Soy Intake and Risk of Chronic Disease.

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During the past 10 years the soybean has been the subject of intense investigation for its potential role in the prevention and even treatment of a variety of chronic diseases. In addition, there is much interest in soyfoods serving as alternatives to conventional hormone replacement therapy (HRT). One gauge by which to judge the scientific interest in soy is to consider the increase in U.S. government funding over the past decade. In 1990, only 9 studies that focused on soy in some capacity were funded; in 2002, that number had increased to 92.

Thus far, not surprisingly, large multi-year, multi-center randomized clinical trials involving soy that look at disease events or outcomes (eg., heart attacks, coronary deaths) have not been conducted. The complexity and expense of these types of trials dramatically limit the number of such studies that can be undertaken. Consequently, assessments of the health benefits of soy are based on a variety of other types of investigations, including animal and epidemiologic studies, and relatively short-term clinical trials that utilize indicators or markers of disease, such as serum cholesterol levels, bone mineral density, and serum prostate specific antigen levels.

These types of evidence allow one to evaluate support for a given hypothesis but do not permit definitive conclusions to be drawn. Dietary recommendations from well respected health organizations, such as the American Cancer Society and the American Heart Association, are primarily based on these kinds of data. The objective of this article is to summarize the relative level of scientific support that exists for protective effects of soy in four specific areas—coronary heart disease, osteoporosis, breast cancer and prostate cancer.

Coronary Heart Disease.

Coronary heart disease (CHD) remains the nation's number one killer. According to the American Heart Association, it is estimated that nearly 13,000,000 Americans have CHD, and that more than 500,000 Americans die from this disease each year.[1] Risk factors include age, obesity, smoking, high blood pressure, and high serum cholesterol levels.

The cholesterol-lowering effects of soy protein were first demonstrated in humans in 1967.[2] By 1995, nearly 40 clinical trials had been conducted but this body of research was largely overlooked until Anderson and colleagues published a meta-analysis in that year on the hypocholesterolemic effects of soy protein.[3] Trials included in this meta-analysis formed the bulk of the research upon which the U.S. Food and Drug Administration (FDA) based their decision in 1999 to award a health claim for soy protein.[4] One year later the American Heart Association endorsed the use of soyfoods for people with elevated cholesterol[5] and in 2002, a health claim for soy protein was approved in the United Kingdom. The hypocholesterolemic effects of soy protein are due to the protein itself, and not because soyfoods are low in saturated fat and cholesterol free.

The meta-analysis cited above found that the average reduction in low-density-lipoprotein cholesterol (LDL-C) was 12.9%[3] but new data suggest a more likely reduction is about 4-5%.[6]. The reduction in cholesterol in response to soy protein has clinically relevant public health implications as each 1% reduction in cholesterol reduces CHD risk by as much as 3-4%.[7-9] Furthermore, soy protein also appears to modestly raise high-density lipoprotein cholesterol levels (HDL-C).[6] The authors of a recent meta-analysis of the effects of soy protein on cholesterol estimated that modest reduction and increase in LDL-C and HDL-C respectively, would reduce CHD by 20%. Also, Jenkins and colleagues recently demonstrated that soy protein in combination with other dietary measures for lowering cholesterol such as phytosterols and soluble fiber can produce effects equal to cholesterol lowering drugs.[10]

The FDA concluded that the amount of soy protein needed for cholesterol reduction is 25 grams/day. By comparison, average Japanese soy protein intake is about 9-11 grams per day.[11, 12] The National Cholesterol Education Program acknowledged a beneficial role for soyfoods in replacing foods high in saturated fat and cholesterol, but did not make a specific recommendation for soy protein intake, citing uncertainty regarding the amount needed to reduce cholesterol levels. Messina recently suggested that fewer than 25 grams of soy protein/day may be needed for cholesterol reduction.[13]

In addition to the hypocholesterolemic effects of soy protein, several recent studies have found that soy protein is hypotensive.[14]

A recent review concluded that two-thirds of the randomized clinical trials showed reductions in blood pressure in response to soyfoods consumption, with the most impressive results being found in the better controlled trials and in people with hypertension. [15] While much more research is needed before definitive conclusions can be reached, the potential public health benefits should not be underestimated since lowering systolic blood pressure by 2-5 mm Hg may reduce stroke and CHD disease by 6 to 14% and 5 to 9%, respectively.[16]

In addition to soy protein, soybean isoflavones may have coronary benefits. Soybeans are essentially a unique dietary source of isoflavones, a group of diphenolic phytochemicals commonly referred to as phytoestrogens because of their weak estrogen-like effects.[17, 18] The two main isoflavones in soybeans are genistein and daidzein.[19] Considerable data suggest isoflavones are selective estrogen receptor modulators such as the drugs tamoxifen and raloxifene.[20, 21] That is, they exert estrogen-like effects in some tissues, but either no effects or antiestrogenic effects in others. However, isoflavones also have potentially important non-hormonal effects.[22]

Some data suggest that isoflavones have direct beneficial effects on blood vessels. This may prove to be as important as the cholesterol lowering effects of soy protein for reducing risk of CHD. Three studies found isolated isoflavones enhanced systemic arterial compliance (SAC).[23-25] SAC, which refers to the elasticity of the blood vessels, and can be non-invasively measured, is thought to be an independent predictor of CHD.[26] In addition to the possible effects of isoflavones on SAC, research suggests isoflavones may favorable effect endothelial function. For example, a recently conducted six-month trial conducted in Italy found that supplements of the genistein taken by postmenopausal women greatly enhanced flow mediated dilation (FMD), which is controlled by the endothelium, the single layer of cells on the inner side of blood vessels.[27] Impaired endothelial function is thought to contribute to atherosclerosis.[28, 29] Isoflavone-rich soy protein has also been found to enhance FMD.[30] However, other studies have not found soy protein or isoflavones to affect FMD.[15, 31]

Finally, some data suggest that isoflavone-rich soy protein inhibits LDL-cholesterol oxidation[32-34] and favorably affects other CHD risk factors[35, 36] but thus far studies have been inconsistent in this regard.

In support of the multiple coronary benefits of soy are results from a prospective study involving over 64,000 Chinese women.[37] In this study, women who consumed at least 11.19 grams soy protein per day were 86% less likely to experience a non-fatal myocardial infarction in comparison to women who consumed fewer than 4.5 grams per day.

Osteoporosis.

Rates of hip fracture are higher in developed countries than in non-developed countries, although the extent to which diet accounts for this difference is unclear.[38] Osteoporosis afflicts an estimated 25 million people in the United States and accounts for 1.5 million new fractures each year. It is estimated that osteoporosis will cost society an estimated $60 billion by the year 2020.[39, 40] On average, men develop fractures approximately 5 years later than women.[41] At menopause, women undergo an accelerated rate of bone loss that is most apparent over the subsequent decade and accounts for cancellous bone losses of 20-30% and cortical bone losses of 5-10%.[42] Osteoporosis risk factors include smoking, underweight, low intakes of vitamin D and calcium, and lack of exercise.[43, 44]

The low rates of hip fracture in soyfood-consuming countries prompted speculation that isoflavone-rich soy protein and isolated isoflavones may promote bone health through their estrogen-like effects. However, the non-hormonal effects of isoflavones may also be relevant. It should be noted though that while hip fracture rates in Asia are low relative to the West, several explanations unrelated to dietary intake have been proposed for this lower rate.[45] Furthermore, the rate of spinal fracture in Asia is similar to the West.[46] More relevant than the gross ecologic comparisons between Asian and non-Asian countries are epidemiologic studies within Asia that have found higher bone mineral density in women who consume above average amounts of soy compared to those who consume average amounts of soy or less.[46-49]

Quite a few studies published within the past few years have examined the effect of isolated isoflavones and isoflavone-rich soy protein on BMD using ovariectomized rodents, a model accepted by the US FDA for studying osteoporosis.[50] With few exceptions, these studies show that isoflavone exposure reduces bone loss.[46]

The first human trial that provided insight into the possible skeletal benefits of isoflavones was published by Potter et al in 1998.[51] In this six month study, postmenopausal women consumed 40 grams of protein either as non-fat dried milk, isolated soy protein (ISP) containing 56 mg isoflavones, or isolated soy protein containing 90 mg of isoflavones. Those consuming the 90 mg of isoflavones experienced an increase in spinal BMD whereas women consuming non-fat dried milk lost BMD. The effects in women consuming 56 mg isoflavones were intermediate between those of the other two groups. Similarly, St. Germain et al found in a nine month trial that isoflavone-rich ISP retarded spinal bone loss in perimenopausal women compared to those women fed either ISP devoid of isoflavones or whey protein.[52]

Research using isolated soy isoflavones is limited, but results suggest that they may be protective in postmenopausal[53, 54] but not premenopausal women.[55] One study found that over the course of one year, isolated genistein was actually as effective as conventional HRT at increasing BMD at the hip and spine in postmenopausal women.[56] Women in the placebo group lost BMD at both sites. These findings are important because they suggest that soy isoflavones may be an efficacious alternative to HRT for improving BMD.[57]

A two-year trial involving postmenopausal women found isoflavone-rich ISP improved spinal BMD compared to ISP low in isoflavones.[58] This trial, although it involved relatively few subjects, is important because it is sufficiently long to demonstrate the likely long-term changes in BMD.[59] Presently, several multi-year, multi-center, trials involving isoflavones are underway. While the estrogen-like effects of isoflavones provide a mechanism by which soy can promote bone health, non-hormonal effects of isoflavones may also play a role.

Of potential equal importance, are studies showing that soy protein when substituted for animal protein may have a beneficial effect on the skeletal system that is independent of isoflavones.

The relationship between dietary protein intake and bone health is complex. Protein increases loss of calcium in the urine and this was once thought to explain why higher dietary protein intakes, especially of animal protein, were associated with increased fracture risk in some populations.[60-62] However, several recent epidemiologic studies have found higher protein intakes to be protective for bone health.[63, 64] The inconsistent results may have a physiological basis.

Protein is an important structural component of bone; thus, adequate protein is needed for optimal bone health.[65] Also, some studies suggest that high quality proteins, such as soy, increase serum levels of insulin-like growth factor, a hormone produced by the liver which is thought to stimulate bone formation and/or inhibit bone resorption.[66] Conversely, as noted above, high protein intake may increase risk of osteoporosis by increasing urinary calcium excretion. This calciuric effect of protein is primarily attributed to its sulfur amino acid content. The acid produced from the metabolism of sulfur amino acids triggers bone dissolution so that the buffering agents in the skeleton can be utilized.[67, 68]

In theory, over time, this increased urinary calcium excretion could potentially lead to substantial bone loss. When expressed on mg/g protein basis, proteins differ markedly in their sulfur amino acid concentration. Since legume proteins have a lower concentration of sulfur amino acids than animal proteins, it is not surprising that several studies show that substituting soy protein for animal protein decreases urinary calcium excretion.[69-71]

Results from short term studies suggest replacing one gram animal protein with soy protein may decrease dietary calcium requirements by as much as 10 mg.[69-72] This is certainly not an insignificant effect given that roughly 30% of U.S. females consume less than 50% of the recommended dietary allowance.[73] However, there is some debate about the long term relevance of the hypercalciuric action of protein on bone health because of the potential for the body to adapt to these effects over time. In addition, the effects of protein may depend to some degree on the amount of calcium consumed. At low calcium intakes, protein may compromise bone health because of its hypercalciuric effects.

When calcium intake is adequate, the bone-building effects of protein may be more important. Finally, a recent unpublished study failed to show differences between meat protein and soy protein on calcium excretion.

Overall, the evidence suggests that both soy protein and soy isoflavones may play a favorable role in bone health. In addition, many soyfoods, such as calcium-set tofu and fortified soymilk are excellent sources of well-absorbed calcium. Nevertheless, long-term studies are needed in order to accurately assess the effects of isoflavone-rich soy protein on bone health.

Cancer.

Soy began to receive widespread attention for its possible anticancer effects in 1990, when the U.S. National Cancer Institute (NCI) first expressed interest in this area of research.[74] The NCI continues to be active in this field, and is currently funding phase I and phase II clinical trials on soy and soybean constituents.[75] In 1998, the Chemoprevention Branch of the NCI judged genistein, the main isoflavone in soybeans, to be a key chemopreventive agent.[76]

Most of the anticancer research has focused on breast and prostate cancer in large part because of the low mortality rates for these cancers in Asia,[77] but also because isoflavones have been shown to exert antiestrogenic effects under some experimental conditions.[78] This offers a possible mechanism for protection against hormone dependent cancers.[79] However, in vitro, genistein inhibits the growth of a wide range of cancer cells including those that are not hormone-dependent. This suggests that the anticancer effects of soy may not be limited to these two cancers.[22]

Breast Cancer.

Generally, animal studies indicate that the addition of soy or isoflavones to a standard laboratory diet decreases mammary tumor carcinogenesis by 25%-50%[80, 81] and tumor growth in rodents implanted with breast cancer cells.[82] However, in contrast, the epidemiologic data are rather unsupportive of the hypothesis that adult soy intake is protective against breast cancer, especially postmenopausal breast cancer.[83, 84]

Also, short-term clinical studies that have examined the impact of isoflavones on markers of breast cancer risk, such as serum hormone levels, breast tissue density, nipple aspirate fluid secretion, and pS2 levels, have produced mixed results.[85]

In contrast, there is evidence suggesting that soy intake early in life substantially reduces breast cancer risk later in life. Increasingly, early life events are recognized for having a profound influence on breast cancer risk.[86-88] One theory is that earlier differentiation of stem cells into mature breast cells protects against later breast cancer development since mature cells are less likely to be transformed into cancer cells.[89] Although still speculative, both animal and epidemiologic studies suggest that soy induces breast stem cell differentiation.

Researchers from the University of Alabama have shown that exposing rats to genistein through the diet or via injection for periods as brief as one week, during the perinatal or prepubertal periods reduces chemically induced mammary cancer by as much as 50% during adulthood.[90] Furthermore, these researchers have also shown that genistein inhibits mammary cancer when given to adult animals only when first given to these animals when young. Soy protein appears to also have a similar effect as isolated genistein.[91]

Two epidemiologic studies support these animal findings. One is a large Chinese case-control study involving approximately 1500 cases and 1500 controls.[92] Chinese women who consumed on average approximately 11 g of soy protein per day between the ages of 13 and 15 years were 50% less likely to develop breast cancer compared to Chinese women who consumed little soy during adolescence. Soy consumption during adulthood did not affect these results. In a U.S. study involving Asian Americans, Wu et al found that lifelong soy consumption, but not consumption during adulthood, was associated with a one third reduction in breast cancer risk.[93] Thus, the key to protection appears to be early soy intake.

Some concerns have been raised about the potential for isoflavones to stimulate the growth of estrogen-receptor positive cancer cells in women with breast cancer. Several organizations have issued cautionary statements. Certainly, this area of research is very controversial but a recent comprehensive review of this subject concluded that the data were insufficient to recommend that women with breast cancer abstain from consuming soy.[85]

Support for this conclusion comes from recent epidemiologic findings and the results from the Women's Health Initiative which suggest that it is the combination of estrogen and progesterone, not estrogen alone, that increases breast cancer risk.[57, 94] Soy does not possess progesterone activity.[95]

Prostate Cancer.

The American Cancer Society on their web site includes soyfoods consumption as one of seven steps to reduce prostate cancer risk. Also, the International Prostate Health Council Study Group concluded that isoflavones retard the progression of latent prostate cancer, the clinically irrelevant form of this disease, to the more advanced and life-threatening stages of prostate cancer.[96] Since prostate cancer is largely a disease of older men, and prostate tumors are generally slow growing, delaying tumor onset and/or slowing tumor growth even slightly can have a profound impact on prostate cancer mortality.

Most animal studies show that isoflavone-rich soy protein and isolated isoflavones significantly inhibit chemically induced prostate cancer and cancer initiated by the implantation of prostate cancer cells.[97-101] Few epidemiologic studies examining the impact of soy intake on prostate cancer risk have been conducted and most of these studies have major flaws in methodology because they were not designed primarily to observe the relationship of soy intake to prostate cancer risk.

Two frequently cited prospective studies, one involving Japanese men in Hawaii[102] and the other, Seventh-day Adventists in California,[103] did find that the consumption of approximately one to two servings of soy/day, tofu in the former and soymilk in the latter, was associated with a 65-70% reduction in the risk of developing prostate cancer. Similarly, in a Chinese case-control study, Lee et al recently found that the odd ratio for prostate cancer for men in the third tertile of tofu intake 0.51 (95% C.I., 0.28-0.95).[104] Certainly, the magnitude of these effects is striking, but in the prospective studies small numbers of men actually developed prostate cancer and none of the studies reported total soy intake.

Four studies have examined the impact of either soy or isoflavones on serum levels of prostate specific antigen (PSA), an indicator of prostate cancer. Three of the four studies found no effects but all were short-term studies.[105-107]

In contrast, are the results from a six month long pilot study involving 41 prostate cancer patients, all of whom had undergone conventional medical treatment without success.[108] After consuming 120 mg of isolated isoflavones/day (average Japanese intake is about 40 mg/day), the rate of increase in serum PSA levels in 50-70% of the men decreased significantly. The results are certainly encouraging considering this is a group of men in whom an effect could be least likely expected.

The mechanism by which soy might decrease prostate cancer risk is unclear. Several short-term clinical trials have examined the impact of soy on serum testosterone levels, but with only one exception no effect was observed.[109-111] In this one study, serum testosterone levels were decreased but only by about 6%; furthermore, the results were compared to the baseline values, not to the changes in the control group.[112] There are many potential non-hormonal mechanisms by which soy can reduce prostate cancer risk.[113, 114]

Conclusions.

Soyfoods are being intensely investigated for their potential roles in reducing the risk of several chronic diseases. Although like all foods the soybean contains several bioactive compounds, most focus has been on the physiological effects of isoflavones and soy protein. The soybean is essentially a unique natural dietary source of isoflavones. Evidence suggests both soy protein and isoflavones have coronary and skeletal benefits. Most evidence points toward isoflavones as the putative anticarcinogens in soyfoods.[115]

The FDA concluded that 25 g soy protein per day are needed for cholesterol reduction although there is evidence suggested fewer than 25 g may also be hypocholesterolemic.[13] However, evidence suggests that a reasonable recommendation for the generally healthy adult to gain the hypothesized health benefits of soy is 15 g soy protein per day and 50 mg isoflavones.[116] Approximately two servings of traditional soyfoods provide these amounts of protein and isoflavones. Since processing does cause some loss of isoflavones, Western soy protein products such as isolated soy protein generally have about 1-2 mg isoflavones per gram soy protein. Thus, to get 50 mg isoflavones from Western soyfoods may require consuming more than 15 g soy protein.

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