Review Article

Soy in benign prostate hyperplasia and prostate cancer: a literature review

Alberto Trinchieri^

School of Urology, University of Milan, Milan, Italy

Correspondence to: Alberto Trinchieri. School of Urology, University of Milan, Milan, Italy. Email: alberto.trinchieri@gmail.com.

Objective: To review the evidence of the effect of soybean on benign prostatic hyperplasia (BPH) and prostate cancer.

Background: Lower incidence of prostate cancer in some Asian countries has been explained by the high consumption of soy foods.

Methods: We performed a systematic review of randomized controlled trials (RCTs) evaluating the effects of dietary supplementation with soy foods or isoflavones on prostatic specific antigen (PSA) and sex hormone levels in healthy subjects or in patients with BPH. The results of systematic reviews that analyzed observational and interventional studies evaluating the effect of soy foods and isoflavones on the risk of prostate cancer were described as a narrative review.

Conclusions: Soy/isoflavone supplementation did not positively change PSA values of healthy subjects or patients with BPH and did not change sex hormone levels. Studies comparing the effect of a load of animal proteins with an equivalent load of soy proteins showed a tendency to modify sex hormone profile after soy consumption (decreasing dihydrotestosterone (DHT) or testosterone or testosterone/estradiol ratio or free androgen index). Meta-analysis of cohort or case-control studies demonstrated that consumption of soy food (or phytoestrogens) was associated with a lower risk of prostate cancer. Other meta-analysis did not confirm the protective effect of fermented soy foods or the association between circulating levels of isoflavones and reduced risk of prostate cancer. Meta-analysis of interventional studies demonstrated a reduction in the risk of prostate cancer after administration of soy foods in patients at risk of prostate cancer although no change in PSA or sex hormones was observed in patients with prostate cancer. Soy foods showed a favorable effect in decreasing the risk of prostate cancer, although the protective mechanism is not fully understood. The hormonal effects related to the weak estrogenic action of isoflavones have not been fully confirmed. The protective effect of soy foods could be related to antioxidant effect or induction of apoptosis or inhibition of angiogenesis.

Keywords: Soy; prostate cancer; benign prostatic hyperplasia (BPH); isoflavones

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Introduction

The soybean (*Glycine max*) is a species of legume native to East Asia. Archaeological findings from Japan, China and Korea support the view that soybean was domesticated in several locations in East Asia from 9000 years BC (1). Over time this crop has progressively spread all over the world.

Nutritional properties of soybean

The edible beans of soy have excellent nutritional properties

^ ORCID: 0000-0002-9394-8292.

because of their content in high-quality proteins, dietary fiber and high unsaturated fatty acid ratio. A 100 g serving of raw soybean provides 36 grams of proteins and 37 grams of fiber. Soybeans also contain other physiologically active substances including oligosaccharides, isoflavones, saponins, lecithin, phytic acid, protease inhibitors, and pinitol (2). They have also high contents of dietary minerals (iron, manganese, zinc, magnesium, potassium, phosphorus) and vitamins (B_1, K, E , A, and C).

Soybean is used as both unfermented and fermented food (3). Unfermented food include soy milk and its derivatives, tofu and tofu skin. Fermented soy foods include soy sauce, tempeh and fermented bean paste. Soybean derivatives are ingredients in meat and dairy substitutes. Fat-free soybean is also an important and cheap source of protein for animal feeds. An oil can be solvent extracted by cracking soybean seeds. It contains phytosterols and it is used in food and industrial applications. Soybean oil is one of the most consumed vegetable oils in Western countries. The consumption of soybean oil is also linked to its use as by-product of chicken and pig protein feed (soybean cake) (4).

Isoflavones

Isoflavones are the most important component of soy-containing foods for health effects (5,6).

Soy isoflavones are classified, based on their chemical structures, as aglycons (daidzein, genistein, and glycitein) or glycosides (daidzin, genistin, and glycitin) or acetyl glycosides or malonyl glycosides.

Isoflavones are absorbed in the intestine after being transformed from glycosides to smaller and hydrophobic glycones by the action of bacterial and intestinal glucosidases (7).

After intestinal absorption, the glycones are re-conjugated with a sugar molecule in the liver to reconstitute their glucosidic form which is distributed to the tissues through the bloodstream. In cells, isoflavones bind to estrogen receptors (ERs) acting as weak agonists or antagonists, depending on their chemical structure or the physiological environment (8).

There are different types of ERs, such as ERα, ERβ, and G protein-coupled ER. When ERs bind to their specific ligands, such as estradiol, they are translocated to the nucleus where they regulate the transcription of their target genes. ERα and ERβ are differently distributed in tissues and ERβ are well represented in the prostate (9). Genistein has a greater affinity for ERβ than for ERα, while daidzein has a much lower binding affinity for both ERs. The lower affinity of phytoestrogens for ERα explains the lack of the side effects commonly associated with the administration of estrogens (cardio-vascular events, risk of endometrial and breast cancer) (10).

Isoflavones have also *in vivo* and *in vitro* antioxidant effects similarly to vitamin E and C.

Fermented soy foods

Fermented soy foods contain isoflavones as aglycones that do not exist in the raw food product, because fermentative bacteria, as *Bacillus subtilis* or *Bacillus licheniformis*, are able to cleave glycosidic linkages by their glucosidases (11-13). Therefore, they do not require to be digested for intestinal absorption. However, a negative aspect of the consumption of fermented soy food could be the risk of increasing the risk of developing some cancers, as gastric cancer.

Equol

Bacterial metabolism of daidzein in the gastrointestinal tract produces equol, a metabolite with higher hormonal and anti-proliferative activity that genistein and daidzein itself (14,15).

The production of equol after the intake of isoflavones varies in different individuals, so the benefits of soy consumption could be conditioned by the ability of a subpopulation of individuals to produce equol (equol-producers). In fact, only 20–50% of individuals would be able to produce equol from isoflavones, although this percentage seems to be higher in Asian populations who are accustomed to consuming soy from an early age (16,17).

Effects of soybean on health

Consumption of soy-containing foods has been associated with several health benefits. Soy foods and isoflavones have been proposed to reduce the risk of heart disease and to counteract the effects of menopause. They could also exert anticancer effects on several tumors including breast, prostate, endometrial and other types of cancer (colorectal, gastrointestinal).

Cardiovascular health

Meta-analyses demonstrated that total and lowdensity lipoprotein (LDL) cholesterol levels (18-21) and blood pressure values (22,23) are modestly reduced by consumption of soy-containing foods, soy protein supplementation and soy isoflavones.

Menopause

Soy isoflavones could be a potential source of estrogens with less side effects to be used as a potential substitute for estrogen in women who have entered menopause (24-26).

They can alleviate hot flashes and lower the risk of osteoporosis by promoting vitamin D activity without inducing common side effects of estrogen administration as hyperlipidemia or increased risk of cancer in the breast and uterus.

Anticancer effects

Anticancer properties of soy isoflavones and protease inhibitors include inhibition of tyrosine kinases, reduction of tumor cell growth, induction of apoptosis, antioxidant activity, and inhibition of angiogenesis (27-29). Most of the anticancer effects of isoflavones are produced by genistein that weakly blind ERs inhibiting cancer cell division (30-32).

Isoflavones may act with other mechanisms on prostate cancer cell proliferation, apoptosis and differentiation (33).

The aim of this work was to review the scientific evidence of the effect of soybean on benign prostatic hyperplasia (BPH) and prostate cancer. The main outcomes of our review were the risk of developing prostate cancer in association with consumption of soy foods or soy isoflavones or levels of circulating isoflavones, the effect of administration of soy foods/isoflavones in patients at risk of developing prostate cancer and the effect of the administration of soy foods/isoflavones on PSA or sex hormones in healthy subjects or in patients with BPH or prostate cancer.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://lcm.amegroups.com/article/view/10.21037/lcm-21-36/rc).

Materials and methods

We conducted a literature search of PubMed using the search string "prostate AND (soy OR soymilk OR soy milk OR isoflavone OR bean curd OR tofu OR soy protein OR daidzein OR genistein)" (up to 30 June 2021). The search was restricted to randomized controlled studies and meta-analyses written in English language.

We did not retrieve any systematic review studies evaluating the effect of soy foods on prostatic specific antigen (PSA) and/or sex hormone levels in healthy men or patients with benign prostatic disease. Consequently, we systematically reviewed the randomized control studies we had retrieved on this topic. In addition, the results of retrieved systematic reviews that analyzed observational and interventional studies evaluating the effect of soy foods and soy isoflavones on the risk of prostate cancer were described as a narrative review.

Results and discussion

Effects of soybean foods on prostate in healthy subjects and in patients with BPH

The intake of soy food has been associated with modification of sex hormone profile and reduction of serum PSA levels of healthy subjects.

In total we retrieved 50 randomized controlled trials (RCTs) from the library search. Out of them, we screened by abstract 9 papers containing potentially relevant information for the review. Two studies evaluated changes of PSA values after administration of soy foods or soy isoflavones (34,35). Two studies evaluated the effects on both PSA and sex hormones (36,37) and five studies evaluated the effect on sex hormones (38-42).

Studies that evaluated the effect of soy foods and soy isoflavones on PSA values showed no significant changes in PSA in elderly subjects and in patients with BPH.

An RCT of soy isoflavone supplementation (83 mg/day isoflavones) for 12 months in healthy older men (50–80 years) found no change of serum PSA concentration or PSA velocity after soy isoflavone supplementation (34).

In elderly men with elevated PSA, daily consumption of soy beverages with high content of isoflavones for a 6-week period decreased serum cholesterol but not serum PSA (35).

In a randomized crossover study healthy adult men consumed a high or a low soy diet (36). Men on high soy diet consumed two daily soy servings whereas on low soy diet they maintained their usual diet. During the high soy diet, a not significant 14% decline in serum PSA levels was observed. Finally, no statistical difference of serum PSA was observed in men with lower urinary tract symptoms diagnosed with BPH on treatment with 40 mg of isoflavones daily (Soylife 40) or placebo for 12 months (37).

The effects of soy foods and soy isoflavones on sex hormone levels were evaluated in seven studies. Out of them, the effect of an animal protein load was compared with a soy protein load in three studies (38-40) and in another study (41) the effect of supplementation with scones made with either wheat or soy flour was compared.

In a randomized crossover study of healthy young men (20–40 years) (38), high soy protein supplementation for 2 months decreased serum dihydrotestosterone (DHT) and DHT/testosterone in comparison with milk protein supplementation. Minor effects were observed on other hormones.

A randomized crossover dietary intervention study (39) replacing meat protein (150 g lean meat) with a soyabean product (290 g tofu) for 4 weeks was not able to demonstrate changes of blood concentrations of sex hormones in healthy adult males although after adjustment for weight change sex hormone binding globulin (SHBG) tended to increase and testosterone/estradiol to decrease after the tofu diet.

A study (40) evaluated the postprandial effects in healthy men of different isocaloric meals containing different type of proteins (lean meat, tofu and meat meals with added animal fat or safflower oil) showing a significant decrease in testosterone and free androgen index after both tofu and lean meat meals with respect to meats with added fat.

A study (41) compared the effect of the supplementation to the diet of male volunteers with scones made with either wheat or soy flour (containing 120 mg/day of isoflavones) for a period of 6 weeks. Taking the soy scones resulted in a decrease of total serum testosterone, but no significant changes of the other serum sex steroids, albumin or SHBG. Moreover, significant improvements in markers of oxidative stress were observed whereas no changes were seen in serum triglycerides or cholesterol.

Other studies (36,37,42) evaluated the effect of the supplementation of soy foods or soy isoflavones to the usual diet.

Adding two daily soy servings to the usual diet of healthy adult men obtained no change in testosterone values (36). Similarly, supplementation with 40 mg of isoflavones (Soylife 40 mg) in men with BPH (37) resulted in no statistical difference of testosterone levels.

Finally, in a randomized study, Japanese men were assigned to consume 400 mL of soymilk daily for 8 weeks or to maintain their usual diet. Serum estrone concentrations tended to decrease in the soy-supplemented group whereas none of the other hormones measured (estradiol, total and free-testosterone, or sex hormone-binding globulin) showed any statistical difference.

Effect of soy foods and isoflavones on prostate cancer

The lower incidence of prostate cancer in some Asian countries has been explained by the high consumption of soy foods in these populations (43-45).

The protective effect of soy foods against the development of prostate cancer could be the result of both hormonal and non-hormonal effect of soy foods.

The isoflavones of soybeans, genistein and daidzein, are weak hormones but also exert a cytotoxic action directed against cancer cells. In experimental studies the genistein upregulates the prostate tumor suppressor genes in the presence of ERs but not in a model with knock out of ERs (46).

Numerous observational and interventional studies have investigated the relationship between soy food consumption and the risk of prostate cancer.

We retrieved 14 meta-analyses by the search of PubMed using the search term "prostate AND (soy OR soymilk OR soy milk OR isoflavone OR bean curd OR tofu OR soy protein OR daidzein OR genistein)". Out of them, seven were considered for the analysis of the effect of the intake of soy foods or soy isoflavones or phytoestrogens or circulating isoflavones on the risk of prostate cancer. Another meta-analysis was included after the lecture of the previous studies. Three studies evaluated the effect of consuming soy foods or soy isoflavones, three studies the effect of phytoestrogens, one study the effect of circulating levels of isoflavones, one study the effect of both soy foods and isoflavones and the levels of circulating isoflavones and one study the results of interventional trials.

Observational studies

Cohort studies having the onset of prostate cancer as endpoint require to follow-up large number of subjects (15,000–30,000) for a long interval of time (5–10 years). Alternatively, case-control studies can be considered. The results of observational studies were reviewed by several meta-analyses, all of which showed a protective association between soy consumption and prostate cancer (47-51).

In 2005, the meta-analysis of Yan *et al.* (47) considered two cohort studies and six case-control studies showing that consumption of soy food was associated with a lower risk of prostate cancer in men (0.70, 95% CI: 0.59–0.83, $P<0.001$).

The same authors (48), revisited their meta-analysis in 2009 evaluating 15 studies on soy consumption and 9 on isoflavones in association with prostate cancer risk. They confirmed a reduced combined RR/OR for soy consumption (0.74, 95% CI: 0.63–0.89; P=0.01). Risk reduction was maintained for nonfermented soy foods (0.70, 95% CI: 0.56–0.88; P=0.01) but not for fermented soy foods (1.02, 95% CI: 0.73–1.42; P=0.92). Furthermore, risk reduction was confirmed from studies with Asian populations (0.52, 95% CI: 0.34–0.81; P=0.01) but not from studies with Western populations (0.99, 95% CI: 0.85–1.16; P=0.91).

In 2009, a meta-analysis from Hwang *et al.* (49) included five cohort studies and 8 case-control studies confirming decreased odds of prostate cancer (OR 0.69, 95% CI: 0.57–0.84) for total soy foods and for nonfermented soy foods (0.75, 95% CI: 0.62–0.89).

Three other meta-analysis (50-52) evaluated the cumulative effect of phytoestrogens on prostate cancer risk by including not only soy foods but other types of legumes.

He *et al.* (50) evaluated two cohort and 9 case-control studies on phytoestrogen intake and 8 studies on serum concentration of isoflavones. Phytoestrogens consumption (OR 0.80, 95% CI: 0.70–0.91) and high serum concentration of isoflavones (OR 0.83, 95% CI: 0.70–0.99) were associated with lower odds for prostate cancer.

The meta-analysis of Zhang *et al.* (51) retrieved 29 studies also including unpublished studies and studies in language other than English. They demonstrated that phytoestrogen intake was significantly associated with a reduced risk of prostate cancer in Asians and Caucasians but not in Africans (OR 0.77, 95% CI: 0.66–0.88; I^2=77.6%).

The relationship between phytoestrogens and prostate cancer risk was updated by another meta-analysis (52) which selected 21 case-control and 2 cohort studies to show that intake of daidzein (OR =0.85; 95% CI: 0.75–0.96), genistein (OR =0.87; 95% CI: 0.78–0.98), and glycitein (OR =0.89; 95% CI: 0.81–0.98) were associated with a reduction of prostate cancer risk.

The most recent meta-analysis by Applegate *et al.* (53) considered 30 studies that assessed the impact of dietary intake of soy, dietary intake of isoflavones and circulating levels of isoflavones on the risk of prostate cancer.

The effect of dietary intake of soy foods or isoflavones was evaluated in 24 studies and association with circulating levels of isoflavones was evaluated in 9 studies (in 3 of which in association with the assessment of dietary intake).

Total soy food, unfermented soy food, genistein and daidzein intakes were significantly associated with a reduced risk of prostate cancer while, conversely, the association was not confirmed for fermented soy food intake, total isoflavone intake, and circulating isoflavones.

Furthermore, the studies that evaluated the impact of soy food intake in patients with advanced prostate cancer did not show any statistically significant association between neither soy food intake nor circulating isoflavones.

The lack of correlation between prostate cancer risk and isoflavones circulating levels was in agreement with the result of the meta-analysis of Perez-Cornago *et al.* (54) which included two prospective studies from Japan and five studies from Europe. They also found that genistein and daidzein concentrations were not significantly associated with the risk of prostate cancer although men from Japan with high circulating equol concentrations showed a lower risk of prostate cancer than those with low concentrations.

Interventional studies

RCTs designed to evaluate the efficacy and safety of soy or isoflavones in prostate cancer evaluated different type of populations:

(I) Patients with histologically diagnosed prostate cancer on active surveillance;
(II) Patients with prostate cancer scheduled for radical prostatectomy who are treated in the 6–8 weeks before surgery to evaluate the effect of intervention on prostate biopsies, surgical specimens or surrogate intermediate markers;
(III) Patients who underwent radical prostatectomy with high recurrence risk due to histological features (positive surgical margins, extracapsular extension, seminal vesicle invasion, positive lymph nodes, Gleason score greater than or equal to 8 or preoperative serum PSA greater than 20 ng/mL);
(IV) Patients without biopsy proven cancer at high risk of developing clinically significant prostate cancer (ASAP, HG-PIN).

A meta-analysis of the effect of soy or soy isoflavones administration (55) revised six studies in men with prostate cancer (scheduled for prostatectomy or watchful waiting or active surveillance) and two studies in men with identified risk of developing prostate cancer. Meta-analysis of the two studies of men at risk of prostate cancer found a significant reduction in prostate cancer diagnosis after administration of soy or soy isoflavones (RR =0.49, 95% CI: 0.26, 0.95). A study investigated the development of cancer in men with a single negative prostate biopsy at baseline over 12 months, and another study evaluated men with atypical small acinar proliferation (ASAP) or high grade prostatic intraepithelial neoplasia (HGPIN) over 6 months.

No significant difference after administration of soy or soy isoflavones was observed for levels of PSA or sex steroid hormone (SHBG, testosterone, free testosterone, estradiol and DHT). The conclusions were limited by heterogeneity of dosages and preparations of soy/isoflavones administered, small sample size and short study duration in individual trials.

The results of this meta-analysis contrast with a previous narrative review (56) in 2006 demonstrating that isoflavones favorably affected PSA in 4 of 8 trials involving prostate cancer patients, although there was not an absolute decrease in PSA concentrations. The findings of no significant effect on SHBG, testosterone and free testosterone are consistent with a 2010 meta-analysis of isoflavone studies (57).

Conclusions

In conclusion, soy foods appear to have a favorable effect in decreasing the risk of prostate cancer, although the protective mechanism is not fully understood. The hormonal effects related to the weak estrogenic action of isoflavones have not been fully confirmed by meta-analyses of studies with heterogeneous design, often underpowered and with insufficient follow up. On the other hand, the protective effect of soy foods could be related to other mechanisms as antioxidant effect or reduction of tumor cell growth by induction of apoptosis or inhibition of angiogenesis.

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Footnote

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