk are limited, but worth noting in particular are the results from two prospective epidemiologic studies. In one, Japanese men in Hawaii who consumed tofu approximately once per day, were 65% less likely to develop prostate cancer in comparison to men eating tofu less than once per week. In the other study, Seventh-day Adventist men in California who consumed soymilk more than once daily were 70% less likely to develop prostate cancer as men who did not consume soy milk. The pronounced protective effects of soy consumption in these studies is striking, but in both studies the number of men who developed prostate cancer was relatively small. Still, the observation that such modest amounts of soy could substantially reduce risk of prostate cancer is encouraging.

Relatively little clinical work has been conducted but Morton et al did find that isoflavone levels in prostatic fluid are higher in men from soyfood-consuming countries than from countries where soy is not consumed, and, that isoflavones are concentrated in the prostatic fluid by about twofold relative to the serum. Thus, the prostate gland is exposed to high concentrations of isoflavones in men who eat soyfoods. Nevertheless, Urban et al failed to find that soy consumption lowered prostate specific antigen (PSA) levels in healthy men, but this was a short-term trial (six weeks), which involved men with relatively low PSA levels. PSA is a protein produced in the prostate but that is found in the blood and which is used as a marker of prostate cancer.
In contrast to the study by Urban et al, researchers from the Karmanos Cancer Institute in Detroit, Michigan (USA), recently reported that in a six-month study, 50-70% of the 40 patients with uncontrolled prostate cancer as determined by a rising PSA level, favorably responded (as judged by a PSA levels) to a daily supplement of 60-70 mg isoflavones. Although preliminary, these findings are extremely impressive for two reasons. First, beneficial effects were observed even though conventional treatment (surgery or radiation) failed to control the prostate cancer. These men would not be expected to respond to dietary treatment. Secondly, the amount of isoflavones given to these men was only modestly (see recommendation section below) higher than the amount recommended for the generally healthy adult population. Ordinarily, much higher amounts of any pharmacological or dietary agent are needed when attempting to treat, rather than just prevent, a disease.

CORONARY HEART DISEASE

Soy may have effects on coronary heart disease risk independent of the cholesterol lowering properties of soy protein. Preliminary data suggest that isoflavones, like estrogen, may exert cardioprotective effects via direct effects on coronary vessels and other physiological processes involved in the etiology of heart disease. For example, several studies in animals and humans indicate isoflavones enhance endothelial function, arterial relaxation, and arterial compliance (the ability of the artery to expand in response to pulse pressure).

In addition, several studies indicate soyfood consumption reduces the extent to which low density lipoprotein cholesterol is oxidized and based on comparisons between isoflavone-rich and isoflavone-poor soy protein, both human and animal studies suggest isoflavones are responsible for this effect. However, curiously, three studies failed to show that isolated isoflavones inhibit LDL-C oxidation. But since none of these studies directly compared the effects of isoflavones with soy, it is not possible to know whether this lack of effect was because isoflavones are not the agents responsible for the antioxidant effects of soy protein, or because the effects of soy protein-rich isoflavones on oxidation still remains to be determined. Isoflavone-rich soy protein may have other benefits as well, such as decreasing blood pressure.

OSTEOPOROSIS

The first study which specifically examined the effect of soy exposure on bone mineral density (BMD) in humans was not published until 1998. Since that publication, at least eight other studies have reported the effects of either soy or isolated isoflavones on BMD although several have been published only as abstracts. These studies included premenopausal, perimenopausal, and postmenopausal women. In addition, several other studies have examined the effect of soy or isoflavones on markers of bone resorption and/or formation.

Generally, the bone studies were of short duration (≤ 1 year), included small numbers of subjects, and few were intended to establish dose-response relationships. Studies lasting three years in duration are best for predicting likely long-term effects on bone health. This is an especially important point considering the recent failure of the synthetic isoflavone, ipriflavone, which had considerable experimental support in shorter-term studies, to affect BMD or fracture risk in a recently conducted three year trial.

Overall, the results of the clinical studies involving soy are encouraging although somewhat inconsistent. Beneficial effects
have been noted primarily only at the spine, which is known to be more responsive than the hip to estrogenic effects because it contains relatively more trabecular than cortical bone. Differences in the amounts of soy protein or isoflavones provided to the subjects in these studies do not appear to be responsible for the inconsistency.

Arguably, the most impressive results are those from a two-year study by Lydeking-Olsen et al involving postmenopausal women, in which improvements in spinal BMD were noted in response to the consumption of soymilk that provided approximately 80 mg isoflavones/d. Although another two-year study did not find differences among three groups of postmenopausal consuming soy protein (25 g) that provided <5 mg, 42 mg, or 58 mg isoflavones/d, only whole body BMD was determined. Furthermore, even women in the low isoflavone group lost relatively little bone over the course of this study, which suggests a possible beneficial effect of the protein. In agreement with the data from Lydeking-Olsen et al are the results from Potter et al who found that in older postmenopausal women, 40 g/d isolated soy protein (ISP) containing 90 mg isoflavones improved spinal BMD compared to the control group and to women consuming 40 g ISP containing 56 mg isoflavone. Similarly, Alekel et al found that in perimenopausal women 40 g ISP containing 80 mg isoflavones retarded spinal bone loss.

Very limited research involving isolated isoflavones has been conducted, but recently in a small study by Uesugi et al involving postmenopausal women the consumption of an isoflavone extract for four weeks that provided approximately 60 mg isoflavones/d was associated with a reduction in urinary excretion of bone resorption markers in comparison to the placebo group. Of course, women in both groups would have been consuming some soy through their typical dietary intake.

COGNITIVE FUNCTION

The publication of a prospective epidemiologic study involving Japanese men in Hawaii which found that tofu consumption was associated with impaired cognitive function was unexpected given the interest in the beneficial effects of estrogen in this regard. However, the Hawaiian results contrast with those from several animal studies and more importantly, with three recently conducted short-term clinical trials, all of which suggest soy and isoflavones have either no detrimental impact, or improve certain aspects of memory and cognitive function. In one study, young adult males and females were provided a high soy diet containing 100 mg isoflavones for 10 weeks, and in the other two studies which involved postmenopausal women, subjects were given isoflavones supplements for 12 weeks and six months. Despite the encouraging clinical data, the evidence is too preliminary to draw conclusions about the relationship between soy and cognition, especially when considering the effects of estrogen on cognitive function are unclear.

INTAKE RECOMMENDATIONS

As noted previously, in issuing a health claim for soy protein, the U.S. FDA set 25 g soy protein/day (no isoflavone recommendation was made) as the target intake goal for cholesterol reduction. However, this level of intake should not be used as a reference for the generally healthy adult population. The health claim is primarily intended for hypercholesterolemics. Furthermore, by almost any measure, 25 g soy protein/day is quite high; it is about half the recommended daily allowance for adult women and is approximately 21/2 times the average Japanese adult soy protein intake. On the basis of several different considerations, a
more appropriate intake recommendation for the generally healthy adult population is 15 g (range, 10-25 g) soy protein and 50 mg (aglycone weight) isoflavones (range, 30-100 mg)/day.

Traditional soyfoods have an isoflavone (mg): protein (mg) ratio of approximately 3.5:1, so consuming 15 g of soy protein will result in consuming approximately 50 mg isoflavones. These amounts of soy protein and isoflavones are provided by approximately two servings of traditional soyfoods and are likely to be efficacious for those diseases for which soy is proven to be beneficial. Furthermore, even traditional Western consumers can easily incorporate this much soy into their diet. Importantly, this recommendation is consistent with the general dietary advice to eat a varied diet and there is little reason to think these intake levels will be associated with any adverse effects.

REFERENCES


