Gaining Insight into the Health Effects of Soy but a Long Way Still to Go: Commentary on the Fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease

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ABSTRACT Research into the health effects of soyfoods and soybean constituents has increased at a phenomenal pace over the past decade. This research includes a wide range of areas, such as cancer, coronary heart disease, osteoporosis, cognitive function, menopausal symptoms and renal function. Importantly, there are an increasing number of clinical studies being conducted in this field, which was quite evident from the findings presented at the Fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease, November 4–7, 2001, in San Diego, California. There is no doubt that progress in understanding the health effects of soy is being made, but much of the data are frustratingly inconsistent. For example, there were conflicting results presented at the symposium on the role of isoflavones in bone health. Similarly, presentations painted an unclear picture of the role of isoflavones in cholesterol reduction. The relatively short duration and small sample size of many of the human studies in this field likely contribute to the inconsistent results. Although there are some controversies regarding the safety of soy for certain subsets of the population, special sessions at the symposium on breast cancer and cognitive function did much to alleviate concerns that soy could have detrimental effects in these areas. Furthermore, published data and new research presented at this meeting suggest that the consumption of even 10 g (typical of Asian intake) of isoflavone-rich soy protein per day may be associated with health benefits. If this modest amount of soy protein were to be incorporated in the American diet, it would represent only ~15% of total U. S. protein intake. J. Nutr. 132: 547S–551S, 2002.

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The marked increase in soyfood consumption that has occurred over the past several years can be partially attributed to the many mainstream food companies, which have taken ownership of small soyfood companies and begun marketing their own soy products. The impetus behind these industry developments is the perception that consumers currently view and will continue to view soyfoods as healthy. In fact, a recent U. S. survey found that in 2000, 76% of consumers considered soy products healthy, up from 59% in 1998 (1).

Not surprisingly, consumer attitudes toward soy have improved as soy has gained recognition by several federal and private health agencies. In 1999 the Food and Drug Administration approved a health claim for the cholesterol-lowering properties of soy protein (2); a year later the American Heart Association recommended that patients with elevated cholesterol include soy protein foods in their diets (3,4). As a testament to the high quality of soy protein, in 2000 the U. S. Department of Agriculture (USDA)3 issued a ruling allowing soy protein (and other high-quality proteins) to completely replace animal protein in the Federal School Lunch Program (5); previous guidelines limited soy to 30% substitution. In 1999 the USDA (in conjunction with Iowa State University) also created an online database of the isoflavone content of foods (6,7). That same year, the National Institutes of Health convened a 3-d workshop on the health effects of isoflavones (8). Finally, in 2000 the increasing popularity of soyfoods led

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3 Abbreviations used: USDA, U. S. Department of Agriculture.
the USDA for the first time to specifically list calcium-fortified tofu and soymilk in the Dietary Guidelines as good sources of calcium (9).

Despite this impressive momentum and the ability of industry to influence consumer attitudes, whether the public will continue to view soy positively will depend primarily on future research findings. In this regard, the International Symposium on the Role of Soy in Preventing and Treating Chronic Disease, the fourth gathering of which was held this past November, represents the largest meeting of scientists convened specifically for presenting and discussing research on soyfoods and soybean constituents. Approximately 150 abstracts were presented at this meeting; these abstracts along with a few invited reviews form the proceedings in the pages that follow.

In this fourth symposium, there was a greater number of human studies than in previous symposia. This was encouraging. Unfortunately, many of these human studies were pilot studies or involved small sample sizes. As has been the case with the previous three symposia, isoflavones were the single component of soy about which there was the most research and discussion. Arguably, the most exciting data presented at the symposium involved a study in which isoflavone supplements seemed to beneficially affect prostate cancer patients. In this study presented by Omer Kucuk from the Karmanos Cancer Institute in Detroit, 41 patients with uncontrolled cancer, as shown by a rising serum prostate-specific antigen level, were given isoflavone supplements (~60 mg isoflavones, aglycone units) daily for 6 mo. Results indicated that more than one-half of the patients responded to treatment as judged by a significant decrease in the linear rise in prostate-specific antigen levels. These data add to the impressive case that is building for soy having a role in reducing prostate cancer risk (10–14).

Although isoflavones may have dominated discussion, at the fourth symposium there was relatively more dialogue than at past symposia about the biologically active nonisoflavone components of soy, especially the protein component. More specifically, there was debate about the extent to which peptides and amino acids derived from soy protein might lower cholesterol and blood pressure, reduce cancer risk, and favorably affect renal function.

Determining the extent to which the effects of soy protein or whole soyfoods are attributable to specific and individual soy components is a particularly important issue for several reasons, not the least of which is because isoflavone supplements are widely available and isoflavones are being used as food forticants. Unfortunately, few studies have directly compared the effects of isolated isoflavones with soy. Even if nutritionists prefer to recommend soyfoods to consumers, establishing similar short-term health effects of supplements and foods would allow investigators to justify using supplements for experimental purposes in human studies. This would make it easier for researchers to conduct large long-term studies and might even increase the pool of investigators working on isoflavones.

One of the areas for which the role of isoflavones relative to the protein has been hotly debated is cholesterol reduction. The Food and Drug Administration does not require that soy protein contain a certain level of isoflavones to qualify for the health claim. At the symposium Mary S. Anthony from Wake Forest University School of Medicine presented fascinating data showing that in female and male cynomolgus monkeys, isoflavone-rich soy (soy”) lowers cholesterol to a greater extent than soy protein from which the isoflavones have been removed by alcohol extraction (soy”) but that neither adding pure isoflavones nor the entire alcohol extract fully restored the hypcholesterolemic effects of soy”. This suggests that alcohol extraction alters the protein, some other component of soy, or the protein-isoavonione matrix in a way that disturbs the cholesterol-lowering properties. Further complicating interpretation of these results were data presented by Thomas B. Clarkson, also from the Wake Forest University School of Medicine, showing that in surgically postmenopausal cynomolgus monkeys although soy” lowers cholesterol more than soy”, serum isoflavone levels of animals fed soy” have a U-shaped response to cholesterol reduction, with higher levels (> 400 nmol/L) causing the soy-induced cholesterol reduction to decline. These results do conflict, however, with a recently published human study (15), although it should be noted that unlike in most humans, in cynomolgus monkeys, the principal circulating isoflavone is equal and not genistein and daidzein.

Certainly, there is almost no evidence to suggest that isoflavones alone affect serum lipid levels, although they may exert other antiatherogenic effects, as might soy protein. For example, a study presented at the symposium by J. Koudy Williams from the Wake Forest University School of Medicine found that genistein enhanced vascular reactivity in aged arteries from mice. Another study presented by Sheila G. West from Pennsylvania State University found that compared with casein, soy protein containing 60 mg isoflavones reduced diastolic blood pressure in response to a 5-min speech stressor or a cold pressor task in 27 healthy middle-aged men.

Perhaps the most striking illustrations of conflicting results were the findings from three studies presented at the symposium that focused on bone health. The area of bone research is a good example of the need for research directly comparing isoflavone supplements with soy protein or soyfoods. In one 2-y study, which was presented by Eva Lydeking-Olsen from the Institute for Optimum Nutrition in Denmark, 23 postmenopausal women given soy” (100 mg isoflavones/d) experienced a statistically significant increase in spinal bone mineral density compared with 22 women given soy”, although the combination of soy” and progesterone (22 women) produced the most spinal bone loss, despite progesterone administration by itself (22 women) increasing bone mineral density in this study. The findings showing that soy” favorably affects bone health compared with soy” agrees with some (16,17) but not all previously published data (18). However, a similarly designed study, also 2 y long, that was presented by Mara Z. Vitolins from Wake Forest School of Medicine, found no differences in spinal bone mineral density among 241 perimenopausal and postmenopausal women who received soy protein (25 g/d) that provided < 5, 42 or 58 mg isoflavones. One obvious difference between these two studies was that the highest dose of isoflavones used in the latter study was only 58 mg/d, considerably less than the 100 mg used in the former study, but this lower level still exceeds that typically consumed in Japan (19).

Consistent with the lack of isoflavone effect are the results from a short-term study in which the effects of protein supplements (40 g/d) on calcium metabolism were examined over 1-mo periods in 15 postmenopausal women. Treatments had no effect on calcium absorption, but soy protein reduced urinary calcium excretion compared with a casein-whey mixture; however, no differences were noted between soy” and soy”. The lower sulfur amino acid content of soy protein and the resulting reduction in acid ash have been suggested as explanations for these results and for previous observations showing reductions in urinary calcium excretion when soy protein is substituted for animal proteins, such as meat (20) and whey protein (21). All other factors being equal, these
animal protein with soy protein would have a desirable effect on bones. However, it is not possible to conclude that isoflavones exert bone-protective effects. This will undoubtedly remain the case until the results of several long-term studies currently planned or about to be undertaken are known. The disappointing results from the 3-y ipriflavone-osteoporosis trial, despite impressive supporting data, attest to the need for large long-term studies (22).

Two studies in a relatively underresearched area regarding soy and potential health benefits found that soy protein, when substituted for animal protein, favorably affected renal function in diabetic patients with diabetic nephropathy. These studies, one from the University of Illinois and the other from the University of Kentucky, are consistent with most but not all of the published research in this area (23). The renal effects of soy are not insignificant given the rising incidence of diabetes that is occurring in many parts of the world (24,25).

Longer-term studies are warranted. One matter that arose on several occasions during the symposium was the importance of determining the relevance of equol. Approximately one-third of subjects fed soy produce equol, a bacterial metabolite of the isoflavone daidzein (26–28). The ability to synthesize equol is determined by the composition and the enzymatic capability of the intestinal microflora. Some studies suggest that equol production may be advantageous but this is not known for certain. Equol production may simply be a marker for some other attribute that affects health (27). Interestingly, the request for applications issued by the Diet and Cancer Branch of the National Cancer Institute in 1991, when that agency first became interested in the anticancer effects of soy, called for research on isoflavone metabolism primarily to establish whether future trials should be limited to or exclude equol producers.

Two controversial areas related to the health effects of soy were addressed at the symposium: breast cancer and cognitive function. Despite some evidence suggesting that soy intake reduces the risk of developing breast cancer, concern has arisen that soy consumption could stimulate the growth of estrogen-dependent tumors. Genistein and soy protein isolate stimulate tumor growth in athymic ovariectomized mice that have been subcutaneously implanted with estrogen-dependent (MCF-7) breast cancer cells (29–31), but this model has been criticized on methodological grounds and the results from this model are opposite to those that occur in intact mice ortho- topically implanted with MCF-7 cells and exposed to genistein via injection (32) or the diet (J.-R. Zhou, Beth Israel Deaconess Medical Center, Boston, unpublished results, 2001). Still, two previously published studies did find that soy seems to exert weak estrogen-like effects on breast tissue in premenopausal women (33,34).

Symposium findings from two 1-y human studies provided some measure of reassurance that detrimental effects were unlikely. In one, presented by Gertraud Maskarinec from the Cancer Research Center of Hawaii, isoflavone (100 mg/d) supplements had no effect on breast tissue density in 34 premenopausal women, and in the other, presented by Charlotte Atkinson from MRC Biostatistics Unit in Cambridge, isoflavone (40 mg/d) supplements derived from red clover had no effect on breast tissue density in 175 perimenopausal and postmenopausal women overall. Furthermore, in post-hoc subgroup analysis of the latter study, when women were divided into age groups, breast tissue density was significantly decreased in those aged 56–65 y. Notably, these two studies were conducted in healthy women, not in breast cancer patients. Breast tissue density is regarded as an excellent marker of breast cancer risk; agents such as hormone replacement therapy that increase breast cancer risk also increase density (35), whereas agents that decrease risk, such as tamoxifen, also decrease density (36,37).

In regard to cognitive function, data from a prospective epidemiological study presented at the Third International Symposium in 1999 and published 1 y later showed that tofu consumption was associated with impaired cognitive function in Japanese men and women (38). Previously published animal studies do not support this finding (39–44) and two human studies presented at this symposium suggested that soy and isoflavones might beneficially affect cognitive function. In one study, presented by Rosanna Duffy from King’s College in London, 27 healthy young male and female subjects (average age: ~25 y) who consumed a high-soy diet that provided 100 mg isoflavones/d for 10 wk experienced an improvement in short-term and long-term memory and mental flexibility (45).

In the other study, presented by Donna Kritz-Silverstein from the University of California, San Diego, 53 postmenopausal women who were given a daily isoflavone supplement (110 mg) for 6 mo experienced an improvement in verbal memory in comparison with the placebo group. Although these studies do not directly refute the epidemiological study cited above because they did not examine the effect of long-term or lifetime soy consumption, they help to allay fears that soy has adverse effects on cognition.

The symposium findings left no doubt that soy contains a number of scientifically interesting constituents. In fairness, though, it is likely that many plant foods when investigated as intensely as soy has been would be found to contain multiple biologically active components. It is, therefore, important to compare the biological data on these soy components with the epidemiological and dietary intake data on which many of the soy-related hypotheses are based. This will provide more insight into the extent to which these biologically active components are pharmacologically or nutritionally related to soy.

Important strides in our understanding of soy have been made especially as a result of moving from rodents to human subjects and from epidemiological to human intervention studies. Unfortunately, this transition has not allowed many of the proposed hypotheses to be confirmed or rejected. Although much of the data continues to intrigue and even excite, research is still relatively limited and results are frustratingly inconsistent.

All scientists, but especially nutritionists, are familiar with having to deal with conflicting data, especially when those data relate to chronic disease. The etiology of all chronic disease is multifactorial and risk is likely affected by a lifetime of subtle influences. Add to this mix the effect of genetic heterogeneity, and it is easy to understand the snail’s pace at which understanding proceeds and why seemingly similarly designed studies often produce inconsistent findings. Demonstrating statistically significant changes in human studies involving dietary interventions is often hindered by the short duration and small sample sizes typical of many of the studies presented at this meeting.

It will be some time before definitive conclusions can be reached about the many hypothesized health effects of soy, but the available data do suggest that the American public would benefit if soy protein made a larger contribution to total U.S. dietary protein intake than it currently does. At the turn of the past century, the ratio of plant to animal protein was ~1:1; today’s ratio is ~1:2 (46). Replacing some of the animal protein in the U.S. diet with soy protein would help to restore the balance of animal to plant protein to a more favorable ratio. Consuming soyfoods in amounts that provide ~10 g/d of...
soy protein—which is similar to Asian intake (19.47–49) and consistent with the amount of soy associated with decreases in coronary heart disease (19.47), certain cancers (13.14,50,51) and improved bone health (52–55) in many epidemiological studies—holds the potential to exert health benefits while still only representing no > 10–15% of total U. S. protein intake (46).

Finally, although progress in understanding the effects of soy on chronic disease risk has been made, this is still a relatively new field; in fact, most researchers have been working in this area for < 5 y. However, a few investigators have been at it for quite a bit longer. At the third symposium, six such investigators were recognized. At the fourth symposium, three more researchers were recognized by their peers for their substantial contribution to this field, each having worked in this area for > 20 y. These researchers are John Erdman, Jr., from the University of Illinois; Patricia Murphy, from Iowa State University; and Masataro Nishimura, from Fugi Oil, in Japan.

**LITERATURE CITED**


