SPECIAL GUEST EDITOR SECTION

An Overview of the Health Effects of Isoflavones with an Emphasis on Prostate Cancer Risk and Prostate-Specific Antigen Levels

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Soybean isoflavones possess hormonal and nonhormonal properties that may reduce the risk of coronary heart disease, osteoporosis, and certain cancers, and alleviate hot flashes in menopausal women. Among the various cancers whose risk may be reduced by isoflavones, there is particular interest in prostate cancer. Eleven trials have examined the effects of isoflavones on serum prostate-specific antigen (PSA) levels. The dose of isoflavones in these trials from supplements or soy protein ranged from 60 to 900 mg/day (typical Japanese intake is 30–50 mg/day), subject number/group ranged from 8 to 62, and study duration from 20 days to 1 year. Isoflavones did not affect serum PSA in healthy subjects. In contrast, in 4 of 8 trials involving prostate cancer patients, isoflavones significantly favorably affected PSA although in no studies was there an absolute decrease in PSA concentrations. The mechanism by which isoflavones affect PSA could not be determined from the existing research, although hormonal changes do not seem to be a factor. The clinical evidence is sufficiently encouraging to justify considering additional Phase II and III clinical trials investigating the efficacy of soy isoflavones in different populations of prostate cancer patients alone and in combination with other treatments.

Foods made from the soybean have been consumed in Asia for centuries and by vegetarians in non-Asian countries for decades. The soybean has long been embraced as a good source of protein from which a wide variety of foods can be made. Recently, however, there has been interest in the potential health benefits of soy foods beyond the role these foods can play in meeting nutrient needs. More specifically, soy foods have been postulated to reduce the risk of a number of chronic diseases, including coronary heart disease (CHD; 1, 2), osteoporosis (3), and certain cancers (4–6). There are a number of biologically active constituents that may contribute to the many proposed benefits of soy foods, but it is the isoflavones that have primarily caught the attention of the research community. Currently, approximately 600 scientific papers on isoflavones are published annually.

Isoflavones, which among commonly consumed foods are found in nutritionally relevant amounts only in the soybean (7), possess both hormonal (8) and nonhormonal (9) properties that may contribute to their in vivo biological activity. The estrogen-like effects of isoflavones are viewed as possibly leading to reductions in the risk of CHD (2), osteoporosis (3), and alleviation of hot flashes (10), whereas the antiestrogenic effects, which were first observed in mice more than 40 years ago, have been proposed as one mechanism by which isoflavones reduce the risk of breast cancer (11). However, it is the nonhormonal properties that account for most of the interest in the potential chemopreventive properties of isoflavones and have led to the considerable speculation that isoflavones reduce the risk of both hormone-dependent and independent cancers (9).

Among the various cancers that might be affected by isoflavones, there is particular interest in prostate cancer. Animal studies demonstrate that isoflavones inhibit the growth and development of experimentally induced prostate tumors (4). These data, along with the low Asian prostate cancer mortality rates (12) and the case-control and prospective epidemiologic data suggesting soy intake reduces prostate cancer risk (6), have undoubtedly provided the basis for investigating the effects of isoflavones on prostate-specific

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antigen (PSA) levels. This review will focus primarily on evaluating these trials but, in addition, background information about isoflavones, as well as brief discussion of the effects of isoflavones on CHD, osteoporosis, breast cancer, and alleviation of hot flashes, are included.

Isoflavones

Absorption and Metabolism

Isoflavones are a subclass of flavonoids but, by comparison with other flavonoids, have a very limited distribution within the plant kingdom. The 3 soybean isoflavone glycosides are genistin, daidzin, and glycitin, and their respective aglycones are genistein (4′5,7-trihydroxyisoflavone), daidzein (4′,7-dihydroxyisoflavone), and glycitein (7,4′-dihydroxy-6-methoxyisoflavone). Typically, more genistin and genistein exist in soybeans and soy foods than daidzin and daidzein, whereas glycitin and glycitein comprise less than 10% of the total isoflavone content of the soybean (13). Japanese adults consume from 25 to 50 mg/day (all values in this text refer to aglycone equivalents) of isoflavones, and ≤10% of the population consumes as much as 100 mg/day (14–19). By comparison, 1 serving (e.g., 250 mL soymilk, 85 g tofu) of traditional soy foods provides approximately 25 mg isoflavones (13).

After the ingestion of soy foods, there is a small peak in serum isoflavone levels approximately 1–2 h later, but the major serum peak occurs 4–6 h postingestion (20). Most research estimates the half-life of isoflavones to be between 4 and 8 h; 24 h after the consumption of soy foods, nearly all of the isoflavones are excreted (20). Serum isoflavone levels increase in a dose-dependent fashion in response to soy food consumption (21–23), although the efficiency of isoflavone absorption decreases somewhat as doses rise above approximately 50 mg (24, 25). There is, however, significant variation in isoflavone metabolism among individuals that leads to a wide range in serum concentrations of both parent isoflavones and their metabolites (20, 26). Most notable in this regard is that only approximately 30 to 50% of individuals harbor the intestinal bacteria that convert the isoflavone daidzein into the isoflavonoid equol; equol has been proposed as an especially beneficial compound in general (27, 28) and specifically for the prevention of prostate cancer (29–31).

Physiological Attributes

Isoflavones have a chemical structure similar to the hormone estrogen, bind to estrogen receptors (ERs), and exert some estrogen-like effects in cells (32, 33). However, the estrogen-like effects of isoflavones are often not observed in vivo (34–36), which is not surprising because it is well established that ER-binding ligands often have very different, and sometimes opposite, biological effects (37). Arguably, isoflavones are more accurately classified as selective ER modulators than as phytoestrogens (38, 39). The selectivity of isoflavones may stem in part from their preferential binding to, and activation of, ERβ in comparison to ERα (40–42).

As noted previously, isoflavones, especially genistein, exert nonhormonal effects. These effects are particularly relevant to cancer prevention and treatment. For example, in vitro, genistein modulates genes that are related to the control of cell cycle and apoptosis and inhibits the activation of NF-κB and Akt signaling pathways (9). More detailed information about the possible mechanisms by which genistein inhibits the growth of prostate cancer cells is provided later.

Isoflavones and the Prevention of Chronic Disease

Coronary Heart Disease

The cholesterol-lowering properties of soy protein were first demonstrated in humans in 1967 (43), although it was not until 1995 (44) that these properties caught the attention of the general nutrition community. The mechanism by which cholesterol is lowered has not been established (45), but some evidence suggests that isoflavones enhance the response to soy protein, although there is little evidence that they are hypocholesterolemic on their own (46). In any event, cholesterol reduction is quite modest (≤5%; 46, 47), although still relevant from a public health perspective (48, 49). In October 1999, the U.S. Food and Drug Administration approved a health claim that daily intake of 25 g or more of soy protein prevents heart disease. It is likely, however, that the postulated coronary effects of isoflavones independent of cholesterol reduction have the greater potential for lowering CHD risk.

Several studies have shown that isoflavones improve systemic arterial compliance (50) and endothelium-dependent and independent vascular reactivity (51–54). Isoflavones may also inhibit low-density lipoprotein cholesterol (LDLC) oxidation (55, 56). Still, the inconsistent data in each of these areas prohibits conclusions from being drawn. Still, the dramatic reduction (86%) in the relative risk of nonfatal myocardial infarction associated with soy consumption in the Shanghai women's study, a prospective epidemiologic study involving approximately 65 000 postmenopausal women, certainly suggests that soy exerts multiple coronary benefits becuase the modest cholesterol-lowering effects of soy protein could not account for these protective effects (1).

Osteoporosis

Asian epidemiologic studies generally show that soy intake is positively associated with bone mineral density (BMD; 3), and in the only epidemiologic study to include fractures as an end point, relative risk was reduced by approximately one-third when comparing Chinese women in the fifth versus first soy protein intake quintile (57). Rodent studies show isoflavones and isoflavone-rich soy protein reduce bone loss in young ovariectomized rats and aged retired breeders, although not in ovariectomized virgin adult rats (58). Both the hormonal and nonhormonal properties of isoflavones may help to reduce bone loss (59).

The first human study suggesting isoflavones favorably affect bone health was published in 1996 (60), and since that time at least 20 additional clinical trials have examined the

effects of isoflavones—from either supplements or isolated soy protein (ISP, by definition ISP is at ≥90% protein)—on BMD in peri- or postmenopaual women (3). Overall, the data are intriguing, but the inconsistent results and relatively small size and short duration of most trials prevent definitive conclusions from being drawn. Those trials in which skeletal benefits have been observed suggest 80 mg/day of isoflavones is efficacious, although few studies used more than 1 dose. Brief discussion of a few trials follows.

One of the better-designed studies found that, over the course of 1 year, postmenopausal women who received 54 mg/day of genistein experienced statistically significant increases in lumbar and femoral neck BMD that were comparable in magnitude to women in this study who were administered conventional hormone replacement therapy (61). In agreement, two 2-year studies demonstrated that, in postmenopausal women in comparison to ISP devoid of isoflavones, isoflavone-rich ISP reduced bone loss at the spine (62) and/or hip and spine (63). In the former study, results were primarily limited to equol producers and, in the latter, to women not on hormone replacement. In contrast to these 3 trials, several well designed trials failed to observe skeletal benefits of isoflavones, although the failure of one such trial to do so may have been because the women in this study were an average 67 years of age (64).

Currently, several large trials evaluating the skeletal effects of isoflavones in postmenopausal women of at least 2 years' duration are underway. The results of these trials will likely allow for more definitive conclusions to be drawn. In the meantime, it seems reasonable for women concerned about bone health to consider including a source of isoflavones in their diet.

Breast Cancer

Research generally shows that isoflavone-rich ISP and isolated isoflavones inhibit mammary cancer in rodents regardless of the method of tumor induction (65–67), although there are exceptions (68, 69), and in many studies tumor inhibition was not particularly robust. Recent data indicate background diet may affect efficacy (70).- A meta-analysis that included 16 epidemiologic studies concurs with the animal data; however, many of these studies were of rather poor quality (5). Furthermore, the clinical data show little evidence of benefit; soy does not lower estrogen levels (8, 71), decrease breast tissue density (72, 73), or breast cell proliferation in vivo (74), although there is some evidence that soy favorably affects estrogen metabolism (75), decreases tumor necrosis factor alpha (76), and increases menstrual cycle length (8) [longer cycles are thought to be protective against breast cancer (77)].

Finally, there is particularly intriguing animal (78, 79) and epidemiologic (80, 81) evidence suggesting that soy consumption during childhood and/or adolescence, likely because of isoflavone exposure, reduces risk of developing breast cancer during adulthood. These observations are consistent with mounting evidence indicating that early life influences—parity, lactation, age at menses, birth weight, etc.—impact risk of developing breast cancer (82–93).

Alleviation of Hot Flashes

In 1992, isoflavones were first suggested to possibly account for the low incidence of hot flashes among Japanese women (10) and, in 1995, the first clinical trial examining this hypothesis was published (94). The more than 20 clinical trials published since then have produced very conflicting findings, however (95–97). The large placebo response typically observed in most trials complicates investigation of this area (98). The different products (e.g., supplements versus foods) used in these trials further complicates interpretation of the data (99). In this regard, some evidence suggests high-genistein supplements are more efficacious than low-genistein supplements. Additional proposed explanations for the inconsistent results are the marked differences in isoflavone metabolism that exist among individuals (26, 27) and the variation (some evidence suggests efficacy is positively related to frequency) in the mean baseline hot flash frequency among study subjects (97). It is certainly not possible to conclude that isoflavones alleviate hot flashes, although arguably the data are sufficiently suggestive to justify that women try isoflavones for relief.

Prostate Cancer

Among men worldwide, cancer of the prostate is the third (100) most common cancer and sixth (101) most common cause of cancer death but, in the United States, prostate cancer is ranked first and second, respectively, in these categories (102). Prostate cancer mortality rates are 3 times higher among developed than among developing countries, but rates in Europe and the United States are 5 to 10 times that of Japan, despite the high socioeconomic status of this country (101). Migration data indicate that this East-West difference is largely, if not completely, environmentally determined (103, 104). Interestingly, autopsy data suggest that prostate cancer in Japan does not progress as readily to the more advanced stages of this disease as it does in high-risk countries (105, 106). Furthermore, Shibata et al. (106) estimated that as much as 80% of prostate cancer in Japan may go undetected, thereby making their low prostate cancer mortality rate even more remarkable.

Recent animal research suggests isoflavones may be one factor contributing to the lack of progression of latent prostate cancer among Japanese men. In male rats, isoflavone supplementation reduced the number of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine-induced prostate tumors but did not affect the development of prostatic intraepithelial neoplasia (107). Similarly, in the transgenic adenocarcinoma of mouse prostate model, genistein delayed the progression from benign to malignant tumors (108). In agreement with these studies is a case report that suggested the high rate of apoptosis in a prostate specimen taken from a 66-year-old prostate cancer patient may have been due to the daily consumption of isoflavones 1 week prior to

radical prostatectomy for moderately high-grade adenocarcinoma (109).

In Vitro and Animal Studies

Genistein inhibits the growth of both androgen-dependent (110–114) and independent (110, 113–117) prostate cancer cells in vitro. Although the concentration required to inhibit growth markedly exceeds serum genistein concentrations in soy food consumers (118–120), several observations suggest these in vitro data are biologically relevant (110, 116, 120). For example, in rats, prostate tissue genistein concentrations that led to a reduction in epidermal growth factor receptor content were at least 100-fold lower than those required to inhibit prostate cancer cell growth in vitro (120). Furthermore, the animal data are consistent with the in vitro inhibitory effects. Although there are exceptions (121), isolated isoflavones and isoflavone-rich soy protein inhibit prostate tumor growth and development, whether tumors are initiated chemically (122–124), via the transplantation of prostate cancer cells (114, 125, 126), or by genetic manipulation (127, 128).

The estrogen-like effect of genistein may, in theory, contribute to the in vitro inhibitory effects of this isoflavone becuase high-dose estrogen has been used in the treatment of prostate cancer (129). Furthermore, isoflavones preferentially activate ERβ in comparison to ERα; some evidence suggests activation of the former leads to prostate tissue differentiation (130, 131). Isoflavones also inhibit the activity of 5-α reductase, thereby possibly reducing cellular concentrations of dihydrotestosterone (DHT; 132, 133). Recent work indicates that another possible mechanism by which genistein decreases prostate cancer risk is by increasing prostate tissue vitamin D levels (134).

Nevertheless, it is the nonhormonal properties of isoflavones that have attracted most of the attention in regard to anticancer effects (9, 135). Kyle and colleagues (116) found that the lack of ERs did not prevent genistein from inhibiting the growth of PC3-M cells in vitro. At high concentrations, genistein has long been identified as an in vitro inhibitor of tyrosine protein kinases (136), a group of mitogenic enzymes, although Peterson and Barnes (110) showed early on that the growth inhibitory effect of genistein against LNCaP cells was not related to phosphorylation inhibition. Similarly, Santibanez et al. (113) found that, although high concentrations of genistein inhibited the growth of PC-3, DU-145, and LNCaP cells, tyrosine phosphorylation was decreased only in the PC-3 cells (113). The growth-inhibitory effects of genistein can be attributed in part to alteration in cell cycle (112, 137), induction of apoptosis (111, 112, 116), and modulation of several signaling and adhesion molecules (112, 117, 137, 138).

In conclusion, it is clear that there are many pathways and mechanisms by which genistein and other isoflavones and their metabolites may inhibit prostate tumorigenesis. This point may be best illustrated by findings by Li and Sarkar (139), who recently reported that, in PC3 cells, 832 genes showed a greater than 2-fold change after genistein treatment.

Prostate-Specific Antigen as a Marker for Early Detection and Monitoring of Treatment Response in Prostate Cancer

Measurement of serum PSA has become the most common event leading to the diagnosis of prostate carcinoma (140, 141). PSA is a serine protease synthesized by prostate epithelial cells, and its functional role is in the liquefaction of the seminal coagulum to allow release of spermatozoa. For the past decade or more, a PSA value of 4.0 ng/mL has been considered to be the upper limit of normal. However, recent research found that approximately 15% of men with prostate cancer had PSA values between 3.1 and 4.0 ng/mL (142). Thus, the optimal upper limit of normal for PSA for prostate cancer screening is unknown (140). Aside from total PSA levels, other PSA-related markers of prostate cancer risk include PSA velocity (an annual increase of 0.75 ng/mL should prompt biopsy regardless of PSA level) and the ratio of free (unbound to plasma proteins) to total PSA (140).

Clearly, PSA is not a perfect marker, as levels of this protein are elevated by benign prostatic hyperplasia, prostatic inflammation, and other prostate conditions (143–145). Nevertheless, in men with prostate tumors, serum PSA concentration is proportional to prostate tumor volume (146), and successful treatments for prostate cancer do lower PSA levels (147–155). However, recent intervention data demonstrate that reducing prostate cancer risk is not dependent upon reductions in PSA levels (156).

Effects of Isoflavones on PSA Levels in Men without Prostate Cancer

Three studies were identified that examined the effects of isoflavone-rich soy protein on PSA levels in healthy subjects (Table 1; 157–159). In 2 of these (157, 158), ISP rich in isoflavones was compared to ISP nearly devoid of isoflavones, whereas in the third study, diets that included or lacked isoflavone-rich ISP were compared (158). In the text that follows, the total number of grams of soy protein consumed by the study subjects precedes "ISP", and the milligrams of isoflavones provided by that amount of ISP follows. For example, a study in which subjects consumed 25 g ISP that provided a total of 50 mg isoflavones would be referred to as "25 g ISP-50".

The first study to examine PSA levels was a randomized, double-blind, crossover pilot study by Urban et al. (157) involving 34 elderly hyperlipidemic men with an initial PSA of >4 ng/mL. Half of the subjects consumed 37.5 g ISP-69 and half 37.5 g ISP-3.4; after 6 weeks, subjects were switched to the opposite protein for another 6 weeks. Irrespective of the order in which the 2 soy proteins were administered, there were no effects on PSA levels. In agreement with these findings are those from a 1-year double-blind, parallel-arm randomized trial by Adams et al. (158) in which 81 healthy older men with low (geometric mean, 1.7 ng/mL) PSA levels were assigned to consume either 40 g ISP-83 or ISP-3. PSA

Table 1. Studies examining the effects of isoflavones supplements or isoflavones-rich soy protein on serum prostate-specific antigen levels in healthy subjects and prostate cancer patients[a,b]

Ref.	Study type	Subjects; *n*, age (years)	Study duration	Intervention	Subject/patient eligibility or description	PSA values (ng/mL; mean unless otherwise indicated)
					Men without histologically confirmed prostate cancer	
157	Crossover	34, 65.4 ± 2.3	6 weeks	Usual diet + 37.5 g ISP-69 mg or ISP-3.4 mg	PSA ≥4 ng/mL	ISP– to ISP+ / ISP+ to ISP– Baseline: 9.1 / 7.6 1st period: 8.7 / 7.8 2nd period: 8.7 / 8.2 Wilcoxon rank sum test; changes from baseline in ISP– and ISP+, $P = 0.622$
158	Parallel	81, approx. 64.4	12 months	Usual diet + 40 g ISP-83 mg or ISP-3	Colorectal adenomatous polyp patients	ISP– / ISP+ Baseline: 1.7 / 1.7 12 months: 2.0 / 2.0 (Geometric means)
159	Crossover	46, 57 ± 2	2–12 weeks	National Cholesterol Education Program (NCEP) Step II ± approx. 44 g ISP-116 mg	Hyperlipidemic; 4 had BPH and 1 intraepith elial neoplasia	Control: Weeks 0 / 3–4; Total 2.4 / 2.4; Free 0.4 / 0.4 ISP: Weeks 0 / 3–4; Total 2.4 / 2.4; Free 0.4 / 0.4 $P = 0.663$ (total); $P = 0.532$ (free, $n = 17$)
					Men with histologically confirmed prostate cancer	
160	Open label	35, 73	5.5 months (0.8–6 months)	120 mg IF	↑ PSA on 3 successive occasions ≥2 weeks apart with a ↑ trend of ≥10 ng/mL at 2 successive readings ≥2 weeks apart	Percent rise in PSA per month^ Status*: Pre** / Post** / *P*-value RP or RT: 14 / 6 / 0.21 HT: 31 / 9 / 0.05 * = Prior treatment; ** = mean ± SE[c]
161	Open label	20, 68.9 ± 7.3	84 days	Days 0–28, 449 mg IF, days 28–84, 898 mg IF	Stage B, C, or D PCa, years (mean ± SD)[d] since diagnosis to study start = 4.8 ± 3.5	Day: 0 / 84 / 112 PSA: 3.6 / 4.8 / 6.3 PSAMR^: 0.28% / 0.70% PSAMR = *P* value for Days 0–84 versus 84–112 = 0.29

Table 1. (*continued*)

Ref.	Study type	Subjects; *n*, age (years)	Study duration	Intervention	Subject/patient eligibility or description	PSA values (ng/mL; mean unless otherwise indicated)
162	Open label	52, approx. 73	6 months	900 mg IF	↑ PSA on 2 consecutive readings; most failed conventional treatment	Status* / Baseline** / Final**: RP 8.7 / 14.2; RT 6.6 / 10.1; RP/RT 2.5 / 4.3; Off cycle 7.0 / 9.8; WW 8.0 / 8.6. *Prior treatment; ** mean
163	Open label	17, 71 (59–81)	5.4 months (3.0–7.2)	Phase I diet (PID): low fat (approximately 20% kcal) + vitamin E, selenium, and multivitamins. Phase II: PID + 33 g ISP-114	Prior treatment, RP (n = 6) or RT (n = 14). ↑ PSA values (on 2 consecutive readings ≥1 week apart) > the post-RP or RT nadir values with the 2nd > 1st. Also, PSA ≥0.5 for RP or ≥1.0 for RT patients; median PSA, 11.0 ng/mL	Phase I / Phase II: PSA doubling time^, months 7.6 / 11.3. Median values P = 0.06, Wilcoxon signed rank test; P = 0.018, proportional hazards model. Time to progression^, months 3.4 / 6.3. P = 0.29, proportional hazards model
164	Open label	19, 69.5 ± 6.6	20 days (7–54)	160 mg red clover IF	Gleason score ≥5	Initial / Final: Control* 8.7 / 9.3; Isoflavones 10.9 / 11.3. *Historical controls. Differences NS
165	Parallel	76, approx. 71.7 ± 5.2	12 weeks	Usual diet + control protein or ISP-120 mg genistein	Met watchful waiting criteria and had Gleason scores ≤6	Control (Initial / Final) / ISP (Initial / Final): Total 7.5 / 6.9 / 7.4 / 6.8; Free 1.0 / 0.9 / 1.0 / .09. Differences between initial and final values and final values for each group NS.

Table 1. (*continued*)

Ref.	Study type	Subjects; *n*, age (years)	Study duration	Intervention	Subject/patient eligibility or description	PSA values (ng/mL; mean unless otherwise indicated)				
166	Parallel	16, 61.1 ± 5.2	22.7 days ± 3.2	Bread from wheat or soy (117 mg IF)	Scheduled to undergo RP and no previous RT		Control		Soy	
							Initial	Final	Initial	Final
						Total	5.8	7.1	7.2	6.3
						Free	0.6	0.6	0.7	0.7
						F/T	0.11	0.09	0.10	0.13 ± 0.04
						Final total and F/T values between wheat and soy, $P = 0.02$ and 0.01, respectively				
							PSA doubling times (weeks)			
167	Crossover	32, 70 (54–81)	6 weeks	Multibotanical supplement (100 mg IF)	Hormonally untreated men with rising PSA >0.1 ng/mL but no recurrent cancer		Control	Supplement	*P*-value	
						Total	41	44	NS	
						Free	68	13	0.02	
							In men with decrease in FAI (≤0)			
						Total	36	115	0.042	
						Free	45	2	0.049	

[a] BPH = Benign prostatic hyperplasia; ISP = isolated soy protein; ISP– = isolated soy protein without isoflavones; IF = isoflavone; NS = not statistically significant; FAI = free androgen index; RP = radical prostatectomy; RT = radiotherapy; Rx = treatment; WW = watchful waiting.

[b] Definitions related to treatment measures: ^ = Percent rise in PSA/month = % increase in serum PSA level over a given period of time compared to the baseline level. PSAMR, PSA multiplicative rate = % change in serum PSA level/day compared to baseline level. PSA doubling time = period of time (days, weeks, months) it takes for the serum PSA to double (i.e., increase by 100%). Time to progression = period of time (days, weeks, months) it takes to observe a predefined increase in PSA (usually >25 or 50%).

[c] SE = Standard error.

[d] SD = Standard deviation.

levels increased approximately 16% in each group, and the proportion of men with a PSA velocity greater than 1 ng/mL/year was 17.6 and 12.8% ($p = 0.54$) in the ISP-83 and ISP-3 groups, respectively. There were no significant differences in either measure between groups.

Finally, Jenkins et al. (159) combined several studies of slightly differing design to examine the effects of isoflavone-rich soy protein on PSA in middle-aged men with normal (2.4 ng/mL) PSA levels. Most of the total number ($n = 46$) of subjects were studied for 3 to 4 weeks and consumed daily a variety of soy products that provided approximately 44 g soy protein and 116 mg isoflavones. This diet was compared to a similar diet that contained the same amount of total, but no soy, protein. There were no effects of soy on PSA levels in men overall, nor in a subset ($n = 13$) of men who consumed for an additional 8 weeks either the control diet or a diet containing approximately 14 g soy protein that provided 42 mg isoflavones daily.

In conclusion, the results from the 3 previously discussed studies indicate that neither isoflavones nor soy protein affect PSA levels in healthy men with normal or moderately elevated PSA levels. The duration of 2 (157, 159) of the 3 studies was ≤6 weeks, but the largest study was conducted for 1 year (158). Thus, short duration is unlikely to be a factor in the failure to observe effects on PSA. Furthermore, because none of the trials found even a trend toward statistically significant results, larger subject numbers would almost certainly not have altered the findings.

Effects of Isoflavones on PSA Levels in Men with Prostate Cancer

Eight studies were identified that examined the effects of soy protein or isolated isoflavones alone or in combination with other biologically active components on PSA levels in prostate cancer patients (Table 1). Of the 8 trials, 5 were open label (results were compared to the prestudy values; 160–164), 2 employed a parallel design (165, 166), and one, a crossover design (167). The dose of isoflavones from supplements or soy protein ranged from 60 to 900 mg/day (in 5 trials, the dose was ≤120 mg/day); subject number/group ranged from 8 (166) to 62 (162), and study duration from 20 days (164) to 1 year (162).

Five trials used isoflavone supplements (160–162, 164, 167), 2 ISP (163, 165), and one, soy grits (a soy product with approximately 50% protein that is similar to soy flour except that the soybeans have been toasted and cracked into coarse pieces rather than a fine powder; 166). In 4 trials, most or all of the patients had failed conventional medical treatment prior to study enrollment (160, 162, 163, 167). Four studies (161, 162, 164, 165) found no statistically significant effects on PSA; in 2 (160, 163), isoflavones slowed the rise in PSA levels in comparison to the preintervention values, and in 2 others (166, 167) the change in a PSA-related measure was statistically significantly different from the placebo or control groups.

Studies Not Showing Statistically Significant Effects

In the longest study and the one that used the highest dose of isoflavones, deVere White et al. (162) administered 900 mg/day of isoflavones for 6 months to 52 cancer patients. This dose of isoflavones is approximately 20-fold higher than typical adult Japanese daily intake (14–19). Of the 52 men in this study, all but 13 had failed conventional medical treatment that included hormone treatment (HT; men were off cycle), radical prostatectomy (RP), radiotherapy (RT), or a combination of the latter 2. No differences between baseline and final PSA levels or Gleason scores were noted in patients belonging to any of these categories. However, in 8 of the 13 men who were in the watchful waiting period, there was a decrease in PSA levels ranging from 3 to 61%; PSA levels on average were 27% lower than otherwise predicted ($P = 0.026$). The differing response between these men and the patients previously treated for their cancer was not attributed to differences in initial Gleason scores nor to changes in free or total testosterone levels, as isoflavones did not affect hormone status.

The possibility that isoflavones specifically affect men undergoing active surveillance is not supported by the results from a 12-week parallel study by Kumar et al. (165), which failed to find differences in final total or free PSA values between the isoflavone and placebo groups. Fifty-nine patients with Gleason scores ≤6 who had no previous treatment for their cancer completed the study. Despite the lack of a statistically significant difference between the 2 groups overall, none of the control, but 19% of the ISP group, experienced a ≥2 ng/mL decrease in PSA. However, this suggests that PSA rose to a greater extent in some men given ISP, because the overall means for the 2 groups did not differ. In this study, serum-free testosterone was reduced or showed no change in 61% of subjects in the isoflavone group compared to 33% in the control group. Conversely, serum-free testosterone increased in 67% of subjects in the control, but in only 39% of the ISP group. However, differences in free testosterone, free or total estradiol, and sex hormone binding globulin between groups were not statistically significant.

Another 12-week study also found no statistically significant effects of isoflavones on PSA levels, although there did appear to be a trend in that direction (161). In this study, 20 men (mean age, 68.9 years) with stage B, C, or D prostate cancer diagnosed on average 4.8 years before the start of the study, were given 449 mg of isoflavones/day for the first 28 days and then, in all but one subject, the dose was increased to 898 mg/day for the next 56 days. PSA levels remained unchanged in the 7 subjects (baseline PSA ≤0.4 ng/mL) in remission. However, the PSA multiplicative rate (*see* Table 1 for definition) for the other 13 subjects during Days 0–84 was substantially, although not statistically significantly, lower (0.28 vs 0.70%, $P = 0.29$) than the rate during Days 84–112, when subjects were no longer consuming isoflavones. No changes in levels of total or free testosterone, DHT, or

luteinizing hormone were noted, but dehydroepiandrosterone levels were significantly reduced (–31.7%, $P = 0.0004$).

Finally, in a short-term study by Jarred et al. (164), 20 men with nonmetastatic prostate cancer with Gleason scores ≥5, who were scheduled for RT were given 160 mg/day of isoflavones (derived from red clover) prior to surgery. On average, patients received isoflavones for 20 days (range, 7–54 days) but, at the end of this period, there were no differences in PSA levels or Gleason scores between the 19 patients who finished the study and historically matched controls. However, apoptosis in radical prostatectomy specimens from isoflavone-treated patients in regions of low- to moderate-grade cancer (Gleason grade 1–3) for the epithelial cell compartment was significantly higher (1.74 vs 0.24%, $P = 0.0003$) than in the controls

Studies Showing Statistically Significant Effects

The first study to demonstrate a favorable effect on PSA levels in prostate cancer patients compared the prestudy rise in PSA levels to the rise in PSA levels following a median exposure time of 5.5 months (range, 0.8 to 6 months) to 120 mg/day of isoflavones (160). Hussain et al. (160) enrolled 3 groups of patients, those undergoing watchful waiting (Group I, $n = 4$), those who had received RP or RT (Group II, $n = 18$), and those who had received HT (Group III, $n = 17$) after failing RP or RT or both. To qualify for enrollment, the patient's PSA had to increase on 3 successive occasions at least 2 weeks apart, with an increasing trend of ≥10 ng/mL at 2 successive readings at least 2 weeks apart.

In Groups I, II, and III, 3 of 4 (75%), 15 of 18 (83%), and 6 of 17 (35%) had stable PSA values, respectively. (No further data on Group I was presented.) The median number of days of observation prior to the start of the study and of exposure to isoflavones in Group II was 238 and 173, respectively. In this group, the rate of percent PSA rise/month (*see* Table 1 for definition) before and after isoflavone supplementation was reduced by more than half (14 ± 3 versus 6 ± 3, $P = 0.21$), but the results were not statistically significant. In Group III, the median number of days of observation prior to the start of the study and of exposure to isoflavones was 121 and 133, respectively. In this group, the percent PSA rise before and after isoflavone supplementation was statistically significantly reduced by approximately 75% (31 ± 5 versus 9 ± 8, $P = 0.05$). There were no effects of treatment on plasma levels of testosterone, insulin-like growth factor I (IGF-1), insulin-like growth factor-binding protein-3 (IGFBP-3), or IGF-1/IGFPB-3 ratio.

The next study by Spentzos et al. (163) involved 2 dietary phases and included 20 patients, 6 of whom had previously undergone RP and 14, RT. To be eligible for enrollment, PSA values had to increase on 2 consecutive readings ≥1 week apart and be greater than the post-RP or -RT nadir values, with the second value being greater than the first. Also, for RP patients PSA had to be ≥0.5 ng/mL and, for RT patients, ≥1.0 ng/mL. The median PSA prior to study start was 11.0 ng/mL. The Phase I diet (PID) was a low-fat diet (approximately 20% kcal from fat) that also included supplements of vitamin E and selenium, and the Phase II (PIID; $n = 17$) diet consisted of the PID plus 33 g ISP-114. The average followup period during PID and PIID was 3.9 and 5.4 months, respectively.

Among the 18 evaluable patients, median PSA doubling time (PSAdT; *see* Table 1 for definition) on the PIID was 11.3 (25th and 75th percentile; 6.7, 39.5) months, approximately 50% longer than the PSAdT of 7.6 (5.3, 13.8) months on the PID ($P = 0.06$). Similarly, the time to progression (*see* Table 1 for definition) on the PIID and the PID was 6.3 (4.4, ∞) and 3.4 (3.0, 9.7) months, respectively ($P = 0.018$). At the conclusion of the PIID, there was an increase in IGF-1 levels ($P = 0.02$ adjusted for changes in weight and IGFBP-3), but no change in IGFBP-3, and a trend toward a decline in testosterone levels.

In a short-term study by Dalais et al. (166), similar in design to the trial by Jarred et al. (164) discussed previously, approximately 20 days prior to surgery prostate cancer patients consumed daily 4 slices of 1 of 3 kinds of bread: wheat bread (control, $n = 8$), soy bread that provided 117 mg isoflavones ($n = 8$), and a soy and flaxseed combination bread ($n = 10$). The percent change (–12.5%) between the initial and final (7.2 ± 3.2, 6.3 ± 3.1) total PSA levels in the soy group was significantly ($P = 0.02$) different from the percent change (+22.4%) between the initial and final (5.8 ± 3.7, 7.1 ± 4.2) PSA values for the control group. Percent changes in initial and final free PSA levels in the control group did not differ significantly from the percent changes in initial and final free PSA levels in the soy group, but the percent increase in the free:total PSA ratio in the soy group was significantly ($P = 0.01$) different from the decrease in the control group.

Unexpectedly, there were no differences between the soy/flax group and wheat groups, whereas the increase in the free:total PSA ratio in the soy group was significantly ($P = 0.007$) different from the decrease in the soy/flax group. There were no significant differences among groups in levels of testosterone, DHT, or sex hormone binding globulin (SHBG), but the free androgen index of the soy group was modestly, although statistically significantly ($P = 0.04$), higher than the soy/flax group.

In the final investigation, men were given a cocktail of biologically active dietary components that included, in addition to 100 mg isoflavones, carotenoids, α-tocopherol, phytosterols, green tea extract, and selenium. Thus, the results of this study by Kranse et al. (167) can not be ascribed specifically to isoflavones. Eligibility inclusion criteria included a confirmed rising PSA level >0.1 ng/mL and no clinical evidence of recurrent prostate cancer after RP, RT, or watchful waiting. Also, prior to entry, PSA levels of >0.1 ng/mL had to be measured on >2 occasions at a >3-month interval.

Thirty-seven patients with a median PSA value of 3.2 ng/mL were enrolled into the study; half consumed the placebo for 6 weeks and half, the cocktail. After a 2-week washout, men were switched to the opposite treatment. Twenty-six of the men had previously undergone RP, 6 were treated with RT, and 5 were managed by watchful waiting.

The PSAdT increased from an average of 41 weeks during the placebo period to 44 weeks during the cocktail period, but this difference was not statistically significant.

When the analysis was restricted to the 21 of 32 men in whom there was a decrease in the free androgen index, the average PSAdT during the placebo and cocktail period was 36 and 115 weeks, respectively ($P = 0.04$). Similarly, among these men, free PSAdT time was 45 weeks during the placebo, which changed to a half-life of 12 weeks during the cocktail ($P = 0.049$). During the cocktail period, testosterone and DHT levels decreased significantly, and there was a trend toward a decrease in free androgen index.

Reports of Adverse Effects

The probability of adverse events occurring as a result of treatment for any condition or disease is an important factor in determining clinical utility. Generally, dietary approaches to cancer prevention and treatment are considered less likely to result in clinical toxicity than are pharmacological approaches. In this regard, these PSA trials provide the clearest picture to date on the possible adverse effects of high-isoflavone consumption in men over an extended period of time. Overall, the unequivocal conclusion is that supplementation with isoflavones is safe over the short (≤12 month) term, as no studies reported clinically relevant adverse events associated with isoflavone exposure.

The studies by Fischer et al. (161) and deVere White et al. (162) are particularly noteworthy in this regard because isoflavone intake was many-fold greater than in any previously published study and, as already noted, approximately 10 to 20 times greater than the typical daily Japanese intake. In the former study, extensive chemical and biological analyses were conducted. More than 40 blood and urinary measures were taken on 12 occasions over the 112 days of the study (161). There was no evidence of toxicity and no adverse events ≥ grade 1 were attributed to isoflavones.

These findings agree with those from Hussain et al. (160) and deVere White et al. (162). deVere White et al. (162) measured alkaline phosphatase, aspartate aminotransferase, total bilirubin, creatinine, cholesterol, and γ-glutamyltransferase. In addition to history and physical examination, assessments in the study by Hussain et al. (160), included complete blood count with differential count, blood chemistry profile (SMA-12), serum electrolytes, and testosterone levels. Hussain et al. (160) did report a few nonspecific grade 1–2 adverse events, but their relationship to the study intervention was unclear and they appeared to be related to preexisting comorbid conditions.

Finally, Urban et al. (157) reported a few cases of constipation and diarrhea, but there were no differences between men consuming the high- and low-isoflavone ISPs, and Jarred et al. (164) noted a very small, but statistically significant, decrease in hemoglobin levels in the isoflavone-treated patients in comparison to the historically matched controls, but no such effect was noted in the much larger and longer trials by Fischer et al. (161) and Hussain et al. (160).

Possible Mechanisms for the Effects on PSA Levels

As discussed previously, there are multiple hormonal and nonhormonal mechanisms by which isoflavones can affect the growth of prostate cancer cells. In the 4 studies that found statistically significant effects on PSA, the evidence that hormonal changes may have contributed to the results is unimpressive. The most persuasive evidence in favor of a hormonal effect comes from the study of Kranse et al. (167). They found significant effects on PSA only among the men in whom there was a decrease in the free androgen index. Neither Hussain et al. (160) nor Spentzos et al. (163) found effects on IGFBP-3 levels, and there was no change, and an increase in IGF-1 levels ($P = 0.02$ adjusted for changes in weight and IGFBP-3), in the former and latter studies, respectively. IGF-1 is typically associated with enhanced, not decreased, cancer risk (168). However, Spentzos et al. (163) noted a trend toward a decline in testosterone levels ($P = 0.06$, adjusted for weight changes). In contrast, Dalais et al. (166) observed no significant differences between the wheat bread and soy bread groups in levels of testosterone, DHT, or SHBG. The lack of effects on testosterone levels observed in these trials in response to soy or isoflavones is consistent with a large body of research involving healthy men (164, 166, 169–175).

Conclusions and Implications of Findings

The available evidence is not sufficient to establish the efficacy of isoflavones for reducing PSA levels in prostate cancer patients. However, the evidence is sufficiently encouraging to justify considering conducting Phase II and III clinical trials investigating the efficacy of soy isoflavones in different populations of prostate cancer patients. Although soy isoflavones did not lead to an absolute decrease in serum PSA levels in any study, PSA velocity was decreased in several. By decreasing the slope of the PSA rise and prolonging the PSAdT, soy isoflavones may delay disease progression and development of symptoms. These effects are particularly beneficial to hormone-refractory patients whose only option at this time is cytotoxic chemotherapy that provides only limited survival benefit and produces considerable toxicity.

Given the results cited in this review, a randomized clinical trial comparing the most efficacious chemotherapy to soy isoflavones in patients with hormone refractory prostate cancer, including quality of life and survival end points in addition to serum PSA and other clinical disease response end points, is warranted. An advantage to isoflavone use is that it is not associated with any adverse effects. Furthermore, it may be suitable as an adjunct for use with other approaches in halting the progression of prostate cancer. Genistein has been shown to enhance the ability of radiation to kill prostate cancer cells in vitro (176) and to enhance the efficacy of a number of different chemotherapeutic agents in different cell lines (177, 178). Isoflavones may be useful in controlling prostate cancer bone metastasis (179).

Additionally, isoflavones may help to offset the bone loss in prostate cancer patients receiving hormonal treatment (180, 181) because, in several trials involving postmenopausal women, isoflavones reduced bone loss (3), although no clinical trials have investigated the skeletal effects of isoflavones in older men. Isoflavones may also be of use to the large percentage of men who develop hot flashes after orchiectomy/luteinizing hormone-releasing hormone therapy (182, 183).

From the available studies, it is not possible to discern information about the optimal isoflavone dose for slowing or halting prostate cancer progression. However, isoflavone exposure in all 4 studies that reported statistically significant effects on PSA levels was ≤120 mg/day. This isoflavone dose is within the dietary range and is likely one that could be continued indefinitely without substantial risk of adverse effects.

In regard to the findings in healthy men, the lack of effects of isoflavones on PSA levels does not suggest that these soybean constituents do not reduce prostate cancer risk. In fact, as noted previously, intervention data demonstrate that, at least among men with low initial levels, reducing prostate cancer risk is not dependent upon reductions in PSA (156). Conceivably, isoflavones prevent the development of prostate cancer in ways that may not be reflected in PSA changes in healthy men with normal PSA levels. Furthermore, because many men will eventually develop latent prostate cancer, taking isoflavones as a preventive measure for slowing the progression of this condition may be worthwhile.

Ideally, isoflavones should be consumed in the form of soy foods, not only because their safety profile is better established than supplements but because the protein itself may offer some health advantages. However, it should be acknowledged that obtaining isoflavones from soy foods in amounts used in most of the clinical trials discussed in this review represents a significant dietary challenge for non-Asians. Thus, isoflavone supplements may be an appropriate option.

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