9th International Soy Symposium
Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment
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Approximately 2000 soy related articles are published every year creating a great deal of interest among consumers, the scientific community, health professionals, as well as the media. A central meeting to discuss the most recent studies is the International Soy Symposium where exciting, original research is presented by eminent speakers. This year was the 9th such Symposium, hosted in Washington DC. This article provides a summary of the presentations of particular relevance to health professionals and their clinical practice, both in terms of soy's health benefits as well as its safety.

Soy and Cardiovascular Disease

The role of soy protein in reducing Low Density Lipoprotein cholesterol (LDLc) has been well established since the first meta-analysis of soy protein studies published in 1995. This analysis, conducted by *Dr James Anderson from the University of Kentucky*, determined that soy protein lowered LDLc by 13%, raised High Density Lipoprotein cholesterol (HDLc) by 3% and lowered Triglycerides (TG) by 10%. Eliminating studies which included patients with severe hypercholesterolemia resulted in an LDLc reduction of 8%. As a result of these significant findings, in 1999 the US Food and Drug Administration (FDA) approved a health claim for soy protein, '25 grams of soy protein a day, as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease'. More recent studies have shown more modest reductions in LDLc and therefore some have questioned the efficacy of soy protein. For this reason Dr Anderson has undertaken an updated meta-analysis, taking into account the more recent studies as well as analysing study quality. This new meta-analysis included 42 randomised, controlled trials (RCT) published since 1995. Studies using isoflavone supplements or that didn't use a non-soy protein control were excluded. These 42 studies included 20 parallel and 22 cross-over intervention studies lasting four to sixteen weeks. A rigorous grading system was used to determine the quality of the study. This system included criteria for the study duration to ensure sufficient time was allowed to achieve a maximum cholesterol lowering effect as well as a long enough period for washout. The twenty parallel trials had significantly higher mean quality scores than the 22 cross over trials. The median amount of soy protein consumed was 30g/ day (ranging between 11 to 62g/ day). Parallel intervention studies found soy protein reduced LDLc by 5.5%, whereas higher quality studies showed LDLc reductions of 6.2%. Cross-over studies resulted in LDLc reductions of 4.2%, with higher quality studies lowering LDL by 5%. Although all studies showed significant LDLc reductions, parallel studies had significantly greater reductions than cross-over. Furthermore, in parallel studies soy protein resulted in a 9.8% reduction in TG and a 3.2% increase in HDLc. Dr Anderson concluded by confirming that soy protein does have a direct effect on serum lipoproteins, specifically reducing LDLc by approximately 5%. Combining the positive effect on all lipid fractions, he predicted consuming 15 to 25g of soy protein a day could reduce the risk of Cardiovascular Disease (CVD) by approximately 20-24%.

The results of Dr Anderson's meta-analysis is in line with the meta-analysis submitted to the EFSA (European Food Safety Agency) for the health claim application 'soy and reduction of cholesterol'; the results of this meta-analysis were presented by *Dr Janice Harland from the UK*.

In addition to the direct (intrinsic) effect of soy protein on LDLc, it has been suggested that soy may also have an indirect (extrinsic) effect by displacing saturated fat and cholesterol in the diet with soy's favourable fat composition. Extensive evidence has shown that replacing saturated fat with unsaturated fat results in decreased LDLc. To quantify this effect, *Dr Berryman from Pennsylvania State University* presented data using a dietary modelling exercise where animal protein in a typical American's diet was substituted for soy protein. Substituting foods containing 13 to 57.8g of soy protein (e.g. from soy milk) for similar foods containing animal protein (e.g. cow's milk) resulted in a decrease in saturated fat (12.1g), cholesterol (113mg), and monounsaturated fat (3.0g) and an

increase in polyunsaturated fat (4.9g). Using an online predictive equation calculator (www.katancalculator.nl) these dietary changes translated into a 3.6% - 6% reduction in LDLc. This effect on LDL-c was dose responsive i.e. the more soy protein, the bigger the reduction.

As soy should be considered within the context of a diet, not as a single component, *Dr Jenkins from the University of Toronto* then went on to discuss the combined impact of both the direct and indirect effect of soy on LDLc reduction. The direct effect of soy protein was derived from an analysis using the soy studies included in the recent American Heart Association (AHA) publication. The conclusion of this analysis was that soy results in a 4.3% reduction in LDLc. Looking at the studies which included full dietary data, i.e. those that were better designed, resulted in a reduction of 5.2%. The indirect effect of soy was calculated using the previously reported dietary modelling and predictive calculations. This indirect affect resulted in a 3.6 to 6% reduction in LDL-c when soy foods were used to substitute foods containing animal protein. Therefore Dr Jenkins concluded by suggesting a LDL reduction of between 7.9%-10.3% could be expected due to the combined direct and indirect effect of soy protein foods. When soy is eaten as part of a diet in the real world this 10% reduction is of clinical significance.

Key Points and Dietary Recommendations

- Recent studies have found that between 15 to 25g of soy protein a day directly lowers LDLc by approximately 5%.
- Substituting foods containing animal protein with soy protein results in a further 3.6% to 6% reduction in LDLc.
- Soy protein also has beneficial effects on other serum lipoproteins such as Triglycerides and HDLc. The direct beneficial effect of soy protein on all serum lipoproteins may reduce the risk of CVD by 20% - 24%.
- Combining both the direct and indirect effect of soy can result in an overall LDLc reduction of approximately 10%.
- **Soyfoods can easily be incorporated into the daily diet during breakfast (e.g. using a soy drink on cereals) or as a snack (e.g. soy desserts and soy yoghurts) or at lunch (replacing meat with delicious soy meat alternatives)**

Soy and the Menopause – Hot Flushes

Soy naturally contains isoflavones which have structural similarities to estrogen and as such may exert weak estrogenic-like effects. Consequently a number of clinical studies have evaluated the effects of soy and isoflavones on post-menopausal hot flushes. However the results have been inconsistent. *Professor Kurzer from the University of Minnesota* presented the results of a recent systematic review and meta-analysis which showed conclusively that soy isoflavones significantly reduce both hot flush frequency and severity.

This meta-analysis included 16 randomised, controlled trials – 12 of which measured frequency and 8 measured severity of hot flushes. Trials varied in duration from between 1.5 months and 24 months and used doses of isoflavones ranging between 30 to 100mg/ day. The difference in hot flushes between the start and the end of the trials were calculated and compared between treatment and placebo groups. When the results were analysed according to frequency and severity, Professor Kurzer found the following:-

- Of the 12 studies measuring frequency, which lasted between 1.5 to 12 months, at a dose of 30-80mg isoflavones per day the frequency of hot flushes was reduced by 20.4%. Including the placebo effect (approximately a 29% reduction) resulted in an overall frequency reduction of about 50%.
- Of the 8 studies measuring severity, which lasted between 4 to 12 months, at a dose of 36 to 100mg isoflavones per day hot flush severity was reduced by 29.5%. Including the placebo effect (on average a 24% reduction) resulted in an overall severity reduction of 53.5%

In conclusion, Professor Kurzer suggested that although the effects of isoflavones on hot flushes were modest, the actual benefit a woman can expect, taking into account the placebo effect, is around 50%. Such an effect represents a significant improvement in the quality of life for women suffering from hot flushes.

Key Points and Dietary Recommendations

- 30 to 100mg of soy isoflavones a day can reduce hot flush frequency and severity by approximately 50%
- **Approximately 50mg of isoflavones can be found in 3 to 4 servings of soy food**

Soy and Breast Cancer

It's been suggested that soy isoflavones are natural selective estrogen receptor modulators (SERMs) that possess both estrogen-like and anti-estrogenic properties. As a result, according to *Dr Messina, Associate Professor at Loma Linda University*, controversy exists in the area of soy and breast cancer. On the one hand, there is evidence to suggest that eating soy early in life can protect girls from breast cancer later in life. On the other hand it has been questioned whether soy is safe to eat in women who are at risk of breast cancer and among breast cancer patients.

Dr Messina explained that the controversy is largely based on findings from studies using a particular animal model. In this model, athymic, ovariectomized mice are implanted with estrogen receptor (ER) positive breast cancer cells. Once breast tumours reach a certain size the animals are randomised to receive either a control or a test diet. Using this model it was found that diets containing genistein (a soy isoflavone) stimulated tumour growth. In contrast to genistein neither the soy isoflavone daidzein, nor its metabolite equol, stimulated tumour growth. On the basis of these findings, these investigators suggested that soy was unsafe for women at high risk of developing or who have breast cancer. They suggested that in a low estrogen environment, such as exists in post-menopausal women, genistein will act as an estrogen agonist and stimulate tumour growth. However Dr Messina noted that the athymic ovariectomized mouse model doesn't reflect the estrogenic environment in either pre or post-menopausal women. He explained that although serum levels of estrogen are much lower in post-menopausal women compared to pre-menopausal women, concentrations of breast tissue estrogen are actually similar in these two groups of women. The breast has the ability to concentrate estrogen relative to the blood and it is the localised estrogen that drives breast tumour growth. Therefore Dr Messina proposed that in post-menopausal women an estrogenic poor environment doesn't exist in relation to breast tissue. He concluded that the clinical decisions should be based on human studies and epidemiological data and not on animal studies.

Professor Setchell, from the Children's Hospital at Cincinnati, then went onto explain how animals metabolise isoflavones very differently to humans. This would also have implications for determining the safety of soy in breast cancer patients. Although genistein has been shown to stimulate breast cells in a specific animal model (athymic ovariectomized mice) this is opposite to findings in other animal models which found soy protein to be chemopreventive. Furthermore, a number of large epidemiological studies have found soy to be beneficial for women with breast cancer. A possible reason for this conflicting data could be that isoflavones are metabolised differently in humans compared to animals.

Isoflavones in the soy bean naturally occur mainly in the conjugated forms which are not bio-available. To be absorbed, they must first undergo hydrolysis in the gut which releases the aglycone (unconjugated) isoflavone, the biologically active form. Once absorbed, these isoflavones are metabolised by the liver and intestine to the less biologically active, conjugated, form. To determine the efficiency of different species at undertaking this type of metabolism, Professor Setchell presented results from a number of human and animal studies. In one human study, after 6 hours of

eating a single dose of soy foods (soy milk, soy nuts or tempeh), the amount of unconjugated isoflavones in the blood, as a percentage of overall isoflavones, was very small (less than 2%). Furthermore there was no significant effect on the type of food consumed. In other human studies the same observation was seen if soy milk was spread over the day, or if a purified isoflavone was given. In an infant study, 10 infants who were fed soy infant formula at 6 months for three and a half days also had very low levels of unconjugated isoflavones. This was the same when these same infants were fed a soy infant supplement at 3 years of age. In contrast, rodents fed a soy diet have a much higher percentage of bioactive, unconjugated isoflavones. In the case of athymic mice, the circulating unconjugated genistein levels are five times higher than humans. Professor Setchell concluded by saying that the metabolism of isoflavones to the less biologically active form in mice is less efficient than in humans. This conjugation is extremely efficient in humans, even in early life, and is not influenced by food processing. The higher circulating levels of unconjugated, biologically active isoflavones in mice may explain why some animal models show genistein stimulates tumour growth whereas in humans, the evidence suggests isoflavones will not have this effect.

The safety of soy foods in women at high risk for breast cancer, as well as breast cancer patients, has previously been questioned due to the potential estrogen-like effect of isoflavones. Results from both epidemiological and clinical studies provide reassurance in this area:-

1. *Professor Shu from the Vanderbilt Epidemiology Center, Vanderbilt University, USA* presented further data from the large, cohort study of breast cancer survivors, the Shanghai Breast Cancer Survival Study (SBCSS). This study included over 5000 breast cancer patients who were enrolled between 2002 and 2006 and followed through to June 2009. Detailed information was collected approximately 6 months after cancer diagnosis, including information on soy intake at this time, and re-assessed at 18, 36 and 60 months after diagnosis. Mortality and relapse was analysed according to soy food intake reported as quartiles (Quartile 1 = 5.31g or less of soy protein a day and quartile 4 = 15.31g or more soy protein a day). Soy food intake was associated with a more favourable outcome; women in the highest quartile for soy had a 33% lower risk for total mortality (Hazard Ratio 0.67) and a 34% lower risk for disease recurrence (Hazard Ratio 0.66) compared to the women in the lowest quartile of soy intake. Five year mortality rates were 13.1% for women in the lowest quartile group versus 9.2% in the highest. Five year recurrence rates were 13% for women in the lowest quartile compared to 8.9% in the highest. This inverse association was also seen among women with either ER-positive or ER-negative breast cancer, pre- and post-menopausal women, and in both users and non-users of tamoxifen.
2. As adjuvant endocrine therapy plays an important role in breast cancer treatment, *Dr Kang from the Cancer Hospital of Harbin Medical University in China* presented results confirming soy's safety in patients receiving anastrozole after surgery. Anastrozole is an aromatase inhibitor that is commonly used as adjuvant endocrine therapy for hormone sensitive breast cancer and is effective in preventing recurrence and prolonging survival.
   Dr Kang examined the associations between dietary soy isoflavones and breast cancer recurrence and survival among 524 post-operative breast cancer patients, recruited between 2002 and 2003, who were receiving adjuvant endocrine therapy. Dietary soy isoflavone intake was assessed using a validated food frequency questionnaire at baseline. Recurrence was reported as quartiles of soy isoflavones (Q1 = <15.2mg/day and Q4 = >42.3mg/ day). After an average follow-up period of 5.1 years, post-menopausal women in the highest quartile had a statistically significant reduced risk of recurrence (Hazard Ratio = 0.67). This inverse association was seen in patients with oestrogen receptor positive (ER) and progesterone receptor (PR) positive breast cancer and in those receiving anastrozole as adjuvant therapy. There was no effect of soy isoflavones on mortality rates in both pre and post-menopausal women.
3. *Professor Khan, from the Feinberg School of Medicine at Northwestern University, USA* concluded that isoflavone supplements do not adversely affect breast cells in healthy women at high risk of breast cancer. In this study 98 randomised women at high risk for breast cancer either took a supplement containing a mixture of soy isoflavones or a placebo for 6 months.

These women underwent a random fine needle aspiration prior to taking the supplement or placebo and then again at 6 months. At the end of the study there was no difference in cell proliferation (a marker for breast cancer risk) in breast aspirate between the 2 groups.Another possible indicator for breast cancer risk is nipple aspirate fluid (NAF) volume. Some data exists to suggest that women who produce NAF are at an increased risk. *Dr Maskarinec from the Cancer Research Center in Hawaii* examined the effect of soyfoods on the production of NAF. Ninety six women were selected on the basis of NAF production and randomised to a high or low soy diet for 6 months. After a 1 month washout period the participants crossed over to the other treatment for 6 months. The high soy diet consisted of 2 servings of soyfoods a day (soy milk, tofu or soy nuts) providing 50mg of isoflavones a day. The low soy diet consisted of the regular diet with less than 3 servings of soy foods a week. NAF samples were obtained at baseline and after 3 and 6 months of each period. Eighty two women completed both diets. At the end of the study period neither diet had an effect on NAF levels suggesting that soy doesn't influence NAF volume. Also the 2/16OT estrone ratio in urine was measured. In the high soy diet all women showed an increased ratio which indicates a beneficial effect.

How can this scientific information be put into context when advising breast cancer patients in clinical practice? This was summed up by Dr Hardy, a clinician, from the University of California. When discussing soy's safety with a patient, Dr Hardy will assess the patient's disease status, as well as risk factors for not only recurrence, but also risk factors for other diseases. She then identifies strategies to reduce modifiable risks, focusing on maintaining a healthy body weight as well as following a healthy plant based diet as advised by the American Cancer Society. Dr Hardy's specific message for soy is:

- Soy is a plant with multiple components which can have an impact on health
- The survival of breast cancer patients is very high and therefore there is a need to address other possible chronic health conditions. As such soy protein is indicated in heart health and may have a protective role in bone health
- Breast cancer treatment can also result in menopausal symptoms in younger women and there is evidence that soy may be beneficial in alleviating these
- Data indicates that 1 to 2 servings of whole soy foods are safe and as such can be recommended
- The data for benefits is accumulating but is not yet sufficient to actively promote soy to reduce breast cancer risk recurrence
- Many breast cancer patients have daughters. Inclusion of soy foods in a young girl's diet, and continuing this throughout life, can have a measurable benefit and are highly recommended.

Key Points and Dietary Recommendations

- Certain animal models to assess soy's safety in relation to breast cancer are inappropriate models to use
- Animals metabolise isoflavones differently to humans and this may be one reason why different results are seen in animal and human studies investigating the safety of soy in breast cancer
- Soy foods do not interfere with breast cancer treatments such as tamoxifen or anastrozole and may actually enhance their effects
- Soy isoflavones, at relatively high doses, do not adversely effect breast cells in healthy women at high risk of breast cancer
- **Consuming soy foods is safe for breast cancer patients at intakes of around 15g a day.**

Novel Uses for Soy

Soy is showing promise in certain health conditions and disease states. One such area is in the treatment of children suffering from mucopolysaccharidoses (MPS) using a soy isoflavone extract. MPS are inherited metabolic disorders which result in problems breaking down molecules called

glycosaminoglycans (GAGs) in lysosomes. These GAGs can build up over time in cells, connective tissue and the blood. As a result there is permanent progressive cellular damage which affects appearance, physical abilities, organ function, and often mental development. *Dr Wegrzyn from the University of Gdansk in Poland* explained how *in-vitro* studies have found that the soy isoflavone genistein reduces the rate of GAG synthesis in cells taken from MPS patients. This has been supported by animal studies and resulted in a pilot clinical study. Ten MPS patients were treated for 12 months with a genistein extract at a daily dose of 5mg/ Kg body weight. Urinary GAG levels were significantly reduced with no adverse effects. Furthermore hair morphology improved and patients achieved higher cognitive function scores (which are normally expected to decrease over time). A two year follow-up study has confirmed the efficacy of the treatment, although a higher dose of genistein maybe needed.

Soy isoflavones may also be beneficial in improving skin appearance. One factor that affects skin ageing is hormonal changes. A deficiency in estrogen during the menopause results in the loss of skin collagen which leads to wrinkles. As soy isoflavones have a similar structure to estrogen it has been suggested that these maybe helpful in maintaining skin collagen. *Dr Van den Berg from the Netherlands* described a recent double blind, placebo controlled, intervention study where 101 women, aged 45-65, were either given a soy isoflavone rich drink or a placebo for 14 weeks. At the end of the intervention, a statistically significant reduction in wrinkle depth in the test group was found compared to the placebo. Furthermore an increase in new collagen synthesis was seen in skin cells taken from biopsies in the test group compared to the placebo. Although consumers believe that topical products for the skin are more effective, these only deal with the upper skin. Dr Van den Berg believes nutrients such as soy isoflavones taken orally can get deeper into the dermis where they could have a greater effect on wrinkle production.

While most of the sports nutrition recovery products are dairy based, soy protein may offer additional benefits following the presentation given by *Professor Rasmussen from the University of Texas*. Consumption of high quality protein immediately following resistance training helps muscle protein synthesis and maximise recovery. Soy protein is a high quality protein that is comparable to animal proteins. It also contains greater quantities of specific amino acids that may offer added benefits to athletes. Further studies in this area are now needed.

A well balanced diet with additional protein is also necessary for a person to maintain (e.g. in the elderly) or to gain muscle mass. For the older person the intake of protein during breakfast, lunch and dinner is important and should be spread evenly among these meals as often the intake at breakfast is too low.

Conclusions

Data presented at the 9th International Symposium on the Role of Soy continues to support the health benefits of soy in a variety of well researched areas. Furthermore, potential new uses for soy and its isoflavones are starting to emerge. Despite this, consumption data presented at the Symposium suggests that the average intake of soy and isoflavones among the US population is low (on average 1.47mg of isoflavones a day). Health professionals are in an ideal position to communicate the benefits of soy, along with providing advice on how to practically include these foods into the diet. Although in the past there may have been concerns about soy's safety among certain groups, the new information presented on breast cancer adds to the growing evidence that soy foods are safe for breast cancer patients and high risk women.

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