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# The Soy Connection

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HEALTH AND NUTRITION NEWS ABOUT SOY

## Symposium Highlights Significant Research On Soy And Human Health

By Mark Messina, Ph.D.

The Fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease was held this past November in San Diego, CA. The first such symposium was held in 1994. During the interval between the first and fourth symposia a phenomenal amount of research has been conducted on soyfoods and soybean constituents. The results of this research have largely been responsible for the marked rise in soyfood consumption that has occurred during this time period. Not surprisingly, findings presented at the Symposium raised more questions than they answered, but they also attest to the amount of progress that has been made in the field. This is best illustrated by the significant extent to which human research comprised the bulk of the information presented.

Over the past several years, in addition to direct research on soy, understanding of soy has been greatly aided by advances in the field of steroid biochemistry. Particularly important in this regard is the identification of a second estrogen receptor (estrogen receptor beta). This discovery has led to development of selective estrogen receptor modulators – compounds that have tissue selective (estrogenic) effects. There is considerable discussion about whether the soybean isoflavones fall into that category. Of course, soy is more than isoflavones and at this Symposium many speak-

ers focused on the protein component of soybeans and speculated that peptides resulting from the digestion of soy protein have important physiological effects.

One issue upon which there seemed to be general agreement was the need to better understand the health consequences of equol production. Equol is not present in soybeans but is produced by intestinal bacteria from the isoflavone daidzein. However, only about one-third of subjects actually produce equol. This varies according to the composition of the intestinal microflora. Some data suggests equol production is beneficial, but this is still speculative. Interestingly, when the National Cancer Institute first allocated funds for soybean research in 1991, part of the intended focus of this research was aimed at determining whether future clinical trials should include or exclude equol producers.

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### Proceedings To Be Published

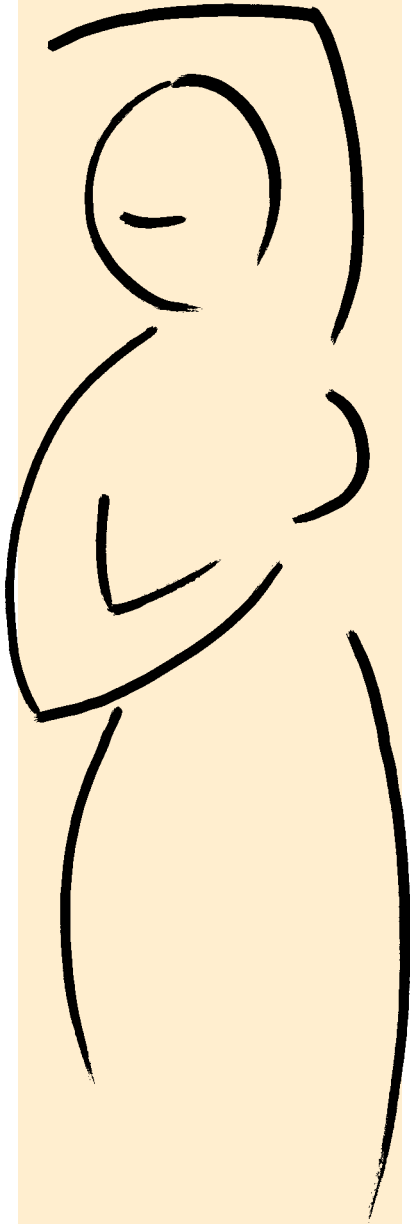
Proceedings from the Fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease are being published and will be available this spring.

The *Journal of Nutrition* will publish abstracts and a few of the papers presented at the Symposium. In addition, abstracts can be reviewed online at these Web sites:  
[www.soyfoods.com](http://www.soyfoods.com)  
[www.talksoy.com](http://www.talksoy.com)  
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★ ★ ★ ★ ★  
Special Report ★ ★ ★ ★ ★  
Highlights from the Fourth International Symposium  
on the Role of Soy in Preventing and  
Treating Chronic Disease  
Nov. 4-7, 2001 in San Diego, CA  
All articles in this issue were  
written by Mark Messina, Ph.D.,  
Symposium co-chairman.

## SUMMARY OF FINDINGS

### Cancer



**F**ocus on the anticancer effects of soy have centered primarily on breast and prostate cancer, largely because of the low rates of these hormone-dependent cancers in Asia. At the Symposium, there was a special session on breast cancer because of concerns that soy might actually stimulate estrogen-dependent breast tumors. Only one presentation focused on prostate cancer, but arguably, the results of this study were the most exciting of the entire Symposium.

Omer Kucuk from the Karmonas Cancer Institute at Wayne State University reported the results of a six-month study that examined the effect of daily isoflavone supplements (77 mg/day) on prostate specific antigen (PSA) levels in prostate cancer patients. There were three groups of patients 1) untreated 2) treated with local therapy and 3) treated with hormone therapy. Importantly, to be eligible for the study, patients had to have either a rising PSA level on three separate occasions or very elevated PSA levels, which indicates their cancer was uncontrolled. Three of four, 15 of 18, and six of nine patients responded to treatment in groups I, II, and III, respectively. The rate of rise in PSA levels decreased by 71 percent in II and 56 percent in group III, respectively. These results suggest that isoflavones may be useful in stabilizing prostate cancer in prostate cancer patients and by inference, that soy may be useful in reducing the risk of developing prostate cancer.

The breast cancer session included several interesting studies that did much to alleviate concerns that soy might be harmful to some women. One year-long study which was presented by Gertraud Maskarinec from the Cancer Research Center of Hawaii found that isoflavone supplements (76 mg/day) had no effect on breast tissue

density in premenopausal women. Charlotte Atkinson from the Institute of Public Health in Cambridge, in a similar study also conducted for one year but involving perimenopausal and postmenopausal women, found no effects of isoflavone supplements (40 mg/day) on breast density in the women overall, but when the subjects were divided into age groups, there was a statistically significant decrease in women aged 56-65 years of age.

The findings from these two studies are important because breast tissue density appears to be an excellent marker of breast cancer risk; agents such as hormone replacement therapy (HRT) that increase breast cancer risk increase density, whereas agents such as tamoxifen, that decrease breast cancer risk, decrease density. Thus, these two studies suggest soy does not exert an estrogen-like or proliferative effect on breast tissue in either pre- or postmenopausal women but may in fact favorably affect risk in older women.

Two animal studies offered interesting insights to the potential value of soy or isoflavones when used in combination with pharmaceutical agents. In one, Andreas Constantinou from the University of Illinois at Chicago reported that the combination of soy and tamoxifen inhibited the development of chemically induced mammary cancer in rats to a greater extent than tamoxifen by itself. In the other, J. Mark Cline from Wake Forest University found that although soy alone had no effect on chemically induced tumor incidence in either ovariectomized or intact (ovaries present) rats, soy reduced the incidence of mammary cancer in ovariectomized rats given estrogen from 50 percent to just 8 percent.

Finally, Pamela Horn-Ross from the Northern California Cancer Center

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## SUMMARY OF FINDINGS

# Coronary Heart Disease



The cholesterol-lowering effects of soy protein were officially recognized by the Food and Drug Administration in 1999 and a year later, by the American Heart Association. Much of the basis for the FDA health claim was the results of a meta-analysis by James Anderson and colleagues from the University of Kentucky published in 1995. At the Symposium, a poster presentation by Anderson included the results of a meta-analysis of eight studies conducted since the publication of the initial analysis. They found that the average decrease in LDL-cholesterol was 6.1 percent, a figure consistent with the original analysis. However, percent reduction was unrelated to baseline cholesterol values. This contrasts with the 1995 meta-analysis which found that higher initial cholesterol values were associated with greater percentage reductions in cholesterol.

One issue addressed at the Symposium dealt with the role of isoflavones in cholesterol reduction. Currently, the FDA does not specify that soy protein contain a certain level of isoflavones to qualify for the health claim but this issue continues to be a matter of scientific debate. To address this issue, Mary Anthony from Wake Forest University conducted a six-month study in monkeys in which animals were fed soy protein with (soy+) or without (soy-) isoflavones, soy- plus isolated (pure) isoflavones, or soy- plus the full alcohol extract (which includes isoflavones and other alcohol soluble components). As previously observed, the results showed that soy+ lowered cholesterol to a much greater extent than soy-. However, neither adding the pure isoflavones nor the alcohol isoflavone extract to soy- restored the hypocholesterolemic effects when compared to soy+. These results suggest that the isoflavone extraction itself disrupts the protein or some other component of soy, which thereby reduces the ability of soy protein to lower cholesterol.

To further complicate this matter, Thomas Clarkson, also from Wake Forest University, presented findings showing that in a 36-month study involving monkeys,

soy+ reduced cholesterol levels and atherosclerosis to a greater extent than soy-. But when monkeys fed soy+ were divided into low, intermediate, and high serum isoflavone levels, cholesterol reduction was inversely related to cholesterol lowering. That is, despite the general observation that soy+ was more effective than soy-, the higher the serum isoflavone levels, the less cholesterol was lowered. This paradoxical finding is hard to explain, but perhaps lower serum levels indicate more isoflavones are present in the intestinal cells, which could favorably impact cholesterol reduction somehow.

Independent of cholesterol reduction, evidence suggests that soy may lower coronary heart disease risk. At the Symposium, several studies addressed this topic. One study, presented by Shelia West from Pennsylvania University found that in healthy young men fed daily 30 g soy protein or casein for 5 weeks, soy protein led to a marked decrease in diastolic blood pressure (in comparison to casein) in response to 5 minute speech stressor or a cold pressor task. The response to the cold pressor task suggests that soy was decreasing vascular resistance. The biological basis for this effect is unknown, but it could be that the higher arginine content of soy protein compared to casein leads to an increase in nitric oxide production. ☺

The Soy Connection

On The Internet

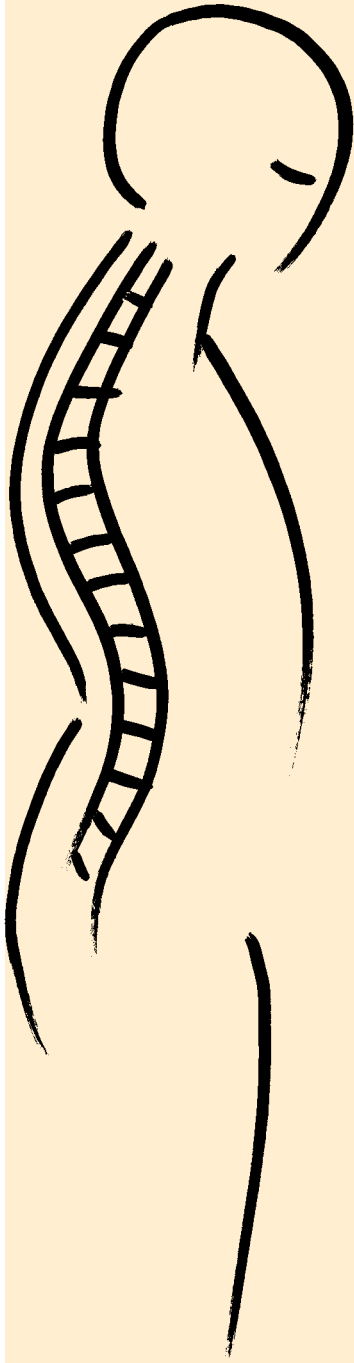
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## SUMMARY OF FINDINGS

# Osteoporosis



The relationship between soy intake and bone health has been vigorously investigated for the past six years, largely because of interest in the estrogen-like effects of isoflavones. However, the data are quite conflicting in this area. Some previously published studies have found isoflavone-rich soy products reduce spinal bone loss in peri- and postmenopausal women compared to isoflavone-poor soy products but several other studies have found no such effects. Unfortunately, results presented at this Symposium did little to clarify this issue.

Unarguably, Eva Lydeking-Olsen, from the Institute for Optimal Nutrition in Denmark presented the most encouraging results. Lydeking-Olsen found that postmenopausal women consuming a diet containing a high isoflavone soymilk (total isoflavone intake was approximately 100 mg/day) experienced an increase in spinal bone mineral density (BMD) whereas the spinal BMD of women consuming a soymilk low in isoflavones decreased. No such benefits were noted at the hip, however. The two-year duration of this study is particularly noteworthy. Somewhat confusing though, was the finding that although women given progesterone experienced an increase in spinal BMD, women given the high isoflavone soymilk and progesterone experienced the largest decrease in BMD.

In direct contrast to the results of Lydeking-Olsen were those from Mara Vitolins from Wake Forest University. In her two-year study, no differences in BMD at any bone site were noted among women consuming soy protein containing <5 mg isoflavones, 42 mg isoflavones, or 58 mg isoflavones/day. One possible explanation for the failure to see beneficial effects is that the highest dose of isoflavones was only 58 mg. Previously published studies that have reported bony benefits have

employed soy products that have provided at least 80 mg of isoflavones. However, 58 mg of isoflavones is not an insignificant amount and is actually higher than typically consumed in Asia. Furthermore, the results from a study described below, which were presented by Lisa Spence from Purdue University, also failed to support the benefits of isoflavones.

Spence compared the effects of soy protein with a casein-whey mixture on calcium metabolism in postmenopausal women. Calcium metabolism can be studied as an indicator of changes in bone density since for density to be increased there has to be an increase in calcium retention, which can be determined by carefully monitoring calcium absorption and urinary calcium excretion. For this study, subjects consumed each of three different diets, one containing 40 g of soy protein that provided 85 mg isoflavones, another that contained the same amount of soy protein but that was nearly devoid of isoflavones, and a third diet that contained 40 g of a casein-whey mixture. Each diet was consumed for one-month periods. Calcium absorption was not affected by treatment. In contrast, 24 hour urinary calcium excretion was markedly reduced (80 mg vs 121 mg) on the soy diet compared to the casein-whey diet, although no differences were noted between the low and high-isoflavone soy proteins. Thus, the decrease in calcium excretion was due to the protein, not the isoflavones. Previously published studies have suggested that the lower sulfur amino acid content of soy protein relative to animal protein leads to a decrease in calcium excretion.

Clearly, all other factors being similar, substituting soy protein for animal protein appears to favorably affect bone health although the precise role of isoflavones in this

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## SUMMARY OF FINDINGS

### *Cognitive Function*

Although animal studies suggest otherwise, an epidemiologic study published in 2000 led to concerns being raised about soy having an adverse effect on cognitive function. However, two studies presented at the Symposium not only help to alleviate any concerns, but raise the possibility that soy has beneficial effects on cognitive function. Certainly, the estrogen-like properties of isoflavones provide a biological basis for benefits. In one study presented by Rossana Duffy from King's College in London, healthy young men and women were fed either a high or low soy diet for 10 weeks. In comparison to the low soy diet, improvements in several measures of cognitive function were noted. For example, subjects were able to remember more of

the pictures they were shown and items of a story they were told. In support of these findings in younger people are those from a study presented by Donna Kritz-Silverstein from the University of California at San Diego, involving postmenopausal women. She found that in subjects provided isoflavones (110 mg/day) in pill form for six months, there was an improvement in several aspects of cognitive function, especially verbal memory. The improvement in verbal memory is interesting because this function is controlled by the hippocampus, a part of the brain that is rich in estrogen-receptor beta. Isoflavones bind with quite high affinity to this receptor. While these results are encouraging both studies should be considered preliminary. ☺

## SUMMARY OF FINDINGS

### *Renal Function*

For more than a decade studies have suggested that soy protein favorably affects renal function in comparison to animal proteins, although the reason for this is not known. Understanding the effects of soy protein on the kidneys is increasingly important since the unfortunate epidemic of diabetes underway in this country will undoubtedly lead to greater numbers of diabetic patients with renal failure. Two studies presented at the Symposium suggest soy protein has an important role in the diets of diabetic renal patients. In one study, presented by John Erdman from the University of Illinois, patients with diabetic nephropathy consumed in random order for eight weeks a Step-I type diet but in which 50 percent of the total

protein was derived from either casein or soy. Results showed that serum cholesterol and urinary albumin excretion was reduced on the soy protein diet, the latter measure an indicator of improved renal function. Similar results were presented by Tammy Stephenson from the University of Kentucky. She found that in 14 type I diabetics with an average age of 29 years, over an eight week period, glomerular filtration rate (GFR, ml/min/1.73 m<sup>2</sup>) was significantly decreased from 159 to 143 when subjects substituted 45-55 g of soy protein for animal protein in their diet. When subjects went back on their habitual diet, GFR increased to the baseline levels. As in the previous study, serum cholesterol levels were also reduced. ☺

### *Osteoporosis* (Continued from Page 4)

regard is yet to be determined. Recent epidemiologic studies do suggest that higher isoflavone

intake is associated with greater BMD. Differences in experimental designs, such as the age

of the women studied, likely contribute to the conflicting clinical data. ☺



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## Symposium Highlights Significant Research On Soy And Human Health *(Continued from Page 1)*

Sometimes it seems as though soy enthusiasts think that this bean and the foods made from it are a cure for all ailments. Of course this is not the case, but in the “emerging areas” session at the Symposium, data were presented on the potential health benefits of soy related to thyroid cancer, osteoarthritis, and skin care (you may have already noticed advertisements emphasizing the soy content of skin care products). In regard to the latter, it is interesting to note that historically among the Chinese, the topical application of soy has been recognized for its desirable effects on

the skin.

Johanna Lampe presented the work of Madeline Rice from the University of Washington, which consisted of a cross-sectional study of the relationship between soy intake and the incidence of osteoarthritis (OA) among a group of Japanese postmenopausal women residing in the Seattle area. Women who consumed the most soy were approximately 50 percent less likely to develop OA than women consuming the least soy. Although soy intake (women in the third tertile of intake consumed as few as 9 mg of

isoflavones per day) was fairly modest in this study and no dose-response was observed, there is a basis for thinking the estrogen-like effects of the soybean isoflavones might be relevant to preventing OA. There is an inverse relationship between bone mineral density and OA and the prevalence of OA is lower in women compared to men before age 50; whereas after 50, the prevalence is higher. Both these observations suggest estrogen is protective against OA, although surprisingly, estrogen use was associated with an increased risk in this study. ☹

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## Summary of Findings - Cancer *(Continued from Page 2)*

presented her results from a cross-sectional study of soy intake and thyroid cancer risk among Caucasian and Asian women residing in the San Francisco area. This cancer is of particular interest because some animal studies (human studies suggest otherwise) suggest soy is goitrogenic and

there may be a link between goiter and thyroid cancer. Although as pointed out by Horn-Ross, cruciferous vegetables are known to contain goitrogens (glucosinolates) and yet the intake of these vegetables is associated with a reduced risk of thyroid cancer. In the study by Horn-Ross, both total

soy consumption and the intake of individual soyfoods were protective against thyroid cancer. While these results should be considered preliminary, they certainly help to dispel any concerns that soy intake may increase thyroid cancer risk. ☹