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# The Soy Connection

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HEALTH AND NUTRITION NEWS ABOUT SOY

## Research Updates

By Mark Messina, Ph.D.

### Prostate Cancer

**I**n vitro and animal data suggest that isoflavones and soyfoods reduce the risk of prostate cancer although relatively little epidemiologic data in this area has been conducted (see “Soy’s Encouraging Role in Prostate Cancer Prevention”). This is one reason why the recently published case-control study which involved 12 different cities in China is noteworthy. This study by Lee and colleagues involved 133 cases and 265 age- and residential community-matched controls between the ages of 50 and 89. A food frequency questionnaire was used to assess the intake of soyfoods and isoflavones. The age- and total calorie-adjusted odds ratio of prostate cancer risk comparing the highest tertile of tofu intake to the lowest tertile was a statistically significant 0.58 (i.e., risk was reduced by nearly 40 percent among the most frequent consumers of tofu). The odds ratio for highest versus lowest intake of total soyfoods (tofu, soymilk, and fermented soy products) and genistein was 0.51 and 0.53, respectively, although neither of these relationships quite reached statistical significance. These results are certainly encouraging and support the hypothesis that soy is protective against prostate

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## Soy’s Encouraging Role in Prostate Cancer Prevention

By Mark Messina, Ph.D.

**M**uch of the discussion over the past decade about potential health benefits of soy has centered on women’s health issues – breast cancer, bone health, and menopausal symptoms. Disappointing results from the Women’s Health Initiative, which raise questions about the wisdom of using conventional hormone replacement therapy long term, serve to further highlight this particular focus. Arguably, however, more men will start to consider incorporating soy into their diets as they become aware of research suggesting soy intake may reduce prostate cancer risk. Certainly, the American Cancer Society’s inclusion of soyfood consumption as one of seven steps to reduce risk of prostate cancer will help to increase such awareness. The brief review below highlights what is known about the relationship between prostate cancer risk and soy intake.

Worldwide, cancer of the prostate is the fourth most common cancer<sup>1</sup> and sixth most common<sup>2</sup> cause of cancer death in men. There are striking differences in prostate cancer rates among regions of the world, however. Compared to Western rates, prostate cancer incidence and mortality in China and Japan is extremely low; in fact, they are as low as the breast cancer rates in those countries. The low rates in soyfood consuming countries provided initial motivation for investigating the impact of soy intake on prostate cancer risk. Unfortunately, relatively little epidemiologic research has been conducted.

A prospective study among 8,000 Japanese men in Hawaii found that daily tofu intake was associated with a 65 percent reduction in prostate cancer risk, but these findings were not quite statistically significant.<sup>3</sup> Also, total soy intake was not reported, the number of prostate cancer cases in this study was small, and miso intake was not protective. In a prospective study among Seventh-Day

Adventists in California, drinking 1-2 cups of soymilk per day was associated with a 70 percent reduced risk. But again, there were only a small number of cases and the only soy product reported was soymilk.<sup>4</sup> Furthermore, an earlier report from this cohort indicated that legumes and beans in general were protective. Other epidemiologic studies provide at best only modest support for protective effects of soy.<sup>5</sup>

Unquestionably, the isoflavones are thought to be responsible for the hypothesized anti-prostate cancer effects of soy. In vitro, the main soybean isoflavone genistein inhibits the growth of testosterone-dependent and independent prostate cancer cells.<sup>5</sup> It also reduces the ability of prostate cancer cells to metastasize independent of cell growth inhibition.<sup>6</sup> In addition, in a dose-dependent manner genistein decreases the growth of human-patient benign prostatic hyperplasia tissue and prostate tumors in histoculture.<sup>7</sup> Finally, genistein has been shown to enhance the ability of radiation to kill prostate cancer cells in vitro.<sup>8</sup>

Although in many cases the concentrations of genistein required to inhibit prostate cancer cell growth in vitro are greater than those found in serum, when prostate cells are exposed to genistein for a prolonged period of time (as in theory would be the case in men regularly eating soyfoods) the concentration required to inhibit growth is similar to the serum genistein levels in people eating soyfoods.<sup>9</sup> Furthermore, isoflavone levels in the prostate exceed those in the serum.<sup>10</sup>

Animal models of prostate cancer provide the clearest support for the hypothesis that soy intake reduces risk, although it should be noted that there is much debate about which animal models are best for studying prostate cancer.<sup>11</sup> Animal models include those in which

*(Continued on Page 2)*

# Soy's Encouraging Role in Cancer Prevention *(Continued from Page 1)*

tumors develop spontaneously, are induced chemically, and are induced by implanting prostate cancer cells directly into the prostate. Feeding soy or isoflavones has been shown to be effective in all three models, but results from recent publications using the latter model are particularly impressive. In one, there was a dose-dependent inhibition between isoflavone consumption and prostate tumor growth, tumor size being approximately 40 percent lower in mice given the highest dietary dose of isoflavones compared to control animals fed a soy-free diet.<sup>12</sup> More recently, isoflavones were found to decrease tumor growth by approximately 50 percent in mice, and in combination with black tea extracts, to reduce tumor size by approximately 80 percent.<sup>13</sup>

The mechanism by which soy inhibits the growth of prostate cancer in animals has not been identified, although much *in vitro* research shows that genistein can influence the activity of enzymes and cellular factors that control the growth and differentiation of cells. Also, isoflavones have weak estrogen-like effects and high-dose estrogen has been used to treat prostate cancer. Some research indicates that higher levels of testosterone and especially of dihydrotestosterone (a testosterone metabolite) increases prostate cancer risk, but clinical studies have failed to show that soy or isoflavones affect serum testosterone levels (see article page 3).<sup>5</sup>

One of the keys to preventing prostate cancer mortality is to prevent the small (often called latent) prostate tumors from progressing to the larger, more aggressive, and potentially life-threatening form of prostate cancer. By 85 years of age, approximately 75 percent of all men have these small prostate tumors.<sup>14, 15</sup> Autopsy data reveal that even in Japan, latent prostate cancer is common, although very few Japanese men die of prostate cancer. The International Prostate Health Council recently concluded that isoflavones prevent latent prostate cancer from progressing to the more lethal form of this disease.<sup>16</sup> There are also intriguing but still speculative data suggesting that soy may be useful to prostate cancer patients. Investigators from the Karmanos Cancer Institute in Detroit reported that in prostate cancer patients (N=40) resistant to conventional medical treatment, daily isoflavone supplementa-

tion (120 mg/day) resulted in a marked decline in the rise in levels of prostate specific antigen (a marker of prostate cancer).<sup>17</sup>

Prostate cancer is a disease of older men; average age of diagnosis is about 73. Also, prostate tumors are slow-growing. Evidence suggests that late life influences do affect prostate cancer development. Thus, men appear to have ample opportunity to decrease their chances of dying of prostate cancer. Even if soy only modestly impacts prostate cancer – by slowing tumor growth and/or delaying tumor onset – the public health implications are significant. Thus far, although no firm conclusions can be drawn about the ability of soy to reduce risk of prostate cancer, the evidence is certainly intriguing. Research into the effects of soy intake on prostate cancer risk in humans is needed and warranted. Because soyfoods provide high quality protein and may offer a number of health benefits, men concerned about their prostate health may want to consider adding soyfoods to their diet. Men should strive to consume about two servings of soyfoods per day; this amount provides approximately 15 g soy protein and 50 mg isoflavones.

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# Sexual Function Normal in Men Consuming Soy

By Jill Hamilton-Reeves and Mindy S. Kurzer, Ph.D.

Although consumption of soy isoflavones has been shown to exert beneficial effects on bone, brain, prostate and cardiovascular health<sup>1</sup>, concerns have been raised that consumption of these dietary estrogens might cause abnormalities in sexual differentiation and feminization in males exposed in utero or during infancy, and might lower testosterone levels and semen quality, adversely affecting fertility in adult men. However, studies investigating hormonal effects of soy consumption by men suggest no effects on sexual function.

These concerns arise mainly from studies in rodents consuming or injected with extremely large quantities of isoflavones during development, although the results of these studies are actually quite variable. For example, perinatal exposure to high doses of purified genistein disrupted sexual differentiation in rats<sup>2,3</sup>, and neonatal exposure altered the pituitary response to gonadotropin-releasing hormone (GnRH)<sup>4</sup> and induced structural changes similar to those caused by diethylstilbestrol (DES), a potent estrogen.<sup>5</sup> However, other rodent studies have shown no effects of genistein on the pituitary response to GnRH<sup>6,7</sup>, sperm count<sup>7</sup>, or gonad histopathology<sup>8</sup> and one study reported that soy might actually improve spermatogenesis.<sup>9</sup> Badger and colleagues reported that male rats fed soy protein isolate did not differ from rats fed whey protein or casein in development, organ weights, in vitro testosterone metabolism, or reproductive performance at short-term, long-term, or multigenerational endpoints.<sup>10</sup> Although no studies have been performed in human infants consuming soy, a follow up study of 120 men who had consumed soy formula as infants also showed no effects on pubertal maturation, fertility or hormonal disorders.<sup>11</sup>

There is great interspecies variability in effects of isoflavone consumption on reproductive capacity in adult animals. For example, while research on cheetahs<sup>12</sup> has demonstrated reproductive toxicity, consumption of up to

9 mg soy isoflavones/kg body weight /day in primates<sup>13,14</sup> and up to 3.5mg/kg body weight /day in pigs<sup>15</sup> is not associated with reproductive disturbances. Studies in adult male rodents treated with soy or genistein have found reduced<sup>5,16</sup>, unchanged<sup>7,8,17</sup>, and increased<sup>18</sup> serum testosterone concentrations.

Two cross-sectional studies evaluating the associations between soy intake and plasma hormones in adult men report conflicting results. Nagata and colleagues<sup>19</sup> reported a weak but statistically significant inverse correlation between soy-food consumption and serum estradiol ( $r = -.32, P = 0.009$ ) and borderline inverse correlations with serum estrone, testosterone and free testosterone in 69 Japanese men. In the second study, with a much larger sample size, Allen and colleagues found no significant associations between consuming dietary soymilk and sex hormone levels in 696 British men.<sup>20</sup>

*On the basis of the available data, there is little reason to think that soy consumption will cause reproductive abnormalities or feminization in men.*

Two intervention studies in men consuming soyfoods or supplements containing very high levels (119-120 mg) of isoflavones/day suggest modest effects on plasma hormones and no effects on semen quality. Habito and colleagues<sup>21</sup> performed a randomized crossover study of 42 men who consumed tofu containing 119 mg isoflavones daily for four weeks. Blood concentrations of estradiol, testosterone, dihydrotestosterone (DHT), and androstenediol glucuronide did not differ between the two diets. The mean testosterone-estradiol ratio was 10 percent lower, sex hormone binding globulin (SHBG) was 9 percent higher, and the free androgen index (total testosterone/SHBG x 100) was 7 percent lower after tofu consumption, suggesting a slight lowering of androgen activity. These data are consistent with those of Gardner-

Thorpe and colleagues<sup>22</sup>, who reported a 6 percent lowering of testosterone, and no significant changes in DHT, estradiol, estrone or SHBG in men consuming soy flour containing 120 mg isoflavones/day for six weeks. However, the relevance of these last results<sup>22</sup> is questionable because control data were not reported.

This slight reduction in androgen activity was not confirmed by two studies using isoflavone doses nearer to the typical intake of regular soy consumers.<sup>23</sup> Nagata and colleagues<sup>24</sup> conducted a parallel-arm study of 34 men, half of whom consumed an average of 343 mL soymilk (48 mg isoflavones) daily for two months. Blood concentrations of estradiol, total and free testosterone, and SHBG did not differ between the two groups, although estrone concentrations tended to decrease in the group consuming soymilk. These results are consistent with those of Mitchell and colleagues<sup>25</sup>, who found no changes in serum concentrations of estradiol, testosterone, follicle-stimulating hormone, or luteinizing hormone in 14 young men consuming a tablet containing 40 mg/day of soy isoflavones for two months. In this same study, no effects were seen on testicular or ejaculate volume or sperm concentration, count or motility.

In summary, although animal studies suggest a theoretical risk of reproductive problems in men exposed to soy isoflavones during development or as adults, it is clear that these effects are quite variable among animal species and are observed only at extremely high doses. Studies investigating hormonal effects of soy or isoflavone consumption in men suggest small reductions in androgen activity and no effects on fertility. The slight reduction in androgen activity observed in two studies of men consuming high quantities of isoflavones are unlikely to be of clinical significance, particularly in light of the lack of effects on sperm quality and fertility reported in

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# TOP 10 Soyfoods for Men

By Juniper Devecis, M.S., R.D., L.D.N.

1. **Have a soy barbecue.** There is a great variety of soy products on the market; add some favorites to your next barbecue. Try veggie burgers, soy hot dogs, soy sausages and even soy ribs. Add some barbecue sauce for extra flavor.
2. Mix up a big batch of **chili.** Cook diced onions and tomatoes over low heat. Add soy protein crumbles and kidney beans for a quick, easy meal. Try the recipe below for soy chili with a kick.
3. Have a hearty serving of **spaghetti and meatballs**, the soy kind, or add soy protein crumbles to tomato sauce – a great source of prostate-boosting lycopene – for a quick, easy sauce. Check your local grocery store’s freezer section for pre-made frozen “soy-balls” or soy protein crumbles. Choose soy pasta for extra nutrition.
4. **Enjoy soy Japanese style.** Order miso soup and steamed edamame (soy beans in the pod) the next time you go out for dinner, or look in your grocery store for miso and frozen edamame and follow the package directions to make them at home.
5. **Munch on vegetables, soy chips and dip** next time you watch the big game. Use soy yogurt or silken tofu for a healthy, soy-filled dip.
6. The next time you hike up a mountain or go to the gym, mix up a batch of **trail mix** with soy nuts, sunflower seeds and dried fruit, like dried cranberries or raisins. You can also try a soy energy bar for an on-the-go boost.
7. **Start your day with soy.** Add soymilk to your cereal or heat up some soy breakfast links or soy waffles, found in your local grocery store’s freezer section.
8. Snack on a soynut butter (think peanut butter) and jelly **sandwich** or try some soynut butter on crackers for a healthy, satisfying snack.
9. **Have a Chinese food night.** Sauté vegetables, like carrots, peppers, zucchini and bok choy, in a frying pan or wok with a dash of soybean oil until tender. (Add water if vegetables start to stick). Add cubes of firm tofu (or tempeh for added flavor) and a dash of soy sauce. Serve with rice. Use chop-sticks for an authentic Chinese feel.
10. Try a **soy protein smoothie.** Mix soymilk, low-fat yogurt or soy yogurt, diced fresh or frozen fruit and a scoop of soy protein powder for a tasty, balanced meal or snack.

## ABOUT THE AUTHOR

**Juniper Devecis, M.S., R.D., L.D.N.** is a registered dietitian with a Master’s degree in Nutritional Biochemistry and Metabolism from Tufts University. She currently counsels patients for the Beth Israel Deaconess Medical Center’s Cardiovascular Health and Lipid Clinic and works as a bionutritionist at the General Clinic Research Center. ☺

### Soy Chili

Makes 8 servings

Prep time 50 minutes

2 tablespoons soybean oil  
 1 medium onion, diced  
 1-1/2 teaspoons chili powder  
 1 teaspoon cumin  
 1/2 - 1/4 teaspoon cayenne pepper  
 1 teaspoon paprika  
 12 ounces soy protein crumbles (approx. 3 cups)  
 2 tablespoons soy sauce or tamari, low-sodium  
 1 large bell pepper, red or green, diced  
 2 cloves garlic, minced  
 28-ounce can crushed tomatoes, no salt added  
 1 cup water  
 Two 15-ounce cans kidney beans, drained and rinsed  
 1 cup edamame (green soybeans)  
 1 cup corn kernels, canned or frozen

Heat oil in a large frying pan over medium heat. Add onion, chili powder, cumin, cayenne and paprika. Continue cooking until onion is translucent, stirring occasionally. Add soy protein crumble and soy sauce and continue to sauté for 2 minutes.

Add remaining ingredients and stir well to combine. Keep pan on medium heat until chili begins to boil. Reduce heat to low and simmer for 25 minutes. Stir occasionally to prevent chili from sticking.

**Nutrition Info:** 307 calories, 23g protein, 46g carbohydrate, 6g fat, <1 g saturated fat, 325 mg sodium, 12g fiber

## Soy Recipes with a Kick!

### Soy Sausage Quesadillas

Makes 4 servings

Prep time 10 minutes

4 whole wheat tortillas  
 2 oz. soy sausage, cut into pieces  
 2 tomatoes, sliced  
 4 Tbsp. fresh basil leaves, chopped  
 3 oz. soy cheese, pepper jack (4 slices)  
 salsa – for topping (optional)

Spread tortillas on flat surface, cover half of each with 1 slice (3/4 oz.) of cheese, 1/2 oz. of soy sausage, 1/2 tomato, 1 Tablespoon basil leaves. Place under broiler, open face, until cheese melts (approx. 1 minute). Fold tortilla over and broil until top crisps (approx. 1 minute). Top with salsa if desired.



**Nutrition Info:** 103 calories, 6g protein, 16g carbohydrate, 1g fat, <1 g saturated fat, 286 mg sodium, 10.5g fiber

# Cornhuskers Flex Muscles with Soy

The Nebraska Cornhuskers consume soy products to improve athletic performance, said James Harris III, coordinator of sports nutrition for the University of Nebraska - Lincoln. For the past two years soy has powered what is widely considered to be the top strength program in the country.

Soy use is recommended for all athletes at Nebraska, and many options are given to them. In their cafeteria, athletes can find soy milk, tofu and soy burg-

ers. Harris also is developing a new soy protein powder that can be mixed with milk or water for extra muscle-building protein. These products are not only available for athletes, but all health conscious students. "Soy is good for those who need to cut fat and want to build muscle," said Harris.

Harris notes the growth of soy use at Nebraska is not only a result of the athletic department urging students to use it. "I think it is a result of people

being more health conscious overall," he said.

Harris said individual soy use depends on each person's health needs. It is a good option for those needing low-fat diets or more protein. He suggests that people substitute soy in at least one meal per day, such as drinking a glass of soy milk instead of regular milk. ☺



## Sexual Function Normal in Men Consuming Soy

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other studies. On the basis of the available data, there is little reason to think that soy consumption will cause reproductive abnormalities or feminization in men.

### ABOUT THE AUTHORS

**Jill Hamilton-Reeves** is a graduate student pursuing her doctoral degree in nutrition at the University of Minnesota. She is currently investigating the effects of soy phytoestrogen consumption on reproductive hormones and prostate tissue markers of cell proliferation and androgen activity in men at high risk of prostate cancer.

**Mindy S. Kurzer, Ph.D.,** teaches and performs research in human nutrition in the Department of Food Science and Nutrition at the University of Minnesota. Her current research focuses on the biological effects of phytoestrogen consumption.

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### For the Record

Ronni Chernoff, Ph.D., R.D., F.A.D.A., who wrote the article on dementia in the July 2003 issue of *The Soy Connection*, is a professor of geriatrics at the University of Arkansas for Medical Sciences in Little Rock. She received her Ph.D. from the University of Pennsylvania.

The Spring 2003 article "Diagnosing and Managing Your Allergies" stated that infants with soy allergies can be fed with fortified rice milk. Fortified rice milk does not have the required amount of protein or other nutrients for an infant. ☺



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- strogens decrease testosterone levels and prostate weight without altering LH, prostate 5 alpha-reductase or testicular steroidogenic acute regulatory peptide levels in adult male Sprague-Dawley rats. J Endocrinol 2001; 170(3): 591-9.*
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## Research Updates *(Continued from Page 1)*

cancer but the findings were not adjusted for the intake of other foods and nutrients. Clearly, more epidemiologic research is needed, especially prospective studies.

*Cancer Epidemiol Biomarkers Prev* 2003; 12:665-8.

### Portfolio Diet

In 1999 the U.S. Food and Drug Administration approved a health claim for the cholesterol-lowering effects of soy protein and one year later the American Heart Association endorsed the use of soyfoods for those with elevated cholesterol. However, lowering cholesterol to the recommended target level requires comprehensive dietary changes, not just the consumption of soy protein. To evaluate whether making multiple dietary

changes can lower cholesterol as effectively as pharmacological approaches, Jenkins and colleagues from the University of Toronto randomly assigned 46 hyperlipidemic adults (25 men and 21 postmenopausal women) to undergo one of three interventions on an outpatient basis for one month: a diet very low in saturated fat, based on milled whole-wheat cereals and low-fat dairy foods (n=16); the same diet plus lovastatin, 20 mg/d (n = 14); or a portfolio diet that was low in saturated fat, high in plant sterols (1.0 g/1000 kcal), soy protein (21.4 g/1000 kcal), viscous fibers (9.8 g/1000 kcal), and almonds (14 g/1000 kcal) (n = 16). The control, statin, and dietary portfolio groups had mean decreases in low-density lipoprotein cholesterol

of 8.0 percent, 30.9 percent, and 28.6 percent, respectively. There were no significant differences in efficacy between the statin and dietary portfolio treatments. In addition to the reductions in cholesterol, C-reactive protein levels decreased 10.0 percent (P =.27), 33.3 percent (P =.002), and 28.2 percent (P =.02) in the control, statin, and portfolio groups, respectively. C-reactive protein is a marker of inflammation and is thought to be an independent predictor of coronary heart disease. These results show that dietary changes can lower cholesterol as much as cholesterol-lowering drugs although it should be acknowledged that not all individuals are likely able to adhere long-term to the portfolio diet. *JAMA* 2003; 290:502-10. ☺