Health Effects of Soy: A Brief Review of the Literature

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Introduction

There is tremendous research interest in the health effects of soyfoods. Proposed benefits include reductions in the risk of several chronic diseases including breast cancer, osteoporosis, and heart disease. There is also evidence that soy alleviates hot flashes in menopausal women. Considerable data suggest that the soybean isoflavones are largely responsible for many of the proposed benefits of soyfoods.

Isoflavones, which are a subclass of flavonoids, are present in many different plants but the soybean is the only commonly consumed food to contain nutritionally relevant amounts of these diphenolic molecules. Each year, approximately 600 peer-reviewed medical and scientific papers are published on isoflavones. The two primary soybean isoflavones are genistein and daidzein.

Isoflavones are referred to as phytoestrogens because they have a chemical structure similar to the hormone estrogen, bind to estrogen receptors (ER), and exert some estrogen-like effects in cells.[1, 2] However, isoflavones affect many genes differently than estrogen as well as affecting some genes that do not respond to estrogen.[3] This is not surprising as it is well known that ER binding ligands often have very different biological effects. In fact, in vivo the estrogen-like effects of isoflavones are often not observed.[4] Furthermore, isoflavones, especially genistein, have a variety of non-hormonal properties that are especially relevant to cancer prevention and treatment.[5, 6] Although comparisons to estrogen are understandable, it is clear that conclusions about the biological effects of isoflavones and soyfoods should be based only on direct experimentation.

Health Effects

Cancer

The U.S. National Cancer Institute has been actively investigating the anticancer effects of soy since 1991.[7] Initial interest in soy stemmed in part from the low rates of breast and prostate cancer in Asia.[8, 9] Most focus continues to be on these two cancers.[10, 11] There are several putative anticarcinogens in soybeans and soyfoods[7] and although the constituent(s) responsible for the hypothesized anticancer effects of soy have not been definitely identified, unquestionably the soybean isoflavones have received the most attention.[6, 12]

Breast Cancer

The animal data are inconsistent but generally show that when added to a typical laboratory diet, soybeans, isoflavone-rich soy protein, or isolated isoflavones, inhibit mammary carcinogenesis by 25-50% in rodents injected with chemical carcinogens or cancer cells.[13, 14] The means by which cancer inhibition occurs has not been identified but most evidence suggests it occurs through a non-hormonal mechanism.[6] Isoflavones do exert anti-estrogenic effects under some conditions but this is unlikely to contribute to the inhibition of carcinogenesis in animals.[15, 16]

A recent statistical analysis of the epidemiologic literature found that high soy intake or high urinary isoflavone excretion was associated with a 20% reduction in risk although in the opinion of this author this estimate is overly optimistic.[17] Furthermore, the human

studies that have examined the effects of soyfoods or isoflavone supplements on markers of breast cancer risk have produced very mixed results.[18-23] Thus, overall, the evidence that adult soy intake reduces breast cancer risk is equivocal. In contrast, there are intriguing data indicating soy intake early in life is protective against breast cancer.

In support of this hypothesis are animal studies showing that brief genistein exposure when rodents are young markedly reduces chemically induced mammary cancer.[24] Also, a large Chinese epidemiologic study reported that high soy consumption during the adolescence was associated with a 50% reduction in adult breast cancer risk whereas adult intake did not impact these findings.[25] Similarly, a U.S. case-control study involving Asian Americans reported high soy consumption during both adolescence and adulthood was associated with a one-third reduction in risk whereas high adult intake alone was not protective.[26]

In regard to mechanism the evidence strongly suggests that early genistein exposure reduces mammary tumorigenesis by increasing mammary tissue differentiation thereby leading to a reduction in the number of terminal end buds (TEB) and an increase in the number of lobules.[27, 28] The TEBs are terminal ductal structures found primarily in young animals and contain many undifferentiated epithelial cells. As a result they are the structures most susceptible to chemical carcinogens.

Prostate Cancer

With few exceptions, animal studies show that isoflavones and isoflavone-rich soy protein inhibit prostate tumors induced by chemical carcinogens or via the implantation of prostate cancer cells.[11] Interestingly, tumor inhibition occurs despite relatively low prostate isoflavone concentrations.[29] Also, isoflavones in combination with tea extracts were shown to reduce tumor growth in mice implanted with androgen-sensitive prostate cancer cells more effectively than either agent alone.[30] Both soyfoods and tea are important parts of the Asian diet.

There has been limited epidemiologic investigation of the relationship between soy intake and prostate cancer risk.[11] However, these data are generally supportive of the hypothesis that soy is protective. A recent analysis of ten epidemiologic studies found that soy intake was associated with a one-third reduction in risk.[17] But the limitations of the data both in terms of quantity and quality should not be overlooked.

Furthermore, in healthy men several studies found neither soy nor isoflavones lowered prostate specific antigen levels, a marker of prostate cancer risk.[31-34] Interestingly, however, several pilot studies involving prostate cancer patients suggest isoflavones can slow the progression of this disease.[35-37] The mechanism by which soy may reduce prostate cancer risk has not been identified but soy does not appear to lower serum testosterone levels.[33, 38-44]

Osteoporosis

The estrogen-like effects of isoflavones in combination with work suggesting the synthetic isoflavone ipriflavone exerted skeletal benefits led to initial speculation that soyfoods help to maintain bone health and prevent osteoporosis.[45, 46] The low Asian hip fracture rates in comparison to the West further supported this speculation.[47]

In a recent review of the relevant literature, Messina et al concluded that although the data are inconsistent, overall, the findings from the clinical trials suggest that isoflavones reduce bone loss in postmenopausal women.[48] The 15 trials identified in this review that

examined the effects of isoflavones or soyfoods on bone loss were conducted in nine countries, included 10-75 subjects per group, although most involved ¡Ü30, and with one exception, were conducted ¡Ü1 year.[48]

Particularly noteworthy are the results from a one-year intervention trial conducted by Italian researchers because it included both a positive (hormone therapy, HT) and negative (placebo) control.[49] Bone gain at both the hip and spine in women taking genistein (54 mg/d) was essentially equivalent to the gain in women taking HT. The placebo group lost bone at both these sites. These findings, while not necessarily representative of the data overall, are clearly impressive given the definitive data that estrogen reduces bone loss and fracture risk when used by postmenopausal women.[50]

In contrast to this favorable finding however, are those from a recently published 1 y study which involved 175 Dutch women that failed to show statistically significant differences between women receiving the control protein casein or isoflavone-rich soy protein.[51] However, women in this study were on average 67 years of age, and both groups lost very little bone during the course of the study. It may be that to derive maximal benefits isoflavones need to be taken during the first ten years after cessation of menses when bone loss is most rapid.

The generally favorable findings from the clinical trial data are consistent with the epidemiologic data which suggest that among Asian women higher soy/isoflavone intake is associated with higher bone mineral density.[48] This having been said, it is likely that the low Asian hip fracture rates although often cited as evidence of the skeletal benefits of soyfoods are due to the lower fall rate and the longer hip axis length of Asians in comparison to non-Asians.[52]

Despite the relatively encouraging data, the small subject number and short duration of the soy and osteoporosis trials prevent definitive conclusions from being drawn.

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However, these data are sufficiently strong to recommend that women concerned about bone health include soyfoods in their diet and appear to have formed the basis for the recent decision of two U.S. government agencies to fund several multi-year, multicentered

clinical trials investigating the skeletal benefits of isoflavones.

Coronary Heart Disease (CHD)

Most research focus in regard to soy and CHD has been on the cholesterol-lowering effects of soy protein.[53] In 1999, the U.S. Food and Drug Administration approved a health claim for soy protein concluding that 25 g/d was sufficient to lower serum cholesterol and risk of CHD. In 2003, the United Kingdom adopted a similar position. However, there is evidence that fewer than 25 g/d is needed for cholesterol reduction[54] but also that the initial estimate (¡Ö13%) of the magnitude of the cholesterol-lowering effects of soy protein was too high. More recent analyses suggest the reduction in LDLcholesterol

is ¡Ö5 percent.[55]

This reduction is clinically relevant but obviously much less than the typical response to cholesterol-lowering medications such as statins. However, a recent analysis which found that soy protein slightly raised HDL-cholesterol levels concluded that as a result of the changes in lipid levels soy could reduce CHD risk by as much as 20 percent.[55]

Furthermore, there is evidence to suggest that soyfoods reduce CHD risk through

mechanisms unrelated to lipid levels. For example, soy protein may decrease blood pressure[56] and increase LDL-cholesterol particle size.[57]

Especially worthy of note are data suggesting isoflavones have independent coronary benefits. In several studies isoflavones have been shown to enhance endothelial function[58-60] and systemic arterial compliance;[61, 62] both of these measures are considered to be indicators of coronary health.[63, 64] In addition, isoflavones and their metabolites are antioxidants[65] and there are speculative data suggesting that isoflavones inhibit LDLoxidation[66, 67] and perhaps platelet aggregation.[68, 69]

Data noted above indicating soy exerts multiple coronary benefits are supported by findings from several epidemiologic studies in which soy consumption was associated with marked reductions in coronary events, including myocardial infarction[70, 71] and CHD mortality[72] although these benefits were noted primarily in women. Nevertheless, it is clear that the marked protection observed in these studies could not be due solely to the modest cholesterol lowering effects of soy protein.

Hot Flashes

Two primary observations led to speculation that isoflavones might alleviate hot flashes and other menopausal symptoms. These are the low incidence of such symptoms in Japan[73, 74] and the estrogen-like effects of isoflavones.[2] Since 1995 more than 20 controlled trials investigating the effects of isoflavone supplements, soyfoods, or isoflavone-rich soy protein have been conducted.[75-78] In 2003, Messina and Hughes analyzed the results of 19 hot flash trials involving soy or isoflavones.[79] They found that

much of the reason for the inconsistent findings was the variation in mean initial hot flash frequency among the studies. In a regression analysis of 13 (six trials were eliminated for methodological reasons) trials Messina and Hughes found that isoflavones and soy were effective but only among women with frequent hot flashes. More specifically, soy/isoflavones decreased hot flash frequency approximately 5% above the placebo/control response for each hot flash ¡Ý5/d.

Conversely however, a recent systematic review that included 25 trials of soyfoods, soybean isoflavones, and red clover, and involved 2,348 participants concluded these agents do not improve hot flushes or other menopausal symptoms.[80] In this review, the mean daily hot flush frequency was 7.1 and the mean study duration 17 weeks. At this point it is certainly not possible to conclude that isoflavones alleviate hot flashes but arguably, the evidence is sufficiently strong to recommend that women with frequent hot flashes try isoflavones for relief. This recommendation appears warranted not only because of the possible skeletal and coronary benefits of soyfoods and isoflavones but because there may be women, perhaps as a result of differences in isoflavone metabolism, in whom isoflavones may be particularly efficacious.[81]

Safety Concerns

Asians have been exposed to isoflavones via soyfoods for centuries as have western vegetarians for decades without suffering any apparent adverse effects. And, a recent comprehensive review of the literature concluded isoflavones as typically consumed in Asian diets are safe.[82] Furthermore, recent individual studies involving prostate cancer patients,[83] healthy men[84] and postmenopausal women[85] who were given isolated isoflavones at levels 10-30 fold higher than typical Japanese intake for one to two months

found little evidence of toxicity.

Nevertheless, as more information about the biological effects of isoflavones has become available safety concerns in two primary areas relevant to menopausal women have arisen. In part, these concerns are based on the estrogen-like effects of isoflavones. The paramount concern is that soyfoods and especially isolate isoflavones stimulate the growth of estrogen-receptor positive breast tumors. The strongest evidence in support of this concern comes from work showing that soy protein and isoflavones stimulate the growth of mammary tumors in *ovariectomized* mice implanted with estrogen-sensitive breast cancer cells.[86, 87] In contrast however, isoflavones have been shown to inhibit the growth of tumors in mice with *intact* ovaries implanted with these same types of cells.[88] Arguably, mice with intact ovaries better reflect the situation in women with breast cancer. This is because in this animal model as in pre- and postmenopausal women breast tumors are able to grow without chemical stimulation whereas in ovariectomized mice, tumors do not grow unless a source of estrogen is added. Also, a recent two-year intervention trial found that the daily consumption of soyfoods that provided approximately 50 mg isoflavones did not increase breast tissue density, which is an accepted marker of breast cancer risk.[89] Still, the issue of whether isoflavones or soyfoods are safe for breast cancer patients remains controversial.[13]

There is also concern that isoflavones adversely affect thyroid function. Investigators from the National Center for Toxicology Research (NCTR) in the United States have shown that a variety of flavonoids including isoflavones inhibit thyroid peroxidase (TPO) in vitro.[90, 91] Genistein and daidzein block TPO-catalyzed tyrosine iodination by acting as alternate substrates.[90] However, although Chang et al did find that TPO was partially inactivated in rats in response to dietary genistein exposure (in utero to 20 weeks of age) no effects on serum thyroid-stimulating hormone, thyroxine, and triiodothyronine levels, thyroid weight, and thyroid histopathology were noted.[92, 93] Thus, even the feeding of genistein to rats, which as a species are very sensitive to goitrogenic agents,[94] does not disrupt normal thyroid functioning. More importantly, numerous clinical trials have failed to show that isoflavone-rich soy protein or isoflavones have clinically relevant effects on thyroid function in healthy postmenopausal women (for review see reference).[95]

This being said, soyfoods but not necessarily isoflavones, may increase by about 25% the dose of synthetic thyroid hormone required by hypothyroid individuals but this effect appears to be due to soy inhibiting absorption of the medication and not to a direct action on the thyroid.[96] Even in hypothyroid patients however, there is no reason for isoflavone intake to be restricted.

Intake Recommendations

Older Japanese adults consume daily approximately 7 to 11 g soy protein and 30 to 50 mg isoflavones.[97] Arguably therefore, these amounts may serve as a basis for Western intake recommendations. However, epidemiologic studies demonstrating health benefits associated with soy consumption involve comparisons across intake categories and the largest reductions in risk are typically associated with intakes greater than the mean.[25, 70, 98-100] Thus, the mean isoflavone intake of 30-50 mg/d may underestimate optimal intake, which may be closer to 50-75 mg/d. These higher amounts are more consistent with the amounts used in clinical trials in which benefits in a variety of areas have been observed

and can be provided by approximately 2-3 servings (e.g., 250 ml soymilk, 100 g tofu, etc.) of traditional Asian soyfoods. Based on Asian intake a reasonable upper intake limit is 25 g/d soy protein and 100 mg/d isoflavones.

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