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Soyfoods may offer men significant health benefits, such as lowering the risk of prostate cancer, heart disease and more. As this factsheet will discuss, men need not fear the risk of feminization.

Introduction

Much of the research on the health effects of soyfoods has focused on postmenopausal women. In large part, this is because the soybean is such a rich source of isoflavones, a group of naturally-occurring plant chemicals that possess estrogen-like properties.¹ As a result, some men are reluctant to eat soyfoods because of the mistaken belief that isoflavones exert feminizing effects. However, not only is this concern without scientific merit, but there is a large amount of evidence suggesting adding soyfoods to the diet can greatly benefit men by reducing the risk of prostate cancer and heart disease. There is also very preliminary evidence that consuming soyfoods might protect against male pattern baldness.²

Health organizations, such as the American Institute for Cancer Research, recommend obtaining a higher percentage of dietary protein from plant foods as a means of reducing cancer risk.

Isoflavones

The two primary isoflavones in soybeans are genistein and daidzein.³ Average isoflavone intake among older Japanese men is about 40 mg/day, which is the amount provided by about 10 to 12 g of soy protein from traditional soyfoods.⁴ Each serving (e.g., 1 cup soymilk or ½ cup tofu or edamame) of a minimally processed soyfood provides about 25 mg of isoflavones or 3.5 mg isoflavones per gram of protein. Generally, more processed soy products have much lower isoflavone concentrations (mg/g protein) than traditional soyfoods.

Isoflavones have a chemical structure similar to the primary female reproductive hormone estrogen (although older men actually produce more estrogen than older women) so not surprisingly they bind to estrogen receptors and possess some estrogen-like properties. For this reason, isoflavones are commonly referred to as phytoestrogens.⁵ However, isoflavones and estrogen are very different molecules and, as such, they often exert different physiologic effects. The literature is replete with examples wherein isoflavones affect biological endpoints differently than estrogen.⁶⁻²⁶ The fact is that isoflavones are more accurately classified as selective estrogen receptor modulators (SERMs) than as phytoestrogens.^{17, 27, 28}

SERMs exert tissue-selective effects. They have estrogen-like effects in some tissues, effects opposite to those of estrogen in other tissues, and in some tissues, no effects at all despite the presence of estrogen receptors. Since there is no "class effect" of SERMs, that is, since each SERM has different physiological properties, the effects of isoflavones can only be determined by direct experimentation.²⁹ Furthermore, because soybeans contain many biologically active components, soyfoods should not be equated with isoflavones.

Research has shown that soy is safe for men to consume and that they may benefit by including soyfoods in their diet.

The ability of isoflavones to exert tissue-selective effects almost certainly stems in part from their preferential binding to and transactivation of estrogen receptor beta (ERβ) in comparison with ERα. This preference is important because these two receptors have different tissue distributions within the body and when activated can have different and sometimes opposite effects. Consequently, the ERα:ERβ ratio within a given cell type greatly influences the effect of estrogen and other ER-binding ligands on that cell. Furthermore, each ligand may induce ligand-ER conformations that preferentially recruit specific cofactors within the cell, thereby inducing differential responses.³⁰ Recent evidence suggests that ligands that target ERβ promote breast and prostate health.³¹ Since ERβ also predominates in the skin, ERβ-preferring ligands may also improve skin health.

Soyfoods as Sources of Protein

Most American men meet or exceed the recommended dietary allowance (RDA) for protein, although this may not be the case for as many as 40% of older men.³² Furthermore, some recent data suggest that the RDA may be too low and that protein intake exceeding the RDA may be advantageous.³³⁻³⁵ For example, evidence suggests that consuming protein in excess of the RDA may be beneficial for weight loss,³⁶ reducing risk of osteoporosis,³⁷ enhancing the benefits of vigorous physical activity³⁸ and lowering blood pressure.^{39, 40} Also, in older men, dietary protein intakes above the RDA may help to prevent sarcopenia or age-related loss in skeletal muscle.^{41, 42} To prevent this disease, researchers from the University of Texas Medical Branch recommended the consumption of at least 30 g of protein at each of the three primary meals.³⁵

Soyfoods can play important roles in helping men meet protein needs while maintaining a healthful diet as they provide ample amounts of high-quality protein but are typically low in saturated fat.⁴³⁻⁴⁷ Since the protein in products such as isolated soy protein is comparable in quality to meat and milk protein, soyfoods can be recommended as

protein-rich options.^{44, 48} Furthermore, there is preliminary evidence that soy protein places less stress on the kidneys in comparison to other high-quality proteins, which over time could reduce the risk of developing renal disease in susceptible individuals, such as those with diabetes.^{49, 50} This potential benefit may take on mounting importance as the prevalence of chronic kidney disease increased 30% during the past 10-years.⁵¹

Finally, soy protein supplementation leads to muscle accretion in response to resistance exercise⁵² and may actually have some advantages over other high-quality proteins by reducing exercise-induced inflammation and oxidation.⁵³⁻⁵⁵ Clearly, there is a role for soy protein in the diets of those seeking to increase muscle mass. In fact, a recently published study found that in comparison to whey protein alone, which is considered to be an excellent quality protein for building muscle, a blend of soy protein, casein and whey, stimulated muscle protein synthesis in response to high-intensity leg resistance exercise to a greater extent.⁵⁶

Coronary Heart Disease Prevention

Soyfoods potentially offer three-way protection against heart disease. First, because they are generally low in saturated fat and high in polyunsaturated fat (PUFA, the essential omega-6 fatty acid linoleic acid comprises ~55% of the total fat content), soyfoods can help reduce blood cholesterol when they displace more traditional sources of protein in Western diets, which tend to be high in saturated fat.^{57, 58} A recent analysis suggested that through displacement, soyfoods can reduce low-density-lipoprotein cholesterol (LDLC) 3-6%.⁵⁹ Recently, the American Heart Association (AHA) highlighted the important role of PUFA in reducing blood cholesterol levels and risk of heart disease.⁶⁰ Importantly, some analyses show that CHD risk is reduced when saturated fat is replaced with PUFA, but not when replaced with carbohydrates,^{61, 62} or monounsaturated fat, and that the ideal substitution is a combination of omega-6 and omega-3 PUFA.⁶³

Therefore, soyfoods will result in an especially desirable change in the fatty acid content of the diet because the soybean is among the few good plant sources of the essential omega-3 fatty acid, alpha-linolenic acid (ALA),⁶⁴ which is thought to have independent coronary benefits.⁶⁵⁻⁶⁷ To this point, a recent study found men with a high intake of ALA had lower inflammatory biomarkers associated with a reduced risk of CHD.⁶⁷

Second, soy protein directly lowers blood cholesterol levels.⁶⁸ The cholesterol-lowering effect of soy protein is very modest compared to statins – the most commonly used class of medication for lowering cholesterol – but even the 4 to 6% reduction in LDLC in response to soy protein⁶⁸⁻⁷¹ can in theory, reduce heart disease risk by 10% over a period of years^{72, 73} (some evidence indicates the hypocholesterolemic effects of soy protein may be greater in men than in women⁶⁸). The combined effect of soy protein plus the improvement in the fatty acid content of the diet when soyfoods are consumed will substantially reduce LDLC and therefore, CHD.⁵⁹

Soyfoods can help lessen blood cholesterol when they displace more traditional sources of protein in Western diets.

Third, research suggests that soyfoods may reduce CHD risk independent of their effects on elevated blood cholesterol, which is just one CHD risk factor. In addition to lowering LDLC, soy protein also lowers triglyceride levels by 5-10%.⁶⁸⁻⁷¹ Although there is debate about the significance of an elevated triglyceride level as an independent predictor of CHD risk,⁷⁴ recent evidence suggests that the role of triglycerides in the etiology of CHD has been underestimated.^{75, 76} Furthermore, new research suggests that soy protein decreases postprandial triglyceride levels, elevated levels of which are increasingly viewed an important CHD risk.⁷⁷ Also, in contrast to some dietary interventions that lower both LDLC and high-density lipoprotein cholesterol (HDL), soy protein intake leads to very modest increases (1-3%) in HDL.⁶⁸⁻⁷¹ Each 1% or 1 mg increase in HDL lowers CHD risk by 2-3%.^{78, 79} A new statistical analysis of the relevant scientific literature conclusively showed that even when LDLC is low, raising HDL levels is beneficial.⁸⁰



The effect of soyfoods on CHD risk factors unrelated to lipid levels is also gaining interest. For example, four recently published meta-analyses found that soy modestly lowers blood pressure.⁴⁷⁻⁵⁰ In the largest of these, which included 27 studies, soy lowered systolic and diastolic blood pressure by 2.21 and 1.44 mgHg, respectively.⁴⁸ Estimates are that lowering blood pressure even by this degree can reduce risk of stroke by about 10% and CHD by about 5%.⁸¹

Soy protein intake has also been shown to increase LDL particle size, shifting LDL particle distribution to a less atherogenic pattern.⁸² Over a period of 5-years, this change was estimated to result in a 5% reduction in risk of ischemic heart disease.⁸² Another study found that the consumption of soy flour led to a decrease in oxidative stress markers in men, reflecting a decreased risk of CHD.⁸³

There is also some, albeit inconsistent, clinical evidence indicating that soy intake and isoflavone exposure reduces levels of C-reactive protein (CRP).⁸⁴ CRP is a general indicator of inflammation; the measurement of this marker was recently designated by the American Heart Association as an optional screening test when risk-based decisions regarding initiation of pharmacological therapy are uncertain following quantitative risk assessment.⁸⁵

Finally, a recently published epidemiologic study from China supports the clinical data regarding the effects of soy on non-lipid CHD risk factors. In this cross-sectional study involving middle-aged adult men and women, habitual soy intake was associated with dose-dependent decreases in mean bifurcation intima-media thickness.⁸⁶ The effect was more apparent in men than women and greater than could be expected from the cholesterol-lowering effect of soy protein alone. Non-invasive assessment of intima-media thickness of the carotid arteries is widely used as an intermediate or proxy measure of generalized atherosclerosis.⁸⁷ However, in contrast to this study, a large prospective study from Shanghai found that over the 5.4-year follow-up period, soy intake was associated with an increased risk of CHD among men.⁸⁸ Although this finding is inconsistent with a considerable amount of data (and contrasts with the effects in women) and was published as a letter to the editor, rather than as a full manuscript, the finding warrants additional investigation.

Prostate Cancer Prevention

Cancer of the prostate is the most common cancer among U.S. men and the second most common cause of cancer death.⁸⁹ Much evidence indicates that an overall healthful diet, as well as specific nutrients and phytochemicals, can reduce prostate cancer risk and perhaps even help treat this disease.⁹⁰⁻⁹² Since prostate cancer is typically diagnosed at an older age and prostate tumors are generally slow-growing, even modestly delaying the onset and/or slowing the growth of these tumors may dramatically reduce the number of prostate cancer deaths.⁹³⁻⁹⁶

In 2000, the International Prostate Health Council suggested that because soyfoods contain isoflavones, they may be one factor contributing to the low Japanese prostate cancer mortality rates.⁹⁷ More recently, researchers at the University Hospital in Bonn, Germany, concluded that the soybean isoflavone genistein has the potential to prevent prostate cancer.⁹⁸

In agreement, researchers from the University of Illinois at Chicago and Xixiang Medical University, in China, concluded that although “the role of soy isoflavones in prostate cancer has traditionally been linked with the suppression of proliferation and the induction of apoptosis, . . . there is a compelling evidence that soy isoflavones regulate other cancer-related cellular processes.”⁹⁹

Research in animals supports these conclusions,^{100, 101} as do the epidemiologic data overall.^{102, 103} the latter of which suggests soy intake reduces prostate cancer risk by as much as one half.¹⁰² Epidemiologic examples of such protection include a Chinese case-control study, which found men who consumed soybean products more than once per day had an odds ratio of 0.29 for prostate cancer compared with men who consumed soybean products less than once per week.¹⁰⁴ In fact, soyfood intake was the only preventive factor in this study. In agreement, in a nested case-control study within the

Japan Public Health Center-based Prospective Study, the odds ratio for localized prostate cancer for those in the highest group of plasma genistein and equol (see below) compared with the lowest was 0.54 and 0.43, respectively.¹⁰⁵

Although speculative, whether soyfoods reduce the risk of prostate cancer in any given person may depend in part on isoflavone metabolism, which varies greatly among individuals. To this point, approximately 25% of Westerners and 50% of Japanese possess the intestinal bacteria capable of converting the isoflavone daidzein into equol.¹⁰⁶ This may be important with respect to prostate cancer because in rodents, equol is able to bind to and sequester 5 α -dihydrotestosterone (the biologically active form of testosterone).¹⁰⁷ This sequestering action led to a decrease in mouse prostate tissue growth, reflecting possible reduction in prostate cancer risk. Furthermore, among Asian men, a recently published epidemiologic study found that the proportion of equol producers was significantly smaller in those with prostate cancer than in the cancer-free control group. Also, fewer equol-producers were found among patients with poorly differentiated adenocarcinoma than in those with well or moderately differentiated adenocarcinoma.¹⁰⁸ The former type of tumor is more aggressive.

Prostate cancer is the most common cancer among U.S. men and the second most common cause of cancer death.



Soyfoods protect against heart disease in the following ways:

- Displacing high saturated fat foods from their diet
- Modestly lowering LDL-cholesterol
- Potentially improving lip-independent risk factors

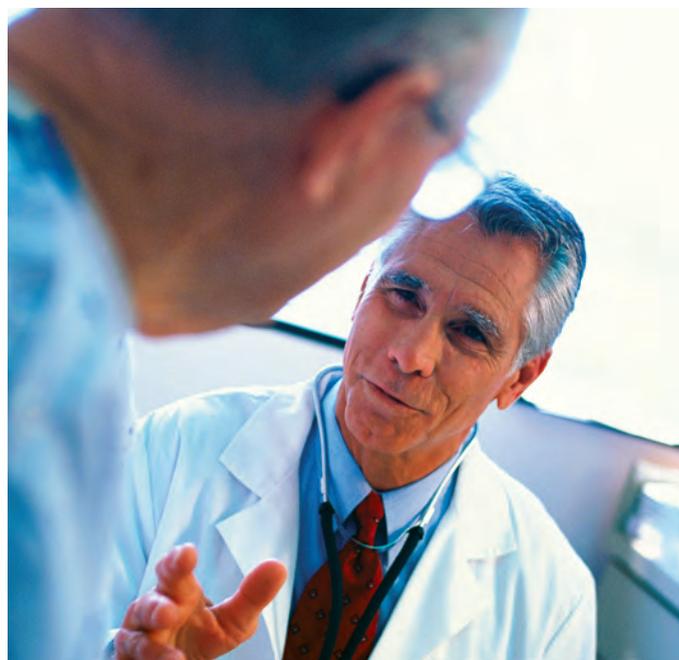
A team of Japanese researchers noted that if equol can reduce risk of prostate cancer, “a possible strategy for reducing the risk . . . may be to increase the proportion of equol-producers by changing the intestinal flora to carrying an equol-producing bacterium with dietary alteration or probiotic technology.”¹⁰⁹

In addition to helping to prevent the development of prostate cancer, there is speculative but intriguing animal and human evidence suggesting soy may also be useful for stopping its spread. Prostate cancer, like many cancers, is fatal only when the tumor metastasizes from the site of origin to vital organs. A study published in the *Journal of the National Cancer Institute* reported that the activity of an enzyme that allows cells to invade tissues — matrix metalloproteinase-2 — was markedly reduced in men with prostate cancer who were given the soybean isoflavone genistein.¹¹⁰ In agreement, adding isoflavones to the diet of mice inhibited prostate tumor metastasis to the lung — the primary site of metastasis in this animal model — by 96%.¹¹¹

Prostate cancer is typically diagnosed at an older age and prostate tumors are generally slow-growing. Even modestly delaying the onset and/or slowing the growth of these tumors may dramatically reduce the number of prostate cancer deaths.

To examine the potential role of soy in reducing prostate cancer risk, numerous investigators have examined the impact of isoflavone-rich products on levels of prostate specific antigen (PSA). PSA is the most common clinical test for the detection of prostate cancer although its use in routine screening has recently been challenged.¹¹²⁻¹¹⁴ PSA is also a measure by which treatment efficacy can be assessed.¹¹³ In men with prostate tumors, serum PSA concentration is proportional to prostate tumor volume¹¹⁵ and successful treatments for prostate cancer lower PSA levels.¹¹⁶⁻¹²⁴

The evidence that soy or isoflavones affect PSA levels is mixed. In a review published in 2006, no effects were noted in healthy participants with low PSA levels.¹²⁵ However, the lack of effect on PSA doesn't necessarily contradict the animal¹²⁶ or epidemiologic data¹⁰² supportive of the protective effects of soy since recent clinical data indicate that, in healthy men with low PSA levels, it is possible to reduce prostate cancer risk without affecting PSA.¹²⁷



In contrast to the results in healthy men, four of the eight trials involving men with prostate cancer that were included in the 2006 review showed isoflavones slowed the rise in PSA levels, although no study reported an absolute decrease.¹²⁵ In support of these findings, a study published subsequent to this review found that in men with prostate cancer, PSA levels increased 56% per year prior to study entry but only 20% per year when men consumed about 3 servings of soymilk daily for 12 months.¹²⁸ More recently, Kwan et al.¹²⁹ found in a pilot study that isoflavones tended to slow the rise in PSA levels in men with prostate cancer. Interestingly, Ide et al.¹³⁰ found that a combination of curcumin and isoflavones markedly decreased PSA levels in men with prostate cancer whose PSA levels were ≥ 10 ng/ml. In agreement, in a pilot study by Lazarevic et al.¹³¹ in men with localized prostate cancer who were given 30 mg/day genistein for 3 to 6 weeks, there was a 7.8% decrease in PSA whereas in the placebo group it increased by 4.4%.

In another pilot study by Joshi et al.¹³² of seven men with prostate cancer who had failed conventional treatment (surgery and radiation therapy) as judged by rising PSA levels:

- Four experienced a favorable response to the consumption of three servings of soyfoods per day over a two-year period (PSA levels that permanently or temporarily declined or remained stable was judged to be a favorable response).
- One of the three patients, who in addition to surgery and radiation opted for androgen deprivation therapy, responded favorably to soy.

These results are impressive considering conventional treatment was unsuccessful.

Finally, in a study involving men with high grade prostatic intraepithelial cells (HGPIN) or atypical small acinar proliferation, it was found that 34 and 21% of the men in the placebo and isoflavone groups developed cancer, respectively. Even greater differences were observed among the older men in this study; among those ≥ 65 -years of age, 57 and 28% of the men in the placebo and isoflavone groups, respectively, developed cancer.¹³³

In contrast to these studies, deVere White et al.¹³⁴ failed to find that extremely high-dose isoflavones affected PSA levels in men with prostate cancer who were enrolled in an active surveillance program. Also, a 3-year study involving 303 men with HGPIN found a combination of soy protein (40 g/day), vitamin E (800 IU/day) and selenium (200 mg/day selenium) did not affect the number of men who developed cancer in comparison to the placebo.¹³⁵ While these results are discouraging, caution is needed when drawing conclusions about the effects of soy in this study because a combination treatment was employed and some evidence indicates that vitamin E supplementation, and possibly selenium, may actually increase risk of developing prostate cancer.^{136, 137}

Epidemiologic evidence suggests that men who eat soyfoods daily are less likely to develop prostate cancer than those who do not.

Nevertheless, two other studies also failed to find isoflavones were not efficacious. In one, the participants were men at high risk of recurrence after radical prostatectomy for prostate cancer. They were randomized to consume a control protein (casein, $n=87$) or soy protein ($n=90$).¹³⁸ In the other study, men who had been diagnosed with prostate cancer were randomized to receive isoflavones or placebo for up to six weeks prior to prostatectomy.¹³⁹ Although the results of these latter two trials are disappointing, they are not entirely surprising because of the low isoflavone dose used in both studies. Men in the isoflavone groups received only either 24¹³⁸ or 81¹³⁹ mg genistein per day. To put this rather low dose into perspective, there are ~ 10 mg of genistein in one cup of soymilk. To expect robust effects on the prognosis of prostate cancer patients in a relatively short time period in response to such low genistein intakes may be unrealistic.

In conclusion, although no definitive conclusions can be made, there are suggestive data indicating that soy consumption may prevent the development of prostate cancer and aid in the treatment of this disease by inhibiting the spread of prostate tumors and slowing prostate tumor growth. There is even preliminary evidence that isoflavones reduce the side effects associated with radiation treatment for prostate cancer.¹⁴⁰

Isoflavones and Feminization

The estrogen-like effects of isoflavones have led to investigation of the effects of soyfoods on male reproductive hormones and sperm and semen parameters. Ironically, given the large populations of soyfood-consuming countries, concern has arisen that soyfoods might even impair male fertility. However, as discussed below, concerns about feminization are without scientific merit.

Two studies that evaluated reproductive hormone levels in men did find statistically significant reductions in testosterone levels in response to soy protein intake. In the first, in addition to their normal diet, 19 young men consumed three scones per day made with either soy or wheat flour for a period of six weeks.⁸³ Serum testosterone levels decreased from baseline values by almost 6% in the soy group. However, because the final values in the control group were not reported, it is not possible to know whether the difference between groups (the most relevant comparison) was statistically significant. Furthermore, isoflavone exposure in this study was about four times the typical Japanese intake. In the other study, there was a much larger decrease (19%) in testosterone levels, but only 12 men were enrolled in this study and the decrease resulted primarily from the change in just two participants.¹⁴¹ Furthermore, this study lacked a control group. Also, in one of the two men in which the large decrease occurred, baseline testosterone levels greatly exceeded the normal range and the decrease continued for several weeks even after discontinuation of soy protein. As in the previous study, soy intake (56 g soy protein/day) was about four times the typical Japanese intake.

In contrast to these two studies, a meta-analysis published in 2010 that included 32 studies (including the two noted above) and 36 treatment groups found there were no significant effects of soy protein or isoflavone intake on levels of total testosterone,

sex hormone binding globulin, free testosterone or the free androgen index.¹⁴² Studies published subsequent to this analysis are supportive of this conclusion.^{133, 143}

Interest in the effects of isoflavones on sperm quality and quantity is due, in part, to reports that sperm count may have declined over the past few decades. Whether environmental estrogens may have contributed to this decrease is a matter of much debate.¹⁴⁴ In fact, there is also debate about whether sperm count has actually decreased.¹⁴⁵ More directly related to soy are the results of a small pilot case-control study conducted by researchers from Harvard University School of Public Health, which found that men who were classified as soy-consumers had lower sperm concentrations than non-consumers of soy.¹⁴⁶ However, there were several limitations to this study that warrant mention.

There is no meaningful clinical evidence that suggests soy protein lowers serum testosterone levels or exerts any estrogen-like or feminizing effects in men.

First, about half of the decreased sperm concentration resulted from an increase in ejaculate volume. Second, the decrease in sperm concentration only occurred in men consuming the most amount of soy — that is, there was a monotonic response. Third, almost no other information about factors that potentially affect sperm concentration was obtained by the investigators. And finally, even in the highest intake group, soy intake averaged only about ½ serving daily, a relatively small amount compared to the amounts shown to exert effects in clinical studies. That such a low exposure was linked with an effect raises questions about the biological plausibility of the findings. And, even if these findings are valid, they likely have no implication for fertility since sperm concentration decreased primarily among men with an above average sperm concentrations.

In any event, definitive conclusions about the impact of soy on sperm can be based only on the results from clinical (intervention) studies. Three such studies, two published as a full manuscript and one described in the proceedings from a scientific meeting, have evaluated the effects of soy or isoflavones on sperm quality or quantity. In one of the studies, healthy volunteers took a daily supplement containing 40 mg isoflavones for two months. They donated blood and semen samples monthly starting two months before and ending four months after supplementation.¹⁴⁷ Semen samples were analyzed for ejaculate volume, sperm concentration, total sperm count, motility and morphology. In addition, testicular volume was measured. As expected, plasma isoflavone levels increased markedly following supplementation, but there was no effect on hormone measurements, testicular volume or semen parameters over the study period.

In agreement with these findings is a crossover study involving 32 healthy young men who consumed diets in random order for 57 days which were supplemented with milk protein isolate or isolated soy protein containing a high or low amount of isoflavones.¹⁴⁸ Analysis of semen samples collected on days 1 and 57 of each treatment period revealed no significant effects of diet on semen parameters including semen volume, sperm concentration, sperm count, total motile sperm count, sperm motility or sperm morphology. In the third study, 20 volunteers were randomized to three different groups in which they were provided 60, 320 or 480 mg/day isoflavones for three months.¹⁴⁹ When compared to baseline, there were no statistically significant differences in ejaculate volume, sperm concentration, count and motility of spermatozoa in men given isoflavones.

Interestingly, a case report described a benefit from isoflavone supplementation in a male with low sperm concentration who was unable to father a child. Daily isoflavone supplementation for six months led to normalization of sperm quality and quantity and to the birth of a healthy infant.¹⁵⁰ As a result, the authors of this report suggested that isoflavones may be a treatment for low sperm concentration.



Finally, there are two case reports in the literature describing feminizing effects that allegedly occurred as a result of soyfood consumption.¹⁵¹ In one, a 60-year-old man developed gynecomastia likely as a result of a dramatic rise in circulating estrogen levels. These levels were 10-fold higher than the levels following discontinuation of soy consumption. In the other, a 19-year old male vegan developed low testosterone levels, loss of libido and erectile dysfunction.¹⁵²

If soy consumption was in fact responsible for the observed feminizing effects it is because such excessive amounts were consumed in the context of unbalanced and likely nutrient-deficient diets. Both men, coincidentally, reportedly ingested 360 mg/day isoflavones, an intake about 10-fold higher than is typical for Japanese men consuming a traditional diet. In fact, in the vegan male, soy accounted for the vast majority of calories consumed. Furthermore, in contrast to the rise in estrogen levels noted in the 60-year-old man, numerous clinical studies in which men are exposed to as much as 150 mg/day isoflavones, have shown that neither soyfoods nor isoflavone supplements increase levels of this hormone.¹⁵³ And as already discussed, the clinical data show that neither soy nor isoflavone supplements affect testosterone levels. These case reports simply illustrate that potentially consuming excessive amounts of essentially any food can lead to abnormalities and nutrient intakes above established upper safe limits.

How Much Soy Protein do Asians and Americans Consume?

There is confusion about the role soy plays in the diets of Asian populations and precisely how much soy Americans consume. Soy protein is widely used by the food industry and is found in small amounts in an extensive array of foods in the United States. However, soy protein is added to foods primarily for functional purposes, i.e., to improve shelf stability and texture. Consequently, U.S. daily per capita soy protein intake is only 1 to 2 g/day. That amount represents about 2% of total protein intake.¹⁵⁴ Obviously, because soy protein intake is so low, U.S. isoflavone intake is also very low (~2 mg/day).¹⁵⁵ Furthermore, although each gram of protein in minimally processed or traditional soyfoods is associated with about 3.5 mg isoflavones, the protein used by the food industry is often quite low in isoflavones.

In Japan, the daily intake of soy protein among those consuming a traditional diet is approximately 10 g, which represents more than 10% of their total protein intake.⁴ Large studies from Shanghai, China, show that men consume about 12 to 13 g of soy protein per day,¹⁵⁶ which represents about 15% of total protein intake,¹⁵⁷ and that women consume about 9 g/day.¹⁵⁸ Individuals in the upper one-quarter of intake consume about 15 to 20 g soy protein daily. Ten grams soy protein translates to about 1.5 servings since 1 serving of a traditional soyfood provides about 7 g protein although some soyfoods can provide considerably more than this amount.

In older men, dietary protein intakes above the RDA may help prevent sarcopenia or age-related loss in skeletal muscle. Researchers recommend the consumption of at least 30 g of protein at each of the three primary meals. Soyfoods can play important roles in helping men meet protein needs.

Approximately half of the soy intake in Japan comes via unfermented foods, with four foods – tofu, miso, natto and fried tofu – accounting for nearly 90% of all soy consumption.^{159,160} In Shanghai, most of the soy consumed is unfermented, and soymilk, tofu and processed soy products other than tofu account for about 80% of total soy consumption.¹⁶¹

Summary and Conclusions

Soyfoods can play an important role in the diets of men. They provide high-quality protein and are generally low in saturated fat, making most soyfoods excellent choices for men who want to increase protein intake from healthful foods. In addition, soyfoods are heart-healthy; they have a beneficial fatty acid profile and soy protein modestly lowers cholesterol levels. Soy isoflavones may have a number of other coronary benefits. More speculative evidence indicates that soyfoods, perhaps because they contain isoflavones, help reduce risk of prostate cancer. Finally, there is no meaningful clinical evidence that suggests soy protein lowers serum testosterone levels or exerts any estrogen-like or feminizing effects in men.

References

1. Franke, A.A., et al., *HPLC analysis of isoflavonoids and other phenolic agents from foods and from human fluids*. Proc Soc Exp Biol Med, 1998. **217**(3): p. 263-73.
2. Lai, C.H., et al., *Androgenic alopecia is associated with less dietary soy, higher blood vanadium and rs1160312 1 polymorphism in Taiwanese communities*. PLoS One, 2013. **8**(12): p. e79789.
3. Murphy, P.A., K. Barua, and C.C. Hauck, *Solvent extraction selection in the determination of isoflavones in soy foods*. J Chromatogr B Analyt Technol Biomed Life Sci, 2002. **777**(1-2): p. 129-38.
4. Messina, M., C. Nagata, and A.H. Wu, *Estimated Asian adult soy protein and isoflavone intakes*. Nutr Cancer, 2006. **55**(1): p. 1-12.
5. Kuiper, G.G., et al., *Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta*. Endocrinology, 1998. **139**(10): p. 4252-63.
6. Ho, J.Y., et al., *Differential effects of oral conjugated equine estrogen and transdermal estrogen on atherosclerotic vascular disease risk markers and endothelial function in healthy postmenopausal women*. Hum Reprod, 2006. **21**(10): p. 2715-20.
7. Lakoski, S.G., B. Brosnihan, and D.M. Herrington, *Hormone therapy, C-reactive protein, and progression of atherosclerosis: data from the Estrogen Replacement on Progression of Coronary Artery Atherosclerosis (ERA) trial*. Am Heart J, 2005. **150**(5): p. 907-11.
8. Helgason, S., et al., *A comparative longitudinal study on sex hormone binding globulin capacity during estrogen replacement therapy*. Acta Obstet Gynecol Scand, 1982. **61**(2): p. 97-100.
9. Serin, I.S., et al., *Long-term effects of continuous oral and transdermal estrogen replacement therapy on sex hormone binding globulin and free testosterone levels*. Eur J Obstet Gynecol Reprod Biol, 2001. **99**(2): p. 222-5.
10. Reid, I.R., et al., *A comparison of the effects of raloxifene and conjugated equine estrogen on bone and lipids in healthy postmenopausal women*. Arch Intern Med, 2004. **164**(8): p. 871-9.
11. Shulman, L.P., *Effects of progestins in different hormone replacement therapy formulations on estrogen-induced lipid changes in postmenopausal women*. Am J Cardiol, 2002. **89**(12A): p. 47E-54E; discussion 54E-55E.
12. Marqusee, E., et al., *The effect of droloxifene and estrogen on thyroid function in postmenopausal women*. J Clin Endocrinol Metab, 2000. **85**(11): p. 4407-10.
13. Abech, D.D., et al., *Effects of estrogen replacement therapy on pituitary size, prolactin and thyroid-stimulating hormone concentrations in menopausal women*. Gynecol Endocrinol, 2005. **21**(4): p. 223-6.
14. Davies, G.C., et al., *Endometrial response to raloxifene compared with placebo, cyclical hormone replacement therapy, and unopposed estrogen in postmenopausal women*. Menopause, 1999. **6**(3): p. 188-95.
15. Meuwissen, J.H. and H. van Langen, *Monitoring endometrial thickness during estrogen replacement therapy with vaginosonography*. Radiology, 1992. **183**(1): p. 284.
16. Kaari, C., et al., *Randomized clinical trial comparing conjugated equine estrogens and isoflavones in postmenopausal women: a pilot study*. Maturitas, 2006. **53**(1): p. 49-58.
17. Yildiz, M.F., et al., *Effects of raloxifene, hormone therapy, and soy isoflavone on serum high-sensitive C-reactive protein in postmenopausal women*. Int J Gynaecol Obstet, 2005. **90**(2): p. 128-33.
18. D'Anna, R., et al., *The effect of the phytoestrogen genistein and hormone replacement therapy on homocysteine and C-reactive protein level in postmenopausal women*. Acta Obstet Gynecol Scand, 2005. **84**(5): p. 474-7.
19. Garrido, A., et al., *Soy isoflavones affect platelet thromboxane A2 receptor density but not plasma lipids in menopausal women*. Maturitas, 2006. **54**(3): p. 270-6.
20. Khoadjiar, L., et al., *Daidzein-rich isoflavone aglycones are potentially effective in reducing hot flashes in menopausal women*. Menopause, 2007. **14**(3 Pt 1): p. 468-73.
21. Hall, W.L., et al., *Soy-isoflavone-enriched foods and markers of lipid and glucose metabolism in postmenopausal women: interactions with genotype and equal production*. Am J Clin Nutr, 2006. **83**(3): p. 592-600.
22. Katz, D.L., et al., *Raloxifene, soy phytoestrogens and endothelial function in postmenopausal women*. Climacteric, 2007. **10**(6): p. 500-7.
23. Cheng, G., et al., *Isoflavone treatment for acute menopausal symptoms*. Menopause, 2007. **14**(3 Pt 1): p. 468-73.
24. Bruce, B., M. Messina, and G.A. Spiller, *Isoflavone supplements do not affect thyroid function in iodine-replete postmenopausal women*. J Med Food, 2003. **6**(4): p. 309-16.
25. Marini, H., et al., *Effects of the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: a randomized trial*. Ann Intern Med, 2007. **146**(12): p. 839-47.

26. Sammartino, A., et al., *Effects of genistein on the endometrium: ultrasonographic evaluation*. *Gynecol Endocrinol*, 2003. **17**(1): p. 45-9.
27. Brzezinski, A., et al., *Short-term effect of phytoestrogen-rich diet on postmenopausal women*. *Menopause*, 1997. **4**: p. 89-94.
28. Diel, P., et al., *The differential ability of the phytoestrogen genistein and of estradiol to induce uterine weight and proliferation in the rat is associated with a substance specific modulation of uterine gene expression*. *Mol Cell Endocrinol*, 2004. **221**(1-2): p. 21-32.
29. Oseni, T., et al., *Selective estrogen receptor modulators and phytoestrogens*. *Planta Med*, 2008. **74**(13): p. 1656-65.
30. Shanle, E.K. and W. Xu, *Endocrine disrupting chemicals targeting estrogen receptor signaling: identification and mechanisms of action*. *Chem Res Toxicol*, 2011. **24**(1): p. 6-19.
31. McPherson, S.J., et al., *Estrogen receptor-beta activated apoptosis in benign hyperplasia and cancer of the prostate is androgen independent and TNFalpha mediated*. *Proc Natl Acad Sci U S A*, 2010. **107**(7): p. 3123-8.
32. Kerstetter, J.E., K.O. O'Brien, and K.L. Insogna, *Low protein intake: the impact on calcium and bone homeostasis in humans*. *J Nutr*, 2003. **133**(3): p. 855S-61S.
33. Humayun, M.A., et al., *Reevaluation of the protein requirement in young men with the indicator amino acid oxidation technique*. *Am J Clin Nutr*, 2007. **86**(4): p. 995-1002.
34. Elango, R., et al., *Evidence that protein requirements have been significantly underestimated*. *Curr Opin Clin Nutr Metab Care*, 2010. **13**(1): p. 52-7.
35. Paddon-Jones, D. and B.B. Rasmussen, *Dietary protein recommendations and the prevention of sarcopenia*. *Curr Opin Clin Nutr Metab Care*, 2009. **12**(1): p. 86-90.
36. Astrup, A., *The satiating power of protein—a key to obesity prevention?* *Am J Clin Nutr*, 2005. **82**(1): p. 1-2.
37. Bonjour, J.P., *Dietary protein: an essential nutrient for bone health*. *J Am Coll Nutr*, 2005. **24**(6 Suppl): p. S26S-36S.
38. Campbell, B., et al., *International Society of Sports Nutrition Position Stand: Protein and Exercise*. *J Int Soc Sports Nutr*, 2007. **4**(1): p. 8.
39. Martin, D.S., *Dietary protein and hypertension: Where do we stand?* *Nutrition*, 2003. **19**(4): p. 385-6.
40. Umesawa, M., et al., *Relations between protein intake and blood pressure in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS)*. *Am J Clin Nutr*, 2009. **90**(2): p. 377-84.
41. Houston, D.K., et al., *Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study*. *Am J Clin Nutr*, 2008. **87**(1): p. 150-5.
42. Tieland, M., et al., *Protein supplementation improves physical performance in frail elderly people: a randomized, double-blind, placebo-controlled trial*. *J Am Med Dir Assoc*, 2012. **13**(8): p. 720-6.
43. U.S. Department of Agriculture, *Modification of the Vegetable Protein Products Requirements for the National School Lunch Program, School Breakfast Program, Summer Food Service Program and Child and Adult Care Food Program*. Federal Register, 2000. **7 CFR Parts 210, 215, 220, 225 and 226**: p. 12429-12442.
44. Rand, W.M., P.L. Pellett, and V.R. Young, *Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults*. *Am J Clin Nutr*, 2003. **77**(1): p. 109-27.
45. Sarwar, G., R.W. Peace, and H.G. Botting, *Corrected relative net protein ratio (CRNPR) method based on differences in rat and human requirements for sulfur amino acids*. *J Am Oil Chem Soc*, 1985. **68**: p. 68:689-693.
46. Sarwar, G., *The protein digestibility-corrected amino acid score method overestimates quality of proteins containing antinutritional factors and of poorly digestible proteins supplemented with limiting amino acids in rats*. *J Nutr*, 1997. **127**(5): p. 758-64.
47. Gilani, G.S. and E. Sepehr, *Protein digestibility and quality in products containing antinutritional factors are adversely affected by old age in rats*. *J Nutr*, 2003. **133**(1): p. 220-5.
48. Hughes, G.J., et al., *Protein digestibility-corrected amino acid scores (PDCAAS) for soy protein isolates and concentrate: Criteria for evaluation*. *J Agric Food Chem*, 2011. **59**(23): p. 12707-12.
49. Anderson, J.W., *Beneficial effects of soy protein consumption for renal function*. *Asia Pac J Clin Nutr*, 2008. **17 Suppl 1**: p. 324-8.
50. Azadbakht, L. and A. Esmailzadeh, *Soy-protein consumption and kidney-related biomarkers among type 2 diabetics: a crossover, randomized clinical trial*. *J Ren Nutr*, 2009. **19**(6): p. 479-86.
51. Coresh, J., et al., *Prevalence of chronic kidney disease in the United States*. *Jama*, 2007. **298**(17): p. 2038-47.
52. Tang, J.E. and S.M. Phillips, *Maximizing muscle protein anabolism: the role of protein quality*. *Curr Opin Clin Nutr Metab Care*, 2009. **12**(1): p. 66-71.
53. DiSilvestro, R.A., et al., *Soy protein intake by active young adult men raises plasma antioxidant capacity without altering plasma testosterone*. *Nutr Res*, 2006. **26**: p. 92-95.
54. Brown, E.C., et al., *Soy versus whey protein bars: Effects on exercise training impact on lean body mass and antioxidant status*. *Nutr J*, 2004. **3**(1): p. 22.
55. Hill, S., W. Box, and R.A. DiSilvestro, *Moderate intensity resistance exercise, plus or minus soy intake: effects on serum lipid peroxides in young adult males*. *Int J Sport Nutr Exerc Metab*, 2004. **14**(2): p. 125-32.
56. Reidy, P.T., et al., *Protein blend ingestion following resistance exercise promotes human muscle protein synthesis*. *J Nutr*, 2013. **143**(4): p. 410-6.
57. Hegsted, D.M., et al., *Dietary fat and serum lipids: an evaluation of the experimental data*. *Am J Clin Nutr*, 1993. **57**(6): p. 875-83.
58. Mensink, R.P. and M.B. Katan, *Effect of dietary fatty acids on serum lipids and lipoproteins: A meta-analysis of 27 trials*. *Arterioscler Thromb*, 1992. **12**(8): p. 911-9.
59. Jenkins, D.J., et al., *Soy protein reduces serum cholesterol by both intrinsic and food displacement mechanisms*. *J Nutr*, 2010. **140**(12): p. 2302S-2311S.
60. Harris, W.S., et al., *Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention*. *Circulation*, 2009. **119**(6): p. 902-7.
61. Mozaffarian, D., R. Micha, and S. Wallace, *Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials*. *PLoS Med*, 2010. **7**(3): p. e1000252.
62. Jakobsen, M.U., et al., *Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies*. *Am J Clin Nutr*, 2009. **89**(5): p. 1425-32.
63. Ramsden, C.E., et al., *n-6 Fatty acid-specific and mixed polyunsaturate dietary interventions have different effects on CHD risk: a meta-analysis of randomised controlled trials*. *Br J Nutr*, 2010. **104**(11): p. 1586-600.
64. Hayes, K.C., *Dietary fatty acids, cholesterol, and the lipoprotein profile*. *Br J Nutr*, 2000. **84**(4): p. 397-9.
65. Brouwer, I.A., M.B. Katan, and P.L. Zock, *Dietary alpha-linolenic acid is associated with reduced risk of fatal coronary heart disease, but increased prostate cancer risk: a meta-analysis*. *J Nutr*, 2004. **134**(4): p. 919-22.
66. Holguin, F., et al., *Cardiac autonomic changes associated with fish oil vs soy oil supplementation in the elderly*. *Chest*, 2005. **127**(4): p. 1102-7.
67. Dai, J., et al., *High habitual dietary alpha-linolenic acid intake is associated with decreased plasma soluble interleukin-6 receptor concentrations in male twins*. *Am J Clin Nutr*, 2010. **92**(1): p. 177-85.
68. Zhan, S. and S.C. Ho, *Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile*. *Am J Clin Nutr*, 2005. **81**(2): p. 397-408.
69. Sacks, F.M., et al., *Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee*. *Circulation*, 2006. **113**(7): p. 1034-44.
70. Balk, E., et al., *Effects of soy on health outcomes. Evidence report/technology assessment No. 126 (prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022.) AHRQ Publication No. 05-E024-2*, July 2005: Rockville, MD Agency for Healthcare Research and Quality.
71. Weggemans, R.M. and E.A. Trautwein, *Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: a meta-analysis*. *Eur J Clin Nutr*, 2003. **57**(8): p. 940-6.
72. Law, M.R., N.J. Wald, and S.G. Thompson, *By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease?* *Bmj*, 1994. **308**(6925): p. 367-72.
73. Law, M.R., et al., *Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study*. *Bmj*, 1994. **308**(6925): p. 363-6.
74. Cullen, P., *Evidence that triglycerides are an independent coronary heart disease risk factor*. *Am J Cardiol*, 2000. **86**(9): p. 943-9.
75. Bansal, S., et al., *Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women*. *Jama*, 2007. **298**(3): p. 309-16.
76. Nordestgaard, B.G., et al., *Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women*. *Jama*, 2007. **298**(3): p. 299-308.
77. Santo, A.S., et al., *Postprandial lipemia detects the effect of soy protein on cardiovascular disease risk compared with the fasting lipid profile*. *Lipids*, 2010. **45**(12): p. 1127-38.
78. Boden, W.E., *High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: assessing the data from Framingham to the Veterans Affairs High-Density Lipoprotein Intervention Trial*. *Am J Cardiol*, 2000. **86**(12A): p. 19L-22L.
79. Gotto, A.M., Jr., *High-density lipoprotein cholesterol and triglycerides as therapeutic targets for preventing and treating coronary artery disease*. *Am Heart J*, 2002. **144**(6 Suppl): p. S33-42.
80. Grover, S.A., et al., *Evaluating the Incremental Benefits of Raising High-Density Lipoprotein Cholesterol Levels During Lipid Therapy After Adjustment for the Reductions in Other Blood Lipid Levels*. *Arch Intern Med*, 2009. **169**(19): p. 1775-1780.
81. Stamler, R., *Implications of the INTERSALT study*. *Hypertension*, 1991. **17**(1 Suppl): p. 116-20.
82. Desroches, S., et al., *Soy protein favorably affects LDL size independently of isoflavones in hypercholesterolemic men and women*. *J Nutr*, 2004. **134**(3): p. 574-9.
83. Gardner-Thorpe, D., et al., *Dietary supplements of soya flour lower serum testosterone concentrations and improve markers of oxidative stress in men*. *Eur J Clin Nutr*, 2003. **57**(1): p. 100-6.
84. Messina, M. and B. Lane, *Soy protein, soybean isoflavones, and coronary heart disease risk: Where do we stand?* *Future Lipidology*, 2007. **2**: p. 55-74.
85. Goff, D.C., Jr., et al., *2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines*. *Circulation*, 2013.
86. Zhang, B., et al., *Greater habitual soyfood consumption is associated with decreased carotid intima-media thickness and better plasma lipids in Chinese middle-aged adults*. *Atherosclerosis*, 2007.
87. Iglesias del Sol, A., et al., *Carotid intima-media thickness at different sites: relation to incident myocardial infarction; The Rotterdam Study*. *Eur Heart J*, 2002. **23**(12): p. 934-40.
88. Yu, D., et al., *Association of soy food intake with risk and biomarkers of coronary heart disease in Chinese men*. *Int J Cardiol*, 2014. **172**(2): p. e285-7.
89. American Cancer Society, *Cancer Facts and Figures*, 2006.
90. Liu, R.H., *Potential synergy of phytochemicals in cancer prevention: mechanism of action*. *J Nutr*, 2004. **134**(12 Suppl): p. 3479S-3485S.
91. Messina, M., et al., *Reductionism and the narrowing nutrition perspective: time for reevaluation and emphasis on food synergy*. *J Am Diet Assoc*, 2001. **101**(12): p. 1416-9.
92. Dagnelie, P.C., et al., *Diet, anthropometric measures and prostate cancer risk: a review of prospective cohort and intervention studies*. *BJU Int*, 2004. **93**(8): p. 1139-50.
93. Johansson, J.E., et al., *Natural history of early, localized prostate cancer*. *Jama*, 2004. **291**(22): p. 2713-9.
94. Ryan, C.J. and E.J. Small, *Progress in detection and treatment of prostate cancer*. *Curr Opin Oncol*, 2005. **17**(3): p. 257-60.
95. Ward, J.F. and J.W. Moul, *Biochemical recurrence after definitive prostate cancer therapy. Part II: Treatment strategies for biochemical recurrence of prostate cancer**. *Curr Opin Urol*, 2005. **15**(3): p. 187-95.
96. Ward, J.F. and J.W. Moul, *Biochemical recurrence after definitive prostate cancer therapy. Part I: Defining and localizing biochemical recurrence of prostate cancer**. *Curr Opin Urol*, 2005. **15**(3): p. 181-6.
97. Griffiths, K., *Estrogens and prostatic disease. International Prostate Health Council Study Group*. *Prostate*, 2000. **45**(2): p. 87-100.
98. Perabo, F.G., et al., *Soy isoflavone genistein in prevention and treatment of prostate cancer*. *Prostate Cancer Prostatic Dis*, 2007.
99. Mahmoud, A.M., W. Yang, and M.C. Bosland, *Soy isoflavones and prostate cancer: A review of molecular mechanisms*. *J Steroid Biochem Mol Biol*, 2013. **140C**: p. 116-132.
100. Hikosaka, A., et al., *Inhibitory effects of soy isoflavones on rat prostate carcinogenesis induced by 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)*. *Carcinogenesis*, 2004. **25**(3): p. 381-7.

101. Mentor-Marcel, R., et al., *Dietary Genistein Improves Survival and Reduces Expression of Osteopontin in the Prostate of Transgenic Mice with Prostatic Adenocarcinoma (TRAMP)*. J Nutr, 2005. **135**(5): p. 989-95.
102. Yan, L. and E.L. Spitznagel, *Soy consumption and prostate cancer risk in men: a revisit of a meta-analysis*. Am J Clin Nutr, 2009. **89**(4): p. 1155-63.
103. Hwang, Y.W., et al., *Soy food consumption and risk of prostate cancer: a meta-analysis of observational studies*. Nutr Cancer, 2009. **61**(5): p. 598-606.
104. Li, X.M., et al., *Mass screening-based case-control study of diet and prostate cancer in Changshu, China*. Asian J Androl, 2008. **10**(4): p. 551-60.
105. Kurahashi, N., et al., *Soy product and isoflavone consumption in relation to prostate cancer in Japanese men*. Cancer Epidemiol Biomarkers Prev, 2007. **16**(3): p. 538-45.
106. Setchell, K.D., N.M. Brown, and E. Lydeking-Olsen, *The clinical importance of the metabolite equol—a clue to the effectiveness of soy and its isoflavones*. J Nutr, 2002. **132**(12): p. 3577-84.
107. Lund, T.D., et al., *Equol is a novel anti-androgen that inhibits prostate growth and hormone feedback*. Biol Reprod, 2004. **70**(4): p. 1188-95.
108. Akaza, H., et al., *Comparisons of percent equol producers between prostate cancer patients and controls: case-controlled studies of isoflavones in Japanese, Korean and American residents*. Jpn J Clin Oncol, 2004. **34**(2): p. 86-9.
109. Sugiyama, Y., et al., *Influence of isoflavone intake and equol-producing intestinal flora on prostate cancer risk*. Asian Pac J Cancer Prev, 2013. **14**(1): p. 1-4.
110. Xu, L., et al., *MEK4 function, genistein treatment, and invasion of human prostate cancer cells*. J Natl Cancer Inst, 2009. **101**(16): p. 1141-55.
111. Lakshman, M., et al., *Dietary genistein inhibits metastasis of human prostate cancer in mice*. Cancer Res, 2008. **68**(6): p. 2024-32.
112. McNaughton-Collins, M.F. and M.J. Barry, *One man at a time—resolving the PSA controversy*. N Engl J Med, 2011. **365**(21): p. 1951-3.
113. Hernandez, B.Y., et al., *Reports: plasma and dietary phytoestrogens and risk of premalignant lesions of the cervix*. Nutr Cancer, 2004. **49**(2): p. 109-24.
114. Moyer, V.A., *Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement*. Ann Intern Med, 2012. **157**(2): p. 120-34.
115. Stamey, T.A., et al., *Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate*. N Engl J Med, 1987. **317**(15): p. 909-16.
116. Agarwal, P.K. and M.G. Oefelein, *Testosterone replacement therapy after primary treatment for prostate cancer*. J Urol, 2005. **173**(2): p. 533-6.
117. Stock, R.G., et al., *Combined modality treatment in the management of high-risk prostate cancer*. Int J Radiat Oncol Biol Phys, 2004. **59**(5): p. 1352-9.
118. Wang, L.G., et al., *The biological basis for the use of an anti-androgen and a 5-alpha-reductase inhibitor in the treatment of recurrent prostate cancer: Case report and review*. Oncol Rep, 2004. **11**(6): p. 1325-9.
119. Fontana, D., et al., *3-month formulation of goserelin acetate ('Zoladex' 10.8-mg depot) in advanced prostate cancer: results from an Italian, open, multicenter trial*. Urol Int, 2003. **70**(4): p. 316-20.
120. Small, E.J., et al., *Ketoconazole retains activity in advanced prostate cancer patients with progression despite flutamide withdrawal*. J Urol, 1997. **157**(4): p. 1204-7.
121. Picus, J. and M. Schultz, *Docetaxel (Taxotere) as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results*. Semin Oncol, 1999. **26**(5 Suppl 17): p. 14-8.
122. Petrylak, D.P., et al., *Phase I trial of docetaxel with estramustine in androgen-independent prostate cancer*. J Clin Oncol, 1999. **17**(3): p. 958-67.
123. Savarese, D., et al., *A phase II study of docetaxel (Taxotere), estramustine, and low-dose hydrocortisone in men with hormone-refractory prostate cancer: preliminary results of cancer and leukemia group B Trial 9780*. Semin Oncol, 1999. **26**(5 Suppl 17): p. 39-44.
124. Sinibaldi, V.J., et al., *Phase II evaluation of docetaxel plus one-day oral estramustine phosphate in the treatment of patients with androgen independent prostate carcinoma*. Cancer, 2002. **94**(5): p. 1457-65.
125. Messina, M., O. Kucuk, and J.W. Lampe, *An overview of the health effects of isoflavones with an emphasis on prostate cancer risk and prostate-specific antigen levels*. J AOAC Int, 2006. **89**(4): p. 1121-34.
126. Messina, M., *Emerging evidence on the role of soy in reducing prostate cancer risk*. Nutr Rev, 2003. **61**: p. 117-131.
127. Meyer, F., et al., *Antioxidant vitamin and mineral supplementation and prostate cancer prevention in the SU.VI.MAX trial*. Int J Cancer, 2005. **116**(2): p. 182-6.
128. Pendleton, J.M., et al., *Phase II Trial of Isoflavone in prostate specific antigen recurrent prostate cancer after previous local therapy*. BMC Cancer, 2008. **8**(1): p. 132.
129. Kwan, W., et al., *A phase II trial of a soy beverage for subjects without clinical disease with rising prostate-specific antigen after radical radiation for prostate cancer*. Nutr Cancer, 2010. **62**(2): p. 198-207.
130. Ide, H., et al., *Combined inhibitory effects of soy isoflavones and curcumin on the production of prostate-specific antigen*. Prostate, 2010. **70**(10): p. 1127-33.
131. Lazarevic, B., et al., *Efficacy and safety of short-term genistein intervention in patients with localized prostate cancer prior to radical prostatectomy: a randomized, placebo-controlled, double-blind Phase 2 clinical trial*. Nutr Cancer, 2011. **63**(6): p. 889-98.
132. Joshi, M., et al., *Effects of commercially available soy products on PSA in androgen-deprivation-naive and castration-resistant prostate cancer*. South Med J, 2011. **104**(11): p. 736-40.
133. Miyanaga, N., et al., *Prostate cancer chemoprevention study: an investigative randomized control study using purified isoflavones in men with rising prostate-specific antigen*. Cancer Sci, 2012. **103**(1): p. 125-30.
134. Devere White, R.W., et al., *Effects of a high dose, aglycone-rich soy extract on prostate-specific antigen and serum isoflavone concentrations in men with localized prostate cancer*. Nutr Cancer, 2010. **62**(8): p. 1036-43.
135. Fleshner, N.E., et al., *Progression from high-grade prostatic intraepithelial neoplasia to cancer: a randomized trial of combination vitamin-E, soy, and selenium*. J Clin Oncol, 2011. **29**(17): p. 2386-90.
136. Klein, E.A., et al., *Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT)*. JAMA, 2011. **306**(14): p. 1549-56.
137. Kristal, A.R., et al., *Baseline selenium status and effects of selenium and vitamin E supplementation on prostate cancer risk*. J Natl Cancer Inst, 2014.
138. Bosland, M.C., et al., *Effect of soy protein isolate supplementation on biochemical recurrence of prostate cancer after radical prostatectomy: a randomized trial*. JAMA, 2013. **310**(2): p. 170-8.
139. Hamilton-Reeves, J.M., et al., *Short-term soy isoflavone intervention in patients with localized prostate cancer: a randomized, double-blind, placebo-controlled trial*. PLoS One, 2013. **8**(7): p. e68331.
140. Ahmad, I.U., et al., *Soy isoflavones in conjunction with radiation therapy in patients with prostate cancer*. Nutr Cancer, 2010. **62**(7): p. 996-1000.
141. Goodin, S., et al., *Clinical and biological activity of soy protein powder supplementation in healthy male volunteers*. Cancer Epidemiol Biomarkers Prev, 2007. **16**(4): p. 829-33.
142. Hamilton-Reeves, J.M., et al., *Clinical studies show no effects of soy protein or isoflavones on reproductive hormones in men: Results of a meta-analysis*. J Am Dietetic Assoc, (in press).
143. Deibert, P., et al., *Soy protein based supplementation supports metabolic effects of resistance training in previously untrained middle aged males*. Aging Male, 2011. **14**(4): p. 273-9.
144. Phillips, K.P. and N. Tanphaichitr, *Human exposure to endocrine disruptors and semen quality*. J Toxicol Environ Health B Crit Rev, 2008. **11**(3-4): p. 188-220.
145. Fisch, H. and R. Golden, *Environmental estrogens and sperm counts*. Pure Appl Chem, 2003. **75**: p. 2181-2193.
146. Chavarro, J.E., et al., *A prospective study of dairy foods intake and anovulatory infertility*. Hum Reprod, 2007. **22**(5): p. 1340-7.
147. Mitchell, J.H., et al., *Effect of a phytoestrogen food supplement on reproductive health in normal males*. Clin Sci (Lond), 2001. **100**(6): p. 613-8.
148. Beaton, L.K., et al., *Soy protein isolates of varying isoflavone content do not adversely affect semen quality in healthy young men*. Fertil Steril, 2010. **94**(5): p. 1717-22.
149. Messina, M., S. Watanabe, and K.D. Setchell, *Report on the 8th International Symposium on the Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment*. J Nutr, 2009. **139**(4): p. 796S-802S.
150. Casini, M.L., S. Gerli, and V. Unfer, *An infertile couple suffering from oligospermia by partial sperm maturation arrest: can phytoestrogens play a therapeutic role? A case report study*. Gynecol Endocrinol, 2006. **22**(7): p. 399-401.
151. Martinez, J. and J.E. Lewi, *An unusual case of gynecomastia associated with soy product consumption*. Endocr Pract, 2008. **14**(4): p. 415-8.
152. Siepmann, T., et al., *Hypogonadism and erectile dysfunction associated with soy product consumption*. Nutrition, 2011. **27**(7-8): p. 859-62.
153. Messina, M., *Soybean isoflavone exposure does not have feminizing effects on men: a critical examination of the clinical evidence*. Fertil Steril, 2010. **93**(7): p. 2095-104.
154. Smit, E., et al., *Estimates of animal and plant protein intake in US adults: results from the Third National Health and Nutrition Examination Survey, 1988-1991*. J Am Diet Assoc, 1999. **99**(7): p. 813-20.
155. Bai, W., C. Wang, and C. Ren, *Intakes of total and individual flavonoids by US adults*. Int J Food Sci Nutr, 2014. **65**(1): p. 9-20.
156. Lee, S.A., et al., *Assessment of dietary isoflavone intake among middle-aged Chinese men*. J Nutr, 2007. **137**(4): p. 1011-1016.
157. Villegas, R., et al., *Validity and reproducibility of the food-frequency questionnaire used in the Shanghai men's health study*. Br J Nutr, 2007. **97**(5): p. 993-1000.
158. Yang, G., et al., *Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women*. Am J Clin Nutr, 2005. **81**(5): p. 1012-7.
159. Wakai, K., et al., *Dietary intake and sources of isoflavones among Japanese*. Nutr Cancer, 1999. **33**(2): p. 139-45.
160. Somekawa, Y., et al., *Soy intake related to menopausal symptoms, serum lipids, and bone mineral density in postmenopausal Japanese women*. Obstet Gynecol, 2001. **97**(1): p. 109-115.
161. Zhang, X., et al., *Soy food consumption is associated with lower risk of coronary heart disease in Chinese women*. J Nutr, 2003. **133**(9): p. 2874-8.



The 70 farmer-directors of USB oversee the investments of the soy checkoff to maximize profit opportunities for all U.S. soybean farmers. These volunteers invest and leverage checkoff funds to increase the value of U.S. soy meal and oil, to ensure U.S. soybean farmers and their customers have the freedom and infrastructure to operate, and to meet the needs of U.S. soy's customers. As stipulated in the federal Soybean Promotion, Research and Consumer Information Act, the USDA Agricultural Marketing Service has oversight responsibilities for USB and the soy checkoff. For more information, please visit SoyConnection.com.