A Review of Soy Isoflavones and Health: Implications for Health Educators

Danette L. Morgan, BS[1]; Linda L. Rankin, PhD, RD, FADA[1]

[1] Department of Health and Nutrition Sciences, Idaho State University

Corresponding author: Linda L. Rankin, Department of Health and Nutrition Sciences, Idaho State University, Pocatello, ID 83209; 208.236.3054 (phone), 208.236.4903 (fax), RANKLIND@ISU.EDU

. Received December 7; revised and approved, February 4, 1998.

Abstract

As an increasing amount of research has focused on the role of soyfoods in health promotion and disease prevention, Western consumers have begun to show an interest in the soybean. Much of the interest in soy has focused on the role of isoflavones. Soy is the main common food source of this phytochemical. Health educators need to become aware of the scope of the research on isoflavones in order to effectively educate consumers.

Introduction

The soybean has been cultivated in China for nearly 5,000 years, but the recent increase in research efforts into health benefits of soy has moved the soybean into the current spotlight. Soy is quickly becoming the "oatbran of the 90s." A study from Wake Forest University was reported in the popular press in November, 1996, with headlines such as "Doctors May Have Found a Cure for Hot Flashes" (Burke, 1996; "Doctors May," 1996). Suddenly soy has become a household word, and consumers are scrambling for information.

Interest in the possible health benefits associated with soy has evolved primarily from epidemiological data. Overall cancer mortality rates for the major cancers common in Western countries are low for populations consuming high levels of soy foods (Kennedy, 1995). For instance, the American breast cancer rate is 22.4 per 100,000, almost four times Japan's rate, and the American prostate cancer rate is 15.7 per 100,000, roughly four times the Japanese rate ("Soybeans," 1993).

One difference between the diets of Americans and Japanese is the consumption of soy. The average American consumes about three pounds of soy foods per year compared with 24 pounds per person per year in Japan ("Soy: The bean," 1994). Therefore, the interest in a possible relationship between soy and improved protection from various disease states has received increasing attention. In 1994 the First International Symposium on the Role of Soy in Preventing and Treating Chronic Disease was held in the United States. Research presented at this conference caused amplified interest in the topic. Within two years the Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease (SISS) was held in Belgium. At this gathering 60 speakers from 28 countries presented their research, more than double the number that took part in the 1994 meeting.

Much of the early research employed soybeans or soy protein in experiments. More recently researchers have begun to examine specific attributes of soy that may be protective in various disease states. The isoflavone component of soy, often referred to as phytoestrogens, have received the majority of the attention in the past two years.

The purpose of this review is to describe the latest medical findings on the health benefits of soy isoflavones.

Isoflavones

Because isoflavones are found almost exclusively in soybeans, much of the recent soy investigation has focused on the role of isoflavones as potentially protective agents. Genistein and diadzein, the most significant isoflavones, are heterocyclic phenols that have a structure similar to estrogen and are therefore often referred to as phytoestrogens. Biological activity of phytoestrogens has been examined and confirmed in many different animal species. Until recently, however, relatively few studies have involved humans (Kaldas & Hughe, 1989). There are several other classes of phytoestrogens including lignans, resorcylic acid lactones, and coumestans.

Soybeans and most soy foods contain approximately 1 to 3 mg of isoflavones per gram of protein. One serving of traditional soy foods provides about 25 to 40 mg of isoflavones (Messina, 1997c). A majority of the isoflavones occur in plants in the bound form as glycosides and are biologically inactive (Lampe, Martini, Kurzer, Adlercreutz, & Slavin, 1994). It is believed that colonic bacteria facilitate phytoestrogen activity in humans, a process that removes the sugar moiety, resulting in the active compounds (Price & Fenwick, 1985; Setchell &

Adlercreutz, 1988). Isoflavones have been found to possess approximately 1/1,000 the estrogen activity of the natural female sex hormone 17 β-estradiol (Messina & Messina, 1991). Due to this characteristic, the isoflavones are able to compete with estradiol for estrogen receptors (Messina, 1991).

Coronary Heart Disease

Much of the investigation into the role of isoflavones in preventing heart disease focuses on the role estrogen plays. Among 45 to 60 year old Americans, approximately three times as many men will have a heart attack as compared to women. However, by the age of 65, rates of coronary heart disease become more similar for men and women. The decrease in estrogen with the onset of menopause is thought to be the major factor accounting for this "catch-up" by women in regard to heart disease (Messina, 1997d).

Arising from the epidemiological studies showing significantly lower rates of heart disease in Asian countries, attention has focused on identifying the differences that may contribute to such disparities. For almost twenty years, small studies examining the role of soy protein in lowering cholesterol have been conducted on both humans and animals (Carroll, 1982; Patterson, 1996). Animal studies have established that consumption of soy protein in place of animal protein leads to a decrease in serum cholesterol concentration (Carroll, 1991).

Anderson, Johnstone, and Cook-Newell (1995) conducted a meta-analysis examining the effects of soy protein intake on serum lipid profiles. The study, which included analysis of 38 controlled clinical trials, found a reduction in serum total cholesterol ranging from a nonsignificant 3.3% in normocholesterolemic individuals (initial values below 200 mg per deciliter), a nonsignificant 4.4% in mild hypercholesterolemic individuals (initial values of 200 to 255 mg per deciliter), a significant 7.4% in moderate hypercholesterolemic individuals (initial values of 259 to 333 mg per deciliter), to a significant 19.6% in severely hypercholesterolemic individuals (above 335 mg per deciliter). Regression analysis indicated that changes in serum lipid concentrations were independent of changes in body weight, or dietary intake of total fat, saturated fat and cholesterol.

In those individuals already consuming a low-fat diet, consumption of soy-containing products further reduced low density lipoprotein (LDL) cholesterol levels. These results suggest that soy may serve as a beneficial addition to a traditional cholesterol-lowering diet by further reducing serum cholesterol (Anderson, Johnstone, & Cook-Newell, 1995). The researchers concluded that a daily consumption of 31 to 47 g of soy protein has the potential to significantly decrease serum and LDL cholesterol. In addition, the study showed a nonsignificant 2.4% increase in serum high-density lipoprotein (HDL) cholesterol (Anderson, Johnstone, & Cook-Newell, 1995).

Unfortunately, no definitive mechanism for the hypocholesterolemic effects from dietary intake of soy has been identified (Bakhit et al., 1994; Carroll, 1982). However, there are numerous studies currently underway to determine this link.

Cancer

Asians consume 20 to 50 times more soy per capita than Americans and have considerably lower incidences of and death rates from breast and prostate cancer (Lee et al., 1991; Severson, Nomura, Grove, & Stemmerman, 1989). The consumption of soybeans is suggested as a contributing factor to the low incidence of breast and prostate cancer in Japanese women and men (Messina, Persky, Setchell, & Barnes, 1994). These statistics have been cited as a primary stimulus for the increased research into soy's anti-cancer effects. In 1991 the National Cancer Institute allocated $3 million to study possible anticarcinogens in soybeans. Researchers have used a large percentage of the money to study breast, colon, prostate and endometrial cancers (Messina, 1997a).

In early animal studies examining the possible role of soy as an anticarcinogen, most researchers were not looking for a specific component of soy which might be protective. A review of 26 of these early studies shows that the majority of sources of soy administered were isolated soy protein (n=10) and whole soybeans (n=6), followed by miso (n=4), and genistein (n=4). Although a specific component of the soybean was not identified as protective, 17 of the 26 animal studies did find a protective effect associated with soy feeding in animals (Messina & Barnes, 1991). Because isoflavones are relatively unique to soy, the results of these studies led to increased attention and experimentation employing isoflavones (Messina & Barnes, 1991; Messina & Messina, 1991).

Additional interest was spurred by the finding that in the laboratory setting soy fractions with the isoflavone component removed by ethanol do not

exhibit the protective effect for breast cancer in rats that is seen with isoflavones present (Barnes, 1995; Barnes, Peterson, Grubbs, & Setchell, 1994). It is noted, however, that such a finding does not pinpoint the anti-cancer effect of isoflavones, since other soy components could have been removed with the ethanol solution. In the past two years, research on animals has focused on using genistein itself rather than soy or fractions of soy (Barnes, 1995).

More than 30 studies have shown that adding genistein at high concentrations to cancer cells in vitro leads to inhibition of growth by blocking cell proliferation (Barnes & Messina, 1993; Fotsis et al., 1995). In vitro, genistein was also found to inhibit angiogenesis. This is important considering that blood vessel development is necessary for tumors to increase in size and provide a port of exit for tumor cells to metastasize (Fotsis et al., 1995).

Breast Cancer

The examination of soy's role in prevention of breast cancer began in 1989 when it was reported that the addition of soybeans to the diets of laboratory rats decreased the rate of mammary tumors by approximately 40% (Barnes, Peterson, Grubbs, & Setchell, 1994; Messina & Barnes, 1991). In that study, the mammary tumor estrogen receptor numbers decreased in the soybean-consuming sample. Since it is known that isoflavones in soybeans exhibit weak estrogenic activity, it was suspected that these phytoestrogen compounds were competing with the female sex hormone 17 β--estradiol for estrogen receptor sites and functioning as antiestrogens (Messina & Barnes, 1991). This may occur as the isoflavones bind to the estrogen receptor without creating a substantial estrogen response. In this capacity they keep the more potent estrogenic agonists from binding to the sites (Adlercreutz, 1990; Folman & Pope, 1969; Messina & Messina, 1991). If this mechanism is occurring, it may be that the isoflavones are contributing to a reduction in the cancers which are thought to be estrogen dependent (endometrial, ovarian and breast) (Henderson, Ross, Pike, & Casagrande, 1982). It is interesting to note that the commonly used breast cancer drug, Tamoxifen, is believed to function in this manner (Messina & Barnes, 1991).

Subsequent studies have shown that the functional estrogen receptor system is not necessary for growth inhibition by genistein (Barnes, 1995; Peterson & Barnes, 1991) and further, that genistein inhibits growth cell lines of receptor-negative breast cancer cells (Herman et al., 1995; Peterson & Barnes, 1991). These data suggest that genistein does not inhibit cell growth via the classical anti-estrogenic mechanism.

Uterine Cancer

Women in Japan and China have historically had lower rates of endometrial cancer than women in the United States. A study of more than 800 women in Hawaii found a reduced risk of endometrial cancer for those who ate low-fat, high-fiber diets rich in legumes (especially soybeans), whole grain foods, fruits, and vegetables. Women who ate the highest amounts of foods rich in phytoestrogens, had a 54 percent reduction in endometrial cancer risk, compared with those who consumed the least amounts (Goodman et al., 1997).

Prostate and Colon Cancer

As with breast cancer, much interest in the role of soy in possible prevention of prostate and colon cancer has evolved from epidemiological data. Although the same incidence of small, noninfiltrative or latent prostatic carcinomas exists in Western and Asian countries, the mortality rate in most Asian countries is low. It has been suggested that this difference could be attributed to the diets of the two groups. The Asian diet is high in isoflavones, which have been shown to inhibit the growth of latent cancers (Herman et al., 1995).

The occurrence of prostate and colon cancers in Finland is much lower than in the United States, although this is an interesting observation considering the dietary habits of men in these population groups are similar. Both Finnish and American men tend to consume diets high in fat (more than 30% calories from fat) (Teppo et al., 1980). It has been speculated that the difference in cancer rates may be due to the Finnish consumption of large quantities of whole-grain products, especially rye bread, which contains lignans. The lignans, although a weaker phytoestrogen than isoflavones, may exhibit the same protective effect that is speculated to be occurring from isoflavones in Asian populations (Herman et al., 1995).

Epidemiological data also reveal that the same lower rate of mortality for these cancers is found in vegetarian Seventh Day Adventist men. The level of soy intake is significantly lower in the Adventist population than the Asians. However, compared to the average American male, Adventist men do consume significantly higher levels of isoflavone-containing

beans, lentils and peas (Mills, Beeson, Phillips, & Fraser, 1989).

Results from the above-mentioned epidemiological data lead one to wonder if it is indeed the isoflavones which are protective. Could it be some other similarity between the Adventist, Asian, and Finnish diets such as a high fruit, vegetable and whole-grain intake that is protective? Sparked by these and other epidemiological comparisons, studies are underway to try and determine the answer to this question.

Menopause

Two major factors have led to an increased examination of the possible role of phytoestrogens in the alleviation of menopausal symptoms. These include data from cross cultural comparisons and the characteristic properties of the phytoestrogens. Epidemiological studies show that in countries such as Asia, where the intake of soy products is high, a low incidence of menopausal symptoms is reported (Boulet, Oddens, Lehert, Vemer, & Visser, 1994). In the United States, the most common menopausal complaint is hot flashes which affects from 58 to 93% of women who have decreasing estrogen levels. Due to the disparity between Asian and American women's reporting of this symptom, researchers began to look at differences in the diets of the two population groups (Kronenberg & Wade, 1997).

As previously noted, the structure of phytoestrogens is similar to that of endogenous estrogen. Therefore, researchers have been examining whether phytoestrogens could play a role in alleviating menopausal symptoms (Lampe, Martini, Kurzer, Adlercreutz, & Slavin, 1994; Price & Fenwick, 1985). Only a few studies have examined this relationship. Adlercreutz, Hamalainen, Gorbach, & Goldin (1992) reported that urinary excretion of phytoestrogens in Japanese women was 20 to 30 times higher than in Finnish women. It was hypothesized that isoflavones might be the reason Japanese women very infrequently report hot flash symptoms. In 1990 Wilcox, Wahlquist, Burger, and Medley found a marked increase in vaginal cytology maturation index, an indicator of estrogenicity, in subjects who consumed a diet high soy foods. Additionally, Murkies et al. (1995) found that adding 45 g of soy flour to the diet of post menopausal women significantly decreased the reporting of hot flashes by 40%. Interestingly, in the same trial it was found that consuming 45 g of wheat flour significantly decreased the rate of hot flashes by 25%.

At the SISS meeting in September of 1996, four studies were presented on soy and menopause. From released abstracts, one of the studies showed that consumption of a soy protein drink significantly decreased hot flash rate (Harding et al., 1996). Three of the studies did not show any significant effects of soy on hot flash rate (Burke, 1996; Dalais et al., 1996; Woods, Senie, & Kronenberg, 1996). However, Burke (1996) noted that soy modestly reduced the severity of menopausal symptoms and Dalais et al. (1996) found significant increase in vaginal cytology maturation index with consumption of bread containing soy. A more recent study by Brezinski et al. (1997) found that a significant decrease in the hot flash rate along with decreased vaginal dryness occurred with consumption of a diet containing products such as tofu, miso, linseed, and soy beverages.

Without a large body of literature to examine, a definite effect of soy intake on the hot flash rate is hard to determine. Some women may be more sensitive to soy than others. Design of the studies has also been noted as a possible factor in the inconclusive findings. The placebo effect is a significant research challenge. For example, Coope, Thomson & Poller (1975), examining hormone replacement therapy and reduction in the hot flash rate, found a 90% reduction in reported hot flash occurrence in the treatment group and a 62% reduction in the women who were taking the placebo, after three months. It has been suggested that long-term research be conducted with larger numbers of subjects, and that studies be dose ranging (Dalais, 1997).

Considering all the unanswered questions regarding the possible role of soy and menopausal symptom relief, it is interesting to note the number of products currently on the market claiming that soy, or components of soy, can alleviate menopausal symptoms. The interest in soy as an alternative to hormone replacement therapy may exist for a number of reasons. First, the number of women entering menopause is increasing. Secondly, women are becoming increasingly concerned about the side effects of hormone replacement therapy. Nearly one-third of the prescriptions for hormone replacement therapy drugs go unfilled, while 40% of older women indicate they have decided not to take hormone replacement drugs due to concern over side effects (Messina, 1997b).

Bone Health

With the decrease in circulating levels of estrogen after menopause, bone health becomes a concern. In fact, women lose three to five percent of their bone mass each year in the five years after the onset of menopause (Cauley, 1997). Genistein and daidzein, the primary isoflavones in soy, exhibit estrogenic activity and have therefore led to increased interest in the role of soy in the prevention of osteoporosis (Erdman & Potter, 1997). Also, there is a similarity in chemical structure between the soy isoflavones and the anti-osteoporosis drug ipriflavone.

In a recent study, Erdman, Stillman, Lee, & Potter (1996) found that postmenopausal women whose diet included 90 mg of soy isoflavones had significantly greater lumbar spine bone-mineral density after six months than did the group whose diet included 55.6 mg of soy isoflavones or the control group given dairy protein. Only a handful of studies (and no long-term human trials) have been conducted on the effects of soybean isoflavones on bone mineral density or fracture risk. However, this area of research holds much potential.

Food Sources

Ninety percent of the soy protein isolate isoflavones can be lost with processing. However, the most commonly consumed soy products such as tofu, soymilk, tempeh, and most soy flours retain a majority of their isoflavone content (Barnes & Messina, 1993). The most commonly consumed soy products and their respective isoflavone content per one-half cup are: tofu, 40 mg; soy milk, 40 mg; tempeh, 40 mg; miso, 40 mg; textured soy protein, 35 mg; soy flour, 50 mg; and soybeans, 35 mg. One ounce of soy nuts contains 40 mg of isoflavones (Wang & Murphy, 1994). Many people obtain soy products through soy protein concentrates (less than 65% soy protein), which are widely used in products such as soy burgers or soy franks. Depending on how these products were processed, they may not contain nutritionally significant levels of isoflavones. Both textured soy protein (often marketed as textured vegetable protein) and soy flour are rich in isoflavones. Only two soy products, soy sauce and soy oil, are devoid of isoflavones (Nutrient Profiles, 1997).

Conclusions and Recommendations

The research examining the role of soy or specific components in soybeans in the prevention, inhibition, or alleviation of various disease states or symptoms is still in its infancy. Many studies have shown that soy intake, and in some cases isoflavone intake in particular, contributes positive health benefits. However, mechanisms of action are still undetermined in almost every situation.

Health educators would be prudent to recommend that Americans include soy foods in their diets. Tofu, miso, tempeh, soy milk, soy flour, soybeans, and textured vegetable protein would be among the foods consumers might choose. In addition to containing isoflavones, soy foods are high in protein, low in saturated fat, and high in complex carbohydrates. They are also a good source of several micronutrients and phytochemicals. Along with the recommendation to consume soy foods as part of a healthful diet, it is essential that consumers are given the information and skills necessary to purchase and prepare soy-containing foods. Soy foods are not a staple of the average American's diet, so "hands-on" nutrition and culinary education are needed. The third edition of the U.S. Soyfoods Directory (1998) is an excellent, comprehensive resource. It is available from the Indiana Soybean Board and contains soyfood descriptions, recipes, nutritional content of soyfoods, and availability of soyfoods in the U.S.

The marketing of isoflavone-containing products has virtually "exploded". Many magazines are carrying advertisements espousing the benefits of taking isoflavone supplements. Products containing phytoestrogens are commonly advertised in magazines and on the internet. A recent web search on isoflavones resulted in a list of thousands of sites devoted to marketing supplements. While the research on the health benefits of soy is very promising, consumers need to be reminded to avoid the isoflavone supplements. The "if some is good, more is better" mentality of Americans needs to be checked. As with other diet and nutrition recommendations, we as health educators cannot stress enough the "moderation message." The safety and effectiveness of isoflavones in varying amounts is not known. Large doses of individual phytochemicals produce only single effects and may be potentially toxic. Setchell (1996) reported that, based on the biological potency of the isoflavones, negative effects could be anticipated from high doses. Conversely, other phytochemicals in soyfoods such as protease inhibitors, phytates, phytosterols, saponins,

and phenolic acids may provide additional health benefits (American Dietetic Association, 1995).

As the authors of many of the studies cited in this paper have pointed out, diets that are moderate in calories, and rich in legumes (especially soybeans), whole grain foods, vegetables, and fruits should be encouraged. Dietary intervention as a method of preventing chronic disease and improving quality of life, is an attractive, cost-effective health promotion strategy.

Web Sites

Following is a list of web sites with information on soy:

http://www.soyfoods.com
Indiana Soybean Board
http://www.oilseeds.org/asa/
American Soybean Association
http://www.talksoy.com
United Soybean Board
http://www.ag.uiuc.edu/~nsrl/nsrlpage.html
National Soybean Research Laboratory at the University of Illinois at Urbana-Champaign
http://www.ag.uiuc.edu/~stratsoy.html
StratSoy Home Page with information for the United States soybean industry

References

Adlercreutz, H. (1990). Western diet and western diseases: Some hormonal and biochemical mechanisms and associations. Scandinavian Journal of Clinical and Laboratory Investigations, 50, 3S-23S.

Adlercreutz, H., Hamalainen, E., Gorbach, S., & Goldin, B. (1992). Dietary phytoestrogens and menopause in Japan. Lancet, 339, 1233.

American Dietetic Association. (1995). Position of the American Dietetic Association: Phytochemicals and functional foods. Journal of the American Dietetic Association, 95, 493-496.

Anderson, J. W., Johnstone, B. M., & Cook-Newell, M. E. (1995). Meta-analysis of the effects of soy protein intake on serum lipids. New England Journal of Medicine, 333, 276-282.

Bakhit, R. M., Klein, B. P., Essex-Sorlie, D., Ham, J. O., Erdman, J. W., & Potter, S. M. (1994). Intake of 25 g soybean protein with or without soybean fiber alters plasma lipids in men with elevated cholesterol concentrations. Journal of Nutrition, 124, 213-222.

Barnes, S. (1995). Effect of genistein on in vitro and in vivo models of cancer. Journal of Nutrition, 125, 777S-783S.

Barnes, S., Messina, M. (1993). Soy and its role in cancer prevention. The Soy Connection, 1 (2), 1-4.

Barnes, S., Peterson, T. G., Grubbs, C., & Setchell, K. R. (1994). Potential role of dietary isoflavones in the prevention of cancer. In M. M. Jacobs (Eds.), Diet and cancer: Markers, prevention and treatment (pp. 135-148). New York, NY: Plenum Press.

Boulet, M. J., Oddens, B. J., Lehert, P., Vemer, H. M., & Visser, A. (1994). Climacteric and menopause in seven southeast Asian countries. Maturitas, 19, 157-176.

Brezinski, A., Adlercreutz, H., Shmueli, A., Shaoul, R., Reosler, A., & Schenker, J. G. (1997). Short-term effects of phytoestrogen-rich diet on postmenopausal women. Journal of the North American Menopause Society, 4, 89-94.

Burke, G. L. (1996). The potential use of a dietary soy supplement as a post menopausal hormone replacement therapy. [On-line]. Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Available: http://soyfoods.com/symposium/0a6b2.html.

Carroll, K. K. (1982). Hypercholesterolemia and atherosclerosis: effects of dietary protein. Federation Proceedings, 41, 2792-2796.

Carroll, K. K. (1991). Review of clinical studies on cholesterol-lowering response to soy protein. Journal of the American Dietetic Association, 91, 820-827.

Cauley, J. (1997). Hormone replacement therapy and osteoporosis. The Soy Connection, 5 (2), 3-4.

Coope, J., Thomson, J. M., & Poller, L. (1975). Effects of "natural oestrogen" replacement therapy on menopausal symptoms and blood clotting. British Medical Journal, 4, 139-143.

Dalais, F. S. (1997). Soy and menopause. The Soy Connection, 5 (4), 1-4.

Dalais, F. S., Ric, G. E., Bell, R. J., Murkies, A. L., Medley, G., Strauss, B. J. G., & Wahlquist, M. L. (1996). Dietary soy supplementation increases vaginal cytology maturation index and bone mineral content in postmenopausal women. [On-line}. Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Available: http://soyfoods.com/symposium/0a5a_5.html.

Doctors may have found a cure for hot flashes: Tofu. (1996, November 5). USA Today, p. 1D.

Erdman, J. W., & Potter, S. M. (1997). Soy and bone health. The Soy Connection, 5 (2), 1-4.

Erdman, J. W., Stillman, R. J., Lee, K. F., & Potter, S. M. (1996). [On-line}. Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Available: http://soyfoods.com/symposium/0a35.html.

Fotsis, T., Pepper, M., Adlercreutz, H., Hase, T., Montesano, R., & Schweigerer, L. (1995). Genistein, a dietary ingested isoflavonoid, inhibits cell proliferation and in vitro angiogenesis. Journal of Nutrition, 125, 790S-797S.

Folman, Y., & Pope, G. S. (1969). Effect of norethistestosterone acetate, diethylstilbestrol, genistein and coumestrol on uptake of (3H) oestradiol by uterus, vagina and skeletal muscle of immature mice. Journal of Endocrinology, 44, 213-218.

Goodman, M. T., Wilkens, L. R., Hankin, J. H., Lyu, L., Wu, A. H., & Kolonel, L. N. (1997). Association of soy and fiber consumption with the risk of endometrial cancer. American Journal of Epidemiology, 146, 294-305.

Harding, C., Morton, M, Gould, V., McMichael, Phillips, D., Howell, A., & Bundred, N. J. (1996). Dietary soy supplementation is oestrogenic in menopausal women. [On-line]. Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Available: http://soyfoods.com/symposium/pa7.html.

Henderson, B. E., Ross, R. K., Pike, M. C., & Casagrande, J. T. (1982). Endogenous hormones as a major factor in human cancer. Cancer Research, 262, 5592-5595.

Herman, C., Adlercreutz, H, Goldin, B., Sherwood, L., Krister, G., Hockerstedt, A., Wantabe, S., Hamalainen, E., Markkanen, H., Makela, T., Wahala, K., Hase, T., & Fotsis, T. (1995). Soybean phytoestrogen intake and cancer risk. Journal of Nutrition, 125, 757S-770S.

Indiana Soybean Board. (1998). United States Soyfoods Directory. Indianapolis, IN: Indiana Soybean Board.

Kaldas, R., & Hughe, C. L. (1989). Reproductive and general metabolic effects of phytoestrogens in mammals. Reproductive Toxicology, 2, 81-89.

Kennedy, A. R. (1995). The evidence for soybean products as cancer preventive agents. Journal of Nutrition, 125, 733S-743S.

Knight, D. C., & Eden, J. A. (1996). A review of the clinical effects of phytoestrogens. Obstetrics and Gynecology, 87, 897-904.

Kronenberg, F., & Wade, C. (1997). Hotflashes and HRT. The Soy Connection, 5 (4), 2.

Lampe, J. W., Martini, M. C., Kurzer, M. S., Adlercreutz, H. & Slavin, J. L. (1994). Urinary lignan and isoflavonoid excretion in premenopausal women consuming flaxseed powder. American Journal of Clinical Nutrition, 60, 122-128.

Lee, H. P., Gourley, L., Duffy, S. W., Esteve, J., Lee, J., & Day, N. E. (1991). Dietary effects of breast cancer risk in Singapore. Lancet, 337, 1197-1200.

Messina, M. (1991). Food phytochemicals and cancer risk. The Soy Connection, 1 (2), 1.

Messina, M. (1997a). Researchers from around the world present on wide range of chronic diseases. The Soy Connection, 5 (1), 1-4.

Messina, M. (1997b). Soy as an alternative to hormone replacement therapy. The Soy Connection, 5 (2), 1,4.

Messina, M. (1997c). Soy as a possible alternative to hormone replacement therapy. [On-line}. 1997 Soyfood Symposium. Available: http://soyfoods.com/symposium97/hormone.html.

Messina, M. (1997d). Women, CHD and estrogen. The Soy Connection, 5 (3), 1-4.

Messina, M., & Barnes, S. (1991). The role of soy products in reducing risks of certain cancers. Journal of the National Cancer Institute, 83, 541-546.

Messina, M., & Messina, V. (1991). Increasing use of soyfoods and their potential role in cancer prevention. Journal of the American Dietetic Association, 91, 836-840.

Messina, M. J., Persky, V., Setchell, K. D., & Barnes, S. (1994). Soy intake and cancer risk: A review of the in vitro and in vivo data. Nutrition and Cancer, 21 (2), 113-131.

Mills, P. K., Beeson, W. L., Phillips, R. L., & Fraser, G. E. (1989). Cohort study of diet, lifestyle and prostate cancer in adventist men. Cancer, 64, 598-604.

Murkies, A. L., Lombard, C., Strauss, B. G., Wilcox, G., Burger, H. G., Morton, M. S. (1995). Dietary flour supplementation decreases post

menopausal hot flashes: Effect of soy and wheat. Maturitas, 21, 189-195.

Nutrient Profiles of Several Soy Foods. (1997). [On-line]. Available: http://www.walford.com/soydata.htm.

Patterson, A. G. (1996). Soy protein - additional defense against heart disease. The Soy Connection, 4 (1), 2.

Peterson, T. G., & Barnes, S. (1991). Genistein inhibition of growth of human breast cancer cells: Independence from estrogen receptors and the multi-drug resistance gene. Biochemical and Biophysical Research Communications, 179, 661-667.

Price, K. R., & Fenwick, G. R. (1985). Naturally occurring estrogens in foods - a review. Food Additives and Contaminants, 2, 73-106.

Setchell, K. R. (1996). Overview of isoflavone structure, metabolism and pharmacokinetics. [On-line]. Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Available: http://soyfoods.com/symposium/0a13.html.

Setchell, K. R., & Adlercreutz, H. (1988). Mammalian lignans and phytoestrogens. Recent studies on their formation, metabolism and biological role in health and disease. In I. R. Rowland (Ed.),. Role of the gut flora in toxicity and cancer (pp. 315-345). New York, NY: Academic Press Limited.

Severson, R. K., Nomura, A. Y., Grove, J. S., & Stemmerman, G. N. (1989). A prospective study of demographics, diet and prostate cancer among men of Japanese ancestry in Hawaii. Cancer Research, 49, 1857-1860.

Soy: The bean most likely to succeed in fending off cancer, heart disease. (1994). Environmental Nutrition, 17 (5), 1-4.

Soybeans - The answer to great health? (1993, May 31). [On-line]. US News and World Report. Available: http://www.eastcoast.com/freelife/tofu.htm.

Teppo, L., Pukkala, E., Hakama, M., Hakulinen, A., Herva, A., & Saxen, E. (1980). Way of life and cancer incidence in Finland. Scandinavian Journal of Social Medicine, 19, 1-84.

Wang, H., & Murphy, P. A. (1994). Isoflavone content in commercial soybean foods. Journal of Agricultural Food Chemistry, 42, 1666-1673.

Wilcox, G., Wahlquist, M. L., Burger, H. G., & Medley, G. (1990). Oestrogenic effects of plant foods in postmenopausal women. British Medical Journal, 301, 905-906.

Woods, M. N., Senie, R., & Kronenberg, F. (1996). Effect of a dietary soy bar on menopausal symptoms. [On-line]. Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Available: http://soyfoods.com/symposium/0a5a5.html.