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Soy and soy isoflavones in prostate cancer: a systematic review and meta-analysis of randomized controlled trials

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Objective

- To evaluate the evidence from randomized controlled trials (RCTs) on the efficacy and safety of soy/isoflavones in men with prostate cancer (PCa) or with a clinically identified risk of PCa.

Patients and Methods

- MEDLINE, EMBASE, the Allied and Complementary Medicine (AMED), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Cochrane Library databases were searched.
- We identified RCTs investigating soy/soy isoflavones as dietary supplements or dietary components for the secondary prevention or treatment of PCa in men with PCa or with a clinically identified risk of developing PCa. Studies of multi-component formulations were excluded.
- Six authors were contacted for further information for the meta-analyses.
- Methodological quality was assessed using the Cochrane Collaboration's risk-of- bias tool.
- The PRISMA statement for reporting systematic reviews was followed.

Results

- Of the eight RCTs that met the inclusion criteria, six restricted recruitment to men diagnosed with PCa, while two included men with clinically identified risk of PCa.
- A large degree of heterogeneity was found with respect to dosages and preparations of soy/isoflavones administered.
- Most studies had small sample sizes and were of short duration.
- The risk of bias was assessed as low in all assessed studies except for one, for which the risk of bias was unclear. Meta-analyses of the two studies including men with identified risk of PCa found a significant reduction in PCa diagnosis after administration of soy/soy isoflavones (risk ratio = 0.49, 95% CI 0.26, 0.95).
- Meta-analyses indicated no significant differences between groups for prostate-specific antigen (PSA) levels or sex steroid endpoints (sex hormone-binding globulin [SHBG], testosterone, free testosterone, oestradiol and dihydrotestosterone).

Conclusions

- The results of a meta-analysis of two studies suggest there may be support for epidemiological findings of a potential role for soy/soy isoflavones in PCa risk reduction; however, a clear understanding of the impact of soy/isoflavones on PSA, total testosterone, free testosterone and SHBG levels in men with, or at identified risk of, PCa could not be derived from these data, given the limitations of sample size and study duration in individual trials.
- A good safety profile is shown by this meta-analysis for soy/soy isoflavones supplementation.

Keywords

prostate cancer, prostatic hyperplasia, soy, isoflavones, phytoestrogens, *Glycine max*

Introduction

Demographic studies of prostate cancer (PCa) show wide regional variation in incidence and mortality, with the highest in Western countries [1], and the lowest in Asian countries [2]. In addition, epidemiological studies find a substantially increased risk among Chinese and Japanese migrants to the West who adopt a Western diet [3,4], but not among those maintaining traditional diets [5]. Epidemiological research has found that increased consumption of soy (*Glycine max* L.) is associated with a lower risk of PCa [6].

The bean of the soy plant (*Glycine max* L., family Fabaceae, formerly Leguminaceae), is used in both foods and phytotherapeutic supplements. It produces isoflavones, principally genistein, daidzein and glycitein. Isoflavones are

 | doi:10.1111/bju.12435
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diphenolic compounds capable of binding to oestrogen receptors and exerting weak oestrogen-like effects, and are therefore classified as phytoestrogens. Genistein and daidzein have also been shown to possess anti-carcinogenic activity not necessarily related to hormonal effects. The mechanisms of action of isoflavones have been extensively reviewed elsewhere [7–9]. They include *in vitro* modulation of cell proliferation, cell cycle regulation, apoptosis, angiogenesis, tumour cell invasion and tumour metastasis by genistein [10], and inhibition of PSA secretion in androgen-sensitive human prostate adenocarcinoma (LNCaP) cells [9]. Reduction of testosterone levels, and down-regulation of androgen receptor (AR) gene expression in the prostate have been observed [9] in animal models and, in men with PCa, isoflavones have favourably affected PSA levels [7].

Daily isoflavone intake in Japan has been estimated to be 25–50 mg/day of aglycone equivalents [11], compared with <1 mg in Europe [12], and 3 mg/day in the UK [13]. The isoflavone content of some common soy foods is shown in Table 1, but the quantification of the phytoestrogen content of food can vary threefold to fourfold, depending on variety, environmental factors, growth, harvesting time and processing [14–16].

Equol is a metabolite of daidzein produced by the intestinal microflora [17] that has higher oestrogenic activity than its parent isoflavone. The 'equol hypothesis' proposes that the clinical effectiveness of soy protein may be a function of the individual's ability to biotransform soy isoflavones to equol, but only 35% of humans are equol-producers [18], and the capacity to produce equol has been found be to lower among American than Japanese and Korean men [19].

Evidence from epidemiological [4,20] and pre-clinical studies [21–23] supports a role for soy/soy isoflavone supplementation, both in reducing the risk of developing PCa, and in inhibiting its progression. The objective of this systematic review was to evaluate the evidence from randomized controlled trials (RCTs) of the role of soy/isoflavones in men with PCa, or clinically identified risk of developing PCa, in reducing the development of PCa and disease progression. Secondary objectives included assessing the impact of supplementation on serum PSA and sex hormone levels, equol production and adverse events.

Table 1 Isoflavone (aglycone) content of some common soy foods.

Food product	Total isoflavones	Daidzein	Genistein
Soy flour, full-fat, roasted	165.04	89.46	85.12
Soy protein isolate	91.05	30.81	57.28
Tempeh	60.61	22.66	36.15
Miso	41.45	16.43	23.24
Soybeans, raw sprouted	34.39	12.86	18.77
Soy yoghurt	33.17	13.77	16.59
Tofu, soft -VITASOY-silken	29.24	8.59	20.65
Tofu, firm – cooked	22.05	10.26	10.83
Soybeans cooked	17.92	7.41	7.06
Soy milk – fortified or unfortified	10.73	4.84	6.07
Vegetarian burger	6.39	2.63	5.01
Soy cheese, cheddar	6.87	1.83	2.11

Values are expressed in mg per 100g of fresh weight of edible portion of food [16].

Methods

Data Sources

The following electronic databases were searched (through to February 2013): EMBASE (Ovid), Medline (ProQuest), the Cochrane Central Register of Controlled Trials (CENTRAL), AMED (Ovid) and CINAHL (EBSCO).

Search Strategy

The search strategy (in EMBASE and adapted for other databases) was as follows: (1) prostate cancer/; (2) prostate tumour/; (3) items 1 or 2; (4) (soy or isoflavone$ or phytoestrogen$ or genistein or daidzein or glycine max).mp; (5) items 3 and 4; and (6) limiting of item 5 to RCTs. No language restrictions were imposed.

Study Selection

Eligible studies included RCTs and trials investigating phytotherapeutic extracts in conjunction with mainstream treatments. The study populations included men with PCa or clinically identified risk of developing PCa (negative biopsies, atypical small acinar proliferation [ASAP], high grade prostatic intraepithelial neoplasia [HGPIN]).

Trials investigating soy or soy isoflavones as tablets or dietary interventions were included. Data from studies investigating multicomponent phytotherapeutic formulations containing two or more ingredients were excluded. Complex dietary and/or lifestyle interventions were also excluded.

Studies that compared the intervention with placebo, other comparator treatment, no treatment or usual care were included.

Outcome Measures

The primary outcome measures of the present review were changes to 5-year survival rates, development of cancer in men with clinically identified risk and disease progression. Given the long timeframe for progression to PCa, several surrogate markers were also included as secondary outcomes: serum PSA levels (surrogate markers of proliferation); serum steroid hormone concentrations. Also included were equol production; and adverse events.

Studies were excluded if they focused only on serum/ tissue levels, potential mechanisms of action of soy isoflavones, or

the effects on symptoms associated with mainstream treatments. Also excluded were endpoints that were not confirmable or not contributory to the present study, such as urinary oestrogens and the ratio of 2:16 α-hydroxyestrone [24], AR and oestrogen receptor-β expression [25], and cholesterol [26].

Data Extraction and Methodological Quality Assessment

Two reviewers (D.v.D and K.B.) independently screened the titles and abstracts of all articles returned from the search strategy. Full-text articles were obtained when required to determine the eligibility of the study for inclusion. Any disagreement between the two authors was to be resolved by a third author (M.P.). The included studies were reviewed by two investigators (D.v.D and K.B.).

Data extracted included details of trial design, the condition under investigation,study duration, sample size, participant characteristics, intervention, outcome measures, adverse events and results.

Six authors were contacted [25–30]to obtain further information to permit meta-analyses to be performed. Four [25,27,29,30] of the six responded.

The quality of each study was assessed using the Cochrane Collaboration's risk-of-bias assessment tool [31]. Two reviewers (D.v.D and K.B.) worked independently to determine selection bias, attrition bias, detection bias, performance bias, reporting bias and other potential bias, such as funding sources. Any discrepancies were resolved by discussion between the two reviewers. If no agreement could be reached, it was decided a third author would be consulted.

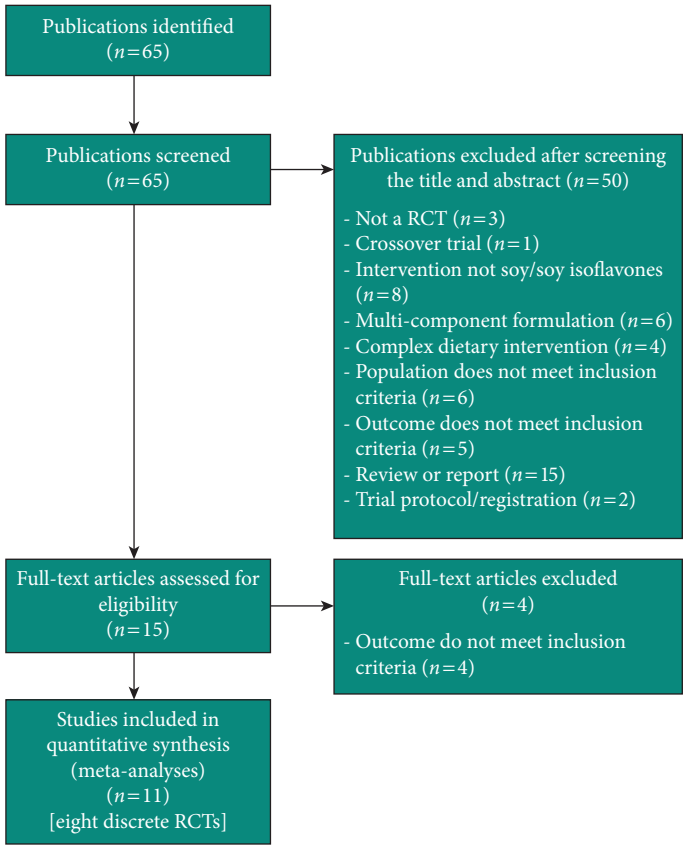
Data Analysis

Data were analysed using RevMan 5.0 software, developed by the Cochrane Collaboration. A quantitative meta-analysis was performed for independent studies where appropriate data could be obtained. Heterogeneity was calculated using chi-squared and I-squared statistics. A random effects model was applied to heterogeneous study data (if the I-squared statistic was >50%). The fixed-effect model was applied where the I-squared statistic was <50%.

Dichotomous data are presented as risk ratios and continuous outcomes as mean difference (MD) with 95% CI. Studies were qualitatively synthesized where appropriate data were not available for quantitative analysis.

The PRISMA statement for reporting systematic reviews was followed (Supporting Information Fig. S1).

Fig. 1. Study selection process.



Results

Description of Studies

Figure 1 shows the study selection process. After the removal of duplicates, 65 articles were located, of which 11 met the selection criteria (Fig. 1); however, only eight discrete RCTs were reported, as findings from two trials were reported in two [32,33] or three [24,25,34] separate articles.

When data were available from three study arms [25,35], the main intervention of interest was included in the meta-analyses. One RCT was a dose-finding study [29]. Data for the 40-mg dose were included in relevant meta-analyses, but because of lack of blinding, the study was not included in the risk-of-bias assessment.

Participants

The characteristics of the identified studies are shown in Table 2 [24–30,32–35]. Of the eight RCTs, the cohorts investigated were men with early-stage PCa scheduled for prostatectomy (in four studies) [26,29,32,35] or watchful waiting (in one study) [28]; and men with PCa and rising PSA on active surveillance (one study) [27]. One study included men with a single negative prostate biopsy, but

Table 2 Characteristics of identified studies.

First author, year and country	Diagnosis and participant characteristics	Study design, participants (*n*) and duration	Extract and dosage vs comparator	Outcomes	Main results between groups and authors' conclusions	Adverse events
Soy/soy isoflavones						
De Vere White et al. 2010 [27], USA	PCa and rising PSA in men enrolled in an active surveillance programme; not previously treated with radiation, surgery, or hormones. Mean age: 70.5 years (soy); 68.6 years (placebo) Excluded: use of isoflavone-rich dietary supplements or intake of three or more servings of soy-based foods per day; or urological agent, Gleason score: ≤ 10 (2–4, *n* = 2; 5–6, *n* = 46; 7, *n* = 4; 8–10, *n* = 1) PSA: 0.7–22.6 ng/mL (five had PSA> 10 ng/mL) (mean 3.7 soy; 4.7 placebo)	RCT (DB) *n* = 66/53 GCP (which produces beta-glucosidase and leaves glucoside forms of isoflavones into the more biologically active aglycone forms) (*n* = 36/28) vs placebo (*n* = 30/25) 6 months	450 mg genistein, 300 mg daidzein, and other isoflavones daily 5 gm/day GCP, (Amino Up Chemical Company, Sapporo, Japan) containing aglycone isoflavones, genistein (93 mg/g) and daidzein (57 mg/g)], or placebo (5 g/day of inert cellulose) Orally administered thrice daily in divided doses	1. PSA concentrations 2. Serum concentrations of genistein and daidzein 3. Equol	1. PSA concentrations stabilized or reduced in 50% of GCP group (14/28) and 32% of the placebo group (8/25) after 6 months, *P* = 0.29. 2. The 6-month serum concentrations of genistein and daidzein (39.85 and 45.59 μmol/L, respectively) were significantly greater than baseline (at least 100% and 40% above baseline values respectively) Changes in isoflavone concentrations showed no significant association with PSA (*P* > 0.25) 3. Equol was low, and did not change in eight participants. Increasing plasma isoflavones did not lower PSA levels	Intervention 'was well-tolerated, with loose stools the most common complaint from a small number of men.'
Kumar et al., 2007 [32,33] USA	Early stage (grade 1–2) localized PCa Age: 50–80 years Excluded: Gleason primary pattern 4 (4 + 1 or 4 + 2); neo-adjuvant hormonal therapy, vegans, and/or soy users Gleason score: 2–6 PSA: not reported	RCT (DB) *n* = 53/50 Soy isoflavones (*n* = 25/23) vs placebo (*n* = 28/27) 12 weeks	80 mg/day purified isoflavones (Prevastein HC; each tablet contained 40% soy isoflavones in the aglycone form) or placebo Both groups received multivitamin supplement (PBA Multi Vitaformula; Pan American Lab Co.)	1. SHBG 2. Steroid hormone levels 3. Changes in plasma isoflavones	1 & 2. No significant changes to serum SHBG, total oestradiol or testosterone in isoflavones group compared with placebo despite 3. Significant increases in plasma isoflavones (*P* < 0.001) Increasing plasma isoflavones failed to produce a corresponding modulation of serum steroid hormone levels. Isoflavone consumption may modulate PCa risk by other mechanisms	Potentially related AEs were all grades I to II and were similar in the two groups. None produced clinical toxicity. Grade I AEs: GI symptoms – bloating, loss of appetite, dyspepsia, and diarrhoea (five in the treatment group and seven in placebo group). Grade II events included abdominal pain. AEs rated possibly related were equal in both arms; AEs rated 'probably related' were greater in the placebo arm.
Kumar et al., 2010 [29] USA	Early-stage localized PCa in men scheduled for prostatectomy Age: 50–80 years Excluded: previous or current therapy for PCa or a history of cancer except non-melanoma skin cancer; vegans, and/or soy users Gleason score: 2–10 PSA: 4.88 ng/mL (40 mg); 6.12 ng/mL (60 mg); 5.08 ng/mL (80 mg); 5.48 ng/mL (control)	RCT (dose-finding) *n* = 45/44 Soy isoflavones (three doses: 40 mg, *n* = 13/12; 60 mg, *n* = 11; 80 mg, *n* = 10) vs no-treatment control (*n* = 11) 30 ± 3 days	40 mg, 60 mg, and 80 mg/ day purified isoflavones (Prevastein HC; each tablet contained 40% soy isoflavones in the aglycone form) or no supplement All groups received multivitamin supplement (PBA Multi Vitaformula; Pan American Lab Co.)	1. SHBG 2. Steroid hormone levels 3. PSA 4. Ki-67	1. No significant change in SHBG. 2. Significant increases in serum total oestradiol with 40 mg and 60 mg arms; significant increase in serum free testosterone in the 60 mg arm, but not compared with controls). 3. PSA: remained stable; no significant increase compared with control 4. Percent cells expressing Ki-67: No significant change Although plasma isoflavones increased in all supplemented arms, only the 40-mg arm showed modulation of serum oestradiol without a significant increase in serum free testosterone or serum PSA. This group also showed the least mean percentage of cells in proliferation at the end of study with no clinical toxicity.	Active: two grade I gastrointestinal AEs, grade I elevations to alanine transaminase, marginal elevations in lipase, amylase, phosphorus, and calcium in 1–2 subjects; Placebo: not reported
Lazarevic, et al., 2011 [26] Norway	Men with localized PCa, clinical stage T1c or T2, before prostatectomy Age: ≥ 18 years Excluded: previous or current hormonal therapy or chemotherapy; history of hormone-dependent malignancies; current thyroid disease or currently taking thyroid hormones; high soy intake, micronutrient or herbal supplements; vegetarian diet Gleason score: 6–8; (6, *n* = 20; 7, *n* = 18; 8, *n* = 2) Mean 6.6 (soy); 6.5 (placebo) PSA: 4.6–13.8 ng/mL Mean 8.9 ng/mL (soy); 8.2 ng/mL (placebo)	RCT (DB) *n* = 47/40 Genistein aglycone (*n* = 23) vs placebo (*n* = 24/17) 3–6 weeks	30 mg/day synthetic genistein aglycone (geniVida, formerly Bonistein from DSM Nutritional Products, Ltd., Basel, Switzerland) or placebo	1. PSA (in serum and prostatic tissue) 2. Serum testosterone, SHBG, LH 3. Gleason score/cancer grade 4. Plasma genistein 5. Other	1. Serum PSA decreased by 7.8% in the genistein arm and increased by 4.4% in the placebo arm (*P* = 0.051). The PSA level in tumour tissue compared with normal tissue was similar in the genistein arm, but was reduced in the placebo arm. 2. No significant effects on sex hormones, SHBG or thyroid hormones 3. Gleason score did not change significantly between the two treatment arms 4. Plasma concentrations of total genistein were on average a hundredfold higher in the genistein arm after treatment (*P* < 0.001). 5. Total cholesterol was significantly lower in the genistein arm (*P* = 0.013). Genistein normalized the intra-cellular expression of PSA in PCa epithelial cells, and reduced serum PSA levels without any effects on hormones.	Active: five AEs (all mild): three gastrointestinal, one cardiovascular, and one general (includes two biochemical: one increase in serum lipase, one increase of serum bilirubin). Placebo: four AEs (two gastrointestinal and two musculoskeletal).

Miyanaga et al., 2012 [30] Japan	Men with a single, negative prostate biopsy (6–12 cores) within previous 12 months. None was using a steroidal or non-steroidal anti-androgen. Excluded: men with HGPIN or ASAP at baseline, or a history of PCa. Age: 50–75 years (median 66 years) Gleason score: 5–9 (6, $n = 17$; 7, $n = 7$, 8, $n = 0$; 9, $n = 1$) PSA: 2.5–10.0 ng/mL Equol producers: $n = 76$ (48%) vs non-producers, $n = 82$ (52%)	RCT (DB) $n = 158/153$ Soy isoflavone tablet ($n = 78/75$) vs placebo ($n = 80/78$) 12 months	60 mg/day isoflavones: (daidzin 19.1 mg [31.9%]; genistin 3.5 mg [5.8%]; glycitin 10.4 mg [17.3%] daidzein 0.2 mg [0.3%] genistein 0.1 mg [0.1%] glycitein 0.2 mg [0.3%]) or placebo.	1. PSA 2. Sex hormones: testosterone, DHT, SHBG and oestradiol. 3. Incidence of biopsy-detectable PCa, HGPIN, and ASAP 4. Serum isoflavones levels	1 & 2. No significant findings within or between groups. 3. No significant difference in cancer incidence between soy and placebo (9/42 vs 16/47 [21.4 vs 34.0%], $P = 0.140$). In the subset of men aged ≥65 years ($n = 53$), PCa incidence in the isoflavone group (7/25) was significantly lower than that in the placebo group (16/28 [28.0 vs 57.1%], $P = 0.031$). Lower incidence of a Gleason score ≤6 and HGPIN in isoflavone group compared with placebo, but not statistically significant. 4. Daidzein was significantly increased in the isoflavone groups ($P < 0.001$ isoflavone producer; $P < 0.001$ non-producer); equol levels were significantly increased in the isoflavones-producer group, ($P < 0.001$). Isoflavone exerts a cancer chemoprevention effect through an action other than hormonal.	Grade 3 AEs: one in active group suffered iliac artery stenosis, one in placebo group suffered ileus.
Soy dietary protein						
Dalais et al., 2004 [35] Australia	Patients with PCa scheduled for radical prostatectomy, not treated with radiotherapy Mean age: 62 (soy), 58 (soy and linseed), 61 (wheat) Excluded: already adhering to a high phytoestrogen diet or tablets. Gleason score: mean 6.50 ± 0.85 (soy); 5.75 ± 0.90 (soy and linseed); 5.71 ± 1.38 (wheat) PSA: 7.16 (soy); 6.31(soy + linseed); 5.81 ± 3.70 ng/mL (wheat)	RCT (DB) $n = 29/28$ Phytoestrogen-rich diet (soy, $n = 8$), soy and linseed, $n = 10$) vs wheat ($n = 8$) 22–27 days	Bread with heat-treated soy grits (50 g) (Prosoy, Cereform, Enfield, Australia) or soy (50g) with linseed (20 g) bread Daily isoflavones levels: 117 mg (genistein, daidzein, and glycitein in aglycone form) or pearled wheat bread.	1. PSA levels 2. Free/total PSA ratio 3. Testosterone, SHBG, free androgen index 4. Urinary isoflavones	1. Change in PSA levels: soy grits superior to wheat (–12.7 vs 40%, $P = 0.02$), 2. Change in free/total PSA ratio: soy grits superior to wheat (27.4 vs −15.6%, $P = 0.01$). Soy alone was superior to soy with linseed (27.4 vs −10%, $P = 0.007$) 3. No significant changes. Free androgen index: Soy alone was superior to soy with linseed (16.4 vs −15.5%, $P = 0.04$). 4. Significant changes in urinary genistein and daidzein for soy group ($P < 0.001$),and soy with linseed group, $P < 0.01$) PSA and the free/total PSA ratio were favourably influenced in men consuming bread high in heat-treated soy grits.	AEs not mentioned
Hamilton-Reeves et al., 2007 [25] USA	Men at high risk of developing advanced PCa (HGPIN, [$n = 40$] +/or – ASAP [$n = 13$]), or with low grade PCa on active surveillance ($n = 5$) Age: 50–85 years Excluded: PCa that required medical treatment; prostatitis Gleason score: <6 (patients with PCa) PSA: 5.4 ng/mL (SPI+), 5.0 ng/mL (SPI–), 5.1 ng/mL (milk protein)	RCT (SB) $n = 66/58$ (at 3 months)/55 SPI high in isoflavones (SPI+; $n = 20$) vs SPI with most of the isoflavones removed (SPI-; $n = 20$) vs MPI ($n = 18$) 6 months	All isolates contained 40 gm/day protein: 1) SPI+ (107 ± 5.0 mg/day isoflavones – 53% genistein, 35% daidzein, and 11% glycitein); 2) alcohol-washed SPI- (<6 ± 0.7 mg/day isoflavones – 57% genistein, 20% daidzein, and 23% glycitein) 3) MPI (0 mg/day isoflavones; The Solae Company) Divided doses – twice daily – as a partial meal replacement.	1. Circulating oestradiol, estrone, SHBG, androstenedione, androstanediol glucuronide, dehydroepiandrosterone sulfate, dihydro-testosterone, testosterone, and free testosterone 2. Prostate biopsies: AR and oestrogen receptor-β expression	1. Consumption of SPI+ did not alter oestrogen receptor-β expression or circulating hormones. SPI- significantly increased oestradiol ($P < 0.05$) and androstenedione concentrations ($P < 0.05$) 2. Consumption of SPI+ significantly suppressed AR expression in prostate biopsies after 6 months compared with the MPI group ($P < 0.04$). AR expression in the prostate is suppressed by SPI consumption, which may be beneficial in preventing PCa.	AEs resulting in withdrawal – treatment group not specified: gastrointestinal tract discomfort ($n = 1$) weight gain ($n = 1$)
Hamilton-Reeves et al., 2008 [34] USA	HGPIN, ASAP, or low grade PCa (as previous)	As previous	As previous	1. Disease progression 2. Cancer tumour markers. Bax, PCNA 3. PSA	1. PCa incidence was more than six times higher in the MPI group (6/16) (38%) than in the combined soy groups (1/17 and 1/16) among men without evidence of cancer at baseline who elected for end-of-treatment biopsy ($P = 0.013$). 2 & 3. No effect on prostate tissue biomarkers There may be multiple constituents of SPI that exert varied effects on PCa biomarkers. We observed a lower rate of PCa development in men in the soy groups compared with the milk group.	As previous
Hamilton-Reeves et al., 2007 [24] USA	As previous	As previous	As previous	1. Oestrogen metabolism	Both soy groups had higher oestradiol excretion than the MPI group at 3 and 6 months ($P < 0.05$). After 6 months of supplementation, the SPI+ group had a significantly higher urinary 2:16 hydroxyestrone ratio than the MPI group ($P < 0.05$) Soy consumption may be beneficial in men at high risk of progressing to advanced PCa as a result of effects on endogenous oestrogen metabolism.	As previous
Kumar et al., 2004 [28] USA	Patients with early-stage PCa on watchful waiting, with a Gleason score of ≤6 Age: 45–85 years Excluded: history of other cancer; history of hormone therapy; vegans and consumers of soy product or other herbal supplements Gleason score: ≤6 PSA: mean 7.38 ng/mL (soy); 7.45 ng/mL (placebo)	RCT (DB) $n = 76/59$ Soy protein beverage supplement ($n = 37/29$) vs placebo ($n = 39/30$) 12 weeks	Soy protein beverage supplement (containing 60 mg of genistein; Protein Technologies International) or isocaloric placebo	1. PSA 2. Serum free testosterone 3. SHBG	1. Total PSA decreased/unchanged in 69 vs 55% placebo (NS); 2. Free testosterone showed decrease/no change in 61% Isoflavone group vs 33% placebo, but increased in 67% of placebo compared with 39% of isoflavone group (NS) 3. SHBG – no increase. Proliferation markers – serum total PSA and free testosterone reduced in larger numbers with isoflavones than with placebo. Soy protein may have potential to slow progression of PCa.	AEs (not specified which arm): constipation ($n = 8$), diarrhoea ($n = 1$), and abdominal bloating ($n = 3$)

AE, adverse event; DB, double-blind; LH, luteinizing hormone; MPI, milk protein isolate; NS, nonsignificant; PCNA, proliferating cell nuclear antigen; SPI+, SPI with isoflavones; SPI–, SPI with isoflavones removed.

excluded men with ASAP, HGPIN or a history of PCa [30],and the other focused on men at high risk of developing clinically significant PCa (ASAP, HGPIN or low grade PCa) [24,25,34].

Interventions

Five studies investigated isoflavones in tablet form, while three studies were on dietary soy protein/interventions. Seven different preparations/products were used (Table 2). Two studies investigated the same isoflavones supplement (Prevastein HC®) [29,32].

Of the dietary supplement studies, a synthetic genistein aglycone was used in one study [26], and purified isoflavones in three studies [29,30,32]. The remaining study investigated genistein-combined polysaccharide (GCP), an aglycone isoflavone-rich extract produced by culturing soybean extract with mycelia from the mushroom *Ganoderma lucidum* [27]. Of the three dietary intervention studies [25,28,35], two administered soy protein isolate/beverage, and the third provided bread containing soy grits [35].

A wide range of doses was used. In studies administering tablets, doses ranged from 40 mg [29] to 80 mg/day total isoflavones [32,33]; in studies administering soy in aglycone form, the range was 16 mg aglycones/day (40 mg isoflavones containing 40% in aglycone form) [29] to 450 mg genistein aglycone with 300 mg daidzeinaglycone as a GCP [27]. Soy isoflavones administered as foods ranged from 60 mg genistein [28] to 117 mg total isoflavones daily [35].

Risk of Bias

Risk of bias was assessed as low in all assessed studies except for one, for which risk of bias was unclear (Fig. 2A,B). A risk-of-bias assessment was not included for the dose-finding study [29]. 'Other risk of bias' included funding sources: all studies reported that they were funded by grants; two were partially funded by grants from the product manufacturers [27,35]. Five of the studies reported donations of trial supplements. Publication bias could not be assessed because of the small number of studies in each meta-analysis.

Power calculations were reported in three studies [26–28], one of which retained adequate participants to meet the predefined sample [26], but, in all three studies, the observed effects were smaller than anticipated.

Effects of Interventions

Incidence of cancer

A meta-analysis of two studies investigating the development of cancer in men with clinically identified risk (men with a single, negative prostate biopsy at baseline over 12 months) [30] or men with ASAP or HGPIN [34] over 6 months found that there was a statistically significant reduction in PCa diagnosis after the administration of soy/soy isoflavones (RR = 0.49, 95% CI 0.26, 0.95 [Fig. 3]).

Prostate-specific antigen

Seven studies included PSA endpoints [26–29,32,34,35]. A meta-analysis of these showed no significant effect on PSA levels in men with, or at risk of, PCa (MD = −0.01, 95% CI −0.74, 0.72 [Fig. 4]), although in two individual studies, the reduction in PSA was significant [35] or approached significance [26].

Sub-population analyses of PSA according to existing PCa or risk of development resulted in no significant findings.

A change in the free/total PSA ratio was reported in one study, which found a significantly greater change with bread containing soy grits than with wheat bread (27.4% vs −15.6%, $P = 0.01$) [35].In another study, immunohistochemical analysis of PSA levels for benign and malignant tissue found that there was a significant difference in PSA expression in Gleason grade 4 between the two treatment arms ($P = 0.044$) [26].

Sex hormone-binding globulin

Seven studies assessed the effect of soy/isoflavones on SHBG [25,26,28–30,32,35]. A meta-analysis of these found no significant effect of soy/isoflavones compared with placebo (MD = 2.21, 95% CI −0.83, 5.26 [Fig. 5]).

Free testosterone

Four studies assessed the effect of soy/isoflavones on free testosterone levels in men with, or at risk of, PCa [25,28,29,32]. A meta-analysis found no significant difference between groups, (MD = 3.84, 95% CI −0.32, 8.00 [Fig. 6]).

Testosterone

Four studies examined serum testosterone levels after tablet [26,30] or dietary interventions [25,35] in men with, or at identified risk of, PCa. No significant effect was observed in a meta-analysis of these studies (MD = 0.62, 95% CI −0.53, 1.78 [Fig. 7]).

Dihydrotestosterone

Three studies measured serum DHT levels after dietary soy administration in men with PCa [35] or soy tablet supplements in men at identified risk of PCa [30]. A meta-analysis of these studies found no significant effect compared with the controls for the soy supplementation (MD = 0.21, 95% CI −0.13, 0.56 [Fig. 8]).

Oestradiol

Five studies reported on serum oestradiol levels [25,28–30,32]. A meta-analysis of these found no significant effect of soy/soy isoflavone administration compared with placebo (MD = 1.02, 95% CI −0.83, 2.86 [Fig. 9]).

Fig. 2 (**A**) Risk of bias summary of included studies. (**B**) Risk of bias graph of included studies.

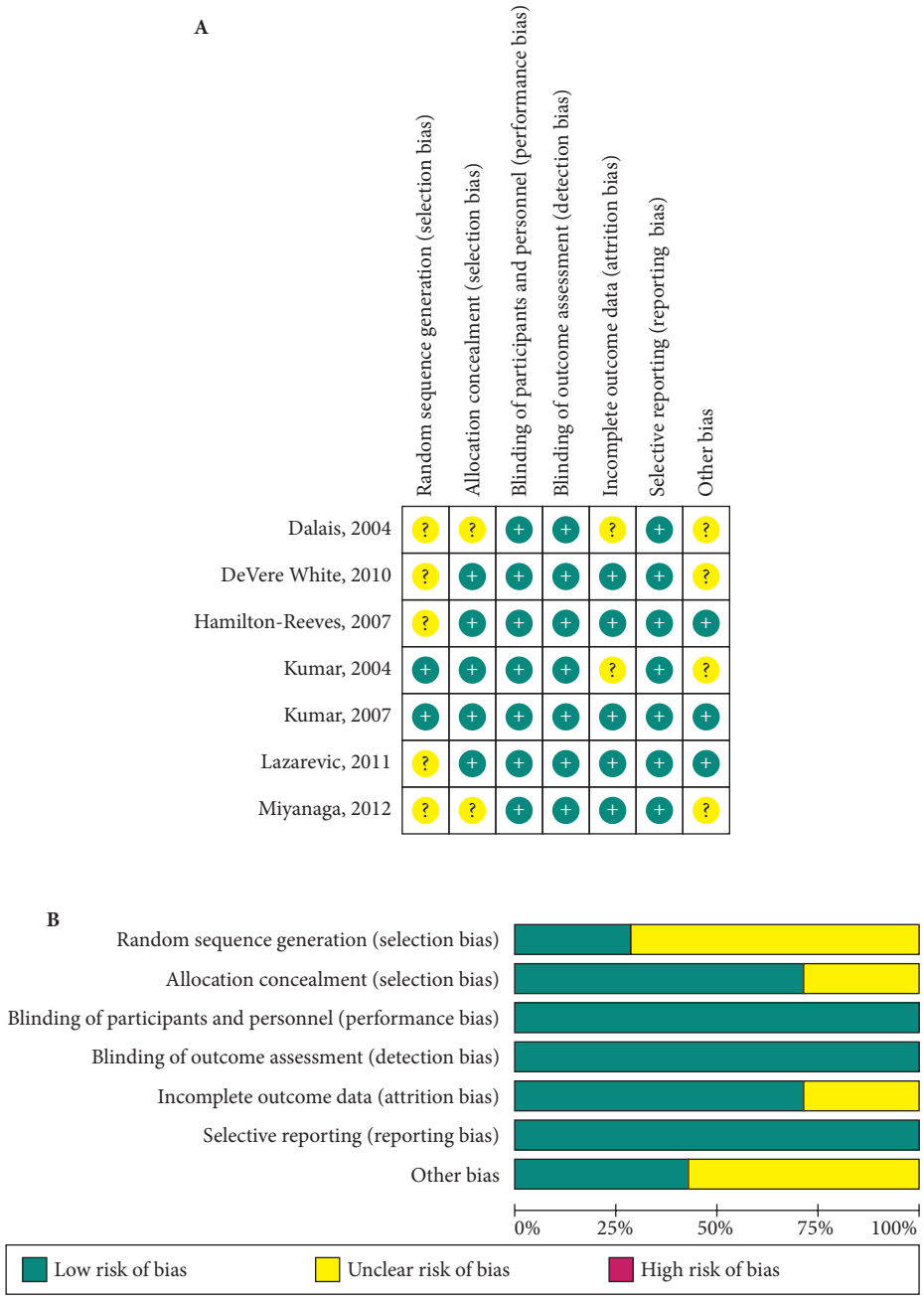


Fig. 3 Soy/isoflavones vs control for outcome of PCa diagnosis. df, degrees of freedom.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Miyanaga, 2012	9	42	16	47	71.0%	0.63 [0.31, 1.27]
Hamilton-Reeves, 2007–08	1	17	6	16	29.0%	0.16 [0.02, 1.16]
Total (95% CI)		59		63	100.0%	0.49 [0.26, 0.95]
Total events	10		22			

Heterogeneity: chi-squared = 1.72, df = 1 ($P = 0.19$); I-squared = 42%

Test for overall effect: Z = 2.13 ($P = 0.03$)

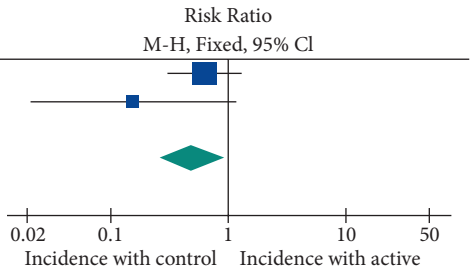


Fig. 4 Soy/isoflavones vs control for outcome of total PSA. df, degrees of freedom.

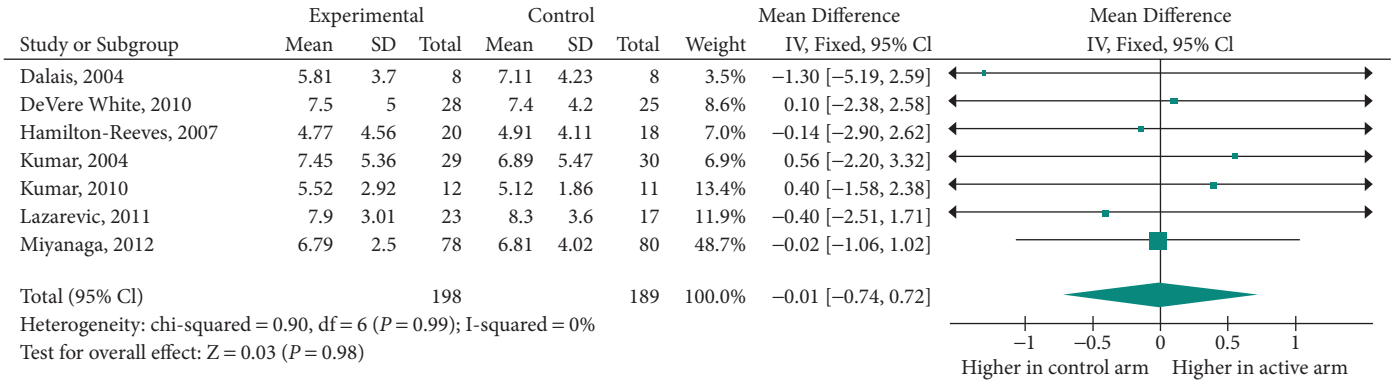


Fig. 5 Soy/isoflavones vs control for outcome of SHBG. df, degrees of freedom.

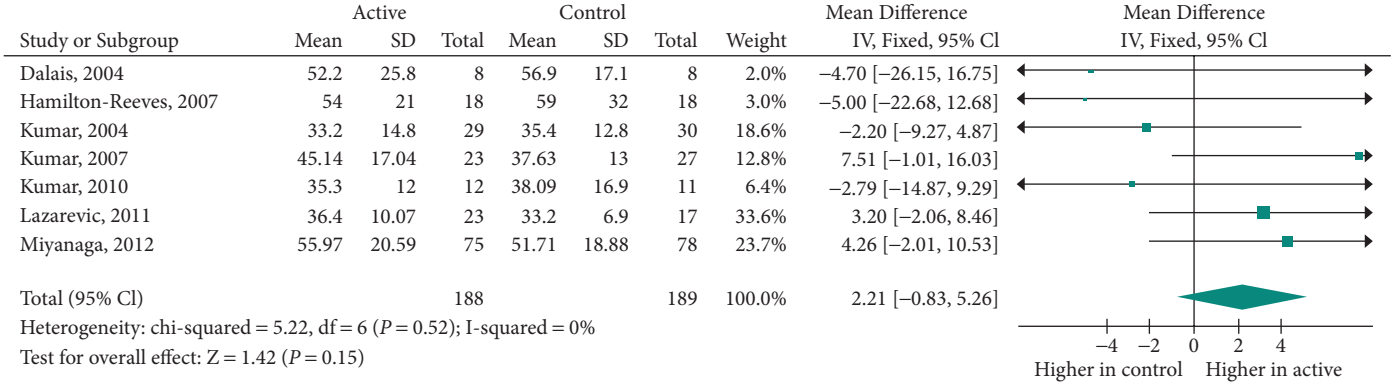
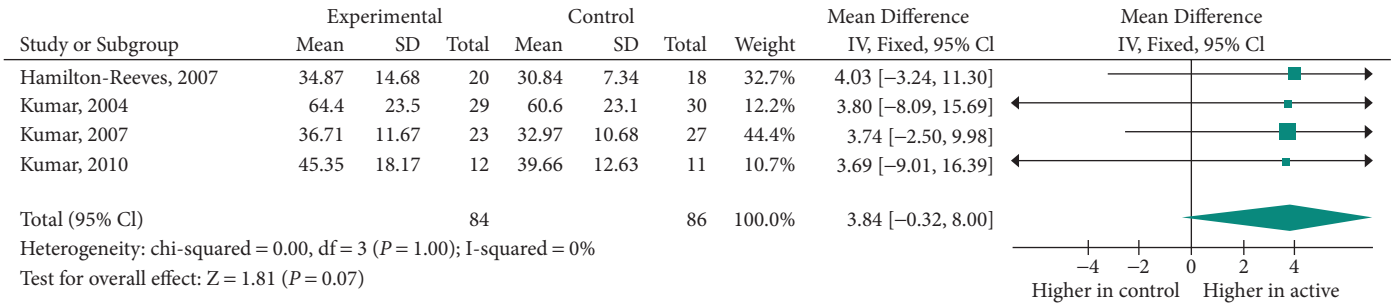


Fig. 6 Soy/isoflavones vs control for outcome of free testosterone. df, degrees of freedom.



Additional analyses

Sub-group analyses of PSA and sex hormone outcomes according to supplementation by tablets vs whole-food sources resulted in no significant findings.

Equol

The production of equol was assessed in three studies [25,27,30]. No significant association between PSA and measured concentrations of equol was found after administration of GCP 5 gm/day for 6 months (16 excretors, eight non-excretors) [27]. Similarly, all measured urinary oestrogen metabolites were the same between equol excretors and non-excretors after 3 months' supplementation with soy protein isolate with isoflavones (four excretors and 15 non-excretors [24]. Equol status did not affect the results of any of the endpoints measured (PSA, SHBG, testosterone, DHA and oestradiol) after administration of 60 mg/day soy isoflavones of placebo for 12 months in the PCa chemoprevention study of at-risk men [30]. An association between PCa risk reduction and equol production was not assessed.

Fig. 7 Soy/isoflavones vs control for outcome of testosterone. df, degrees of freedom.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dalais, 2004	18.6	6.8	8	19.1	6.9	8	3.0%	−0.50 [−7.21, 6.21]
Hamilton-Reeves, 2007	12.49	3.47	20	11.45	3.47	18	27.3%	1.04 [−1.17, 3.25]
Lazarevic, 2011	12.9	5.09	23	13.1	3.5	17	18.8%	−0.20 [−2.86, 2.46]
Miyanaga, 2012	16.89	4.32	75	16.12	5.79	78	51.0%	0.77 [−0.84, 2.38]
Total (95% CI)			126			121	100.0%	0.62 [−0.53, 1.78]

Heterogeneity: Tau-squared = 0.00, chi-squared = 0.64, df = 3 (P = 0.89); I-squared = 0%
Test for overall effect: Z = 1.06 (P = 0.29)

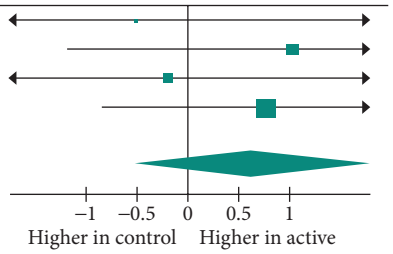


Fig. 8 Soy/isoflavones vs control for outcome of DHT. df, degrees of freedom.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Dalais, 2004	1.73	0.92	8	1.68	0.74	8	17.7%	0.05 [−0.77, 0.87]
Hamilton-Reeves, 2007	2.38	1.3	20	1.77	0.83	18	25.1%	0.61 [−0.08, 1.30]
Miyanaga, 2012	3.21	1.34	75	3.12	1.53	78	57.2%	0.09 [−0.37, 0.55]
Total (95% CI)			103			104	100.0%	0.21 [−0.13, 0.56]

Heterogeneity: chi-squared = 1.72, df = 2 (P = 0.42); I-squared = 0%
Test for overall effect: Z = 1.22 (P = 0.22)

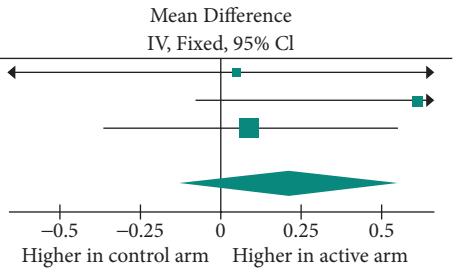
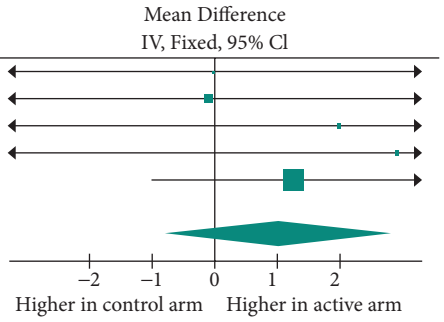


Fig. 9 Soy/isoflavones vs control for outcome of oestradiol. df, degrees of freedom.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hamilton-Reeves, 2007	66.08	22.03	20	66.08	11.01	18	2.9%	0.00 [−10.91, 10.91]
Kumar, 2004	23.6	7.34	29	23.7	8.14	30	21.7%	−0.10 [−4.05, 3.85]
Kumar, 2007	31.72	15.93	23	29.74	14.11	27	4.8%	1.98 [−6.43, 10.39]
Kumar, 2010	41.3	2.47	12	38.4	17.15	11	3.2%	2.90 [−7.33, 13.13]
Miyanaga, 2012	26.53	7.03	75	25.27	7.14	78	67.4%	1.26 [−0.99, 3.51]
Total (95% CI)			159			164	100.0%	1.02 [−0.83, 2.86]

Heterogeneity: chi-squared = 0.57, df = 4 (P = 0.97); I-squared = 0%
Test for overall effect: Z = 1.08 (P = 0.28)



Adverse events

Seven of the eight studies reported on adverse events; however, two of these neglected to specify the arm in which the events occurred. Reported adverse events were predominantly mild, although abdominal pain, classified as a grade II (moderate) event, was reported in one study [32], and one severe (grade III) event in each arm was reported in another (iliac artery stenosis in active group; ileus in placebo group) [30]. Mild events included loose stools, diarrhoea, constipation, bloating, loss of appetite, dyspepsia, biochemical events (increase in serum lipase [1], increase of serum bilirubin [1]; grade I elevations in alanine transaminase, marginal elevations in lipase, amylase, phosphorus, and calcium [in 1–2 subjects]. Overall, only two adverse events resulted in withdrawal (gastrointestinal discomfort [1] and weight gain [1]); however the treatment group was not specified [25]. In studies reporting on both arms, adverse events occurred with similar frequency in both the treatment and placebo arms. In one study, the incidence of adverse events rated as 'probably related' was greater in the placebo arm [32]. Details of events and frequency are shown in Table 2.

Discussion

The objective of the present study was to evaluate the evidence from RCTs of soy/soy isoflavones in men with, or at identified risk of, PCa. A total of eight RCTs, whose study data were reported in 11 separate articles, were included in this systematic review. Eight different doses and seven different preparations of soy/isoflavones were administered. Six studies recruited only men with histologically confirmed PCa, while two included men with identified risk of PCa. Overall, the

findings support a risk reduction for the development of PCa in men with clinically identified risk, but no effect was found on PSA or sex hormone endpoints; however, most studies were small and underpowered. The reviewed studies supported a good safety profile for soy/soy isoflavones.

No studies reported on 5-year survival. The finding that supplementation with soy/isoflavones could significantly lower progression to PCa in men with identified risk is consistent with the results of a 2009 meta-analysis of 15 epidemiological publications on soy consumption and nine on isoflavones, which found a significant association with reduced PCa risk [6]; however, unlike the present study, that meta-analysis was not restricted to men with PCa or identified risk of developing PCa.

No effect on PSA was found in our meta-analysis. A 2006 review of trials measuring PSA levels found that in four of eight trials involving patients with PCa, isoflavone supplementation significantly favourably affected PSA: in two open-label studies, it significantly slowed the rise in PSA in comparison with pre-intervention levels; in two others, the change in PSA was statistically significant compared with the control [7]. One of these two studies [35] is included in our meta-analysis; in the other study, a crossover trial, plant oestrogens were part of a multicomponent intervention comprising antioxidants, carotenoids, selenium and other putative PCa-inhibiting substances, making the contribution of the phytoestrogens impossible to assess [36].

No significant effects were observed on sex hormone levels in our meta-analyses. The findings with regard to SHBG, testosterone and free testosterone are consistent with a 2010 meta-analysis of isoflavone studies that found no significant effect on reproductive hormones in men [37]; however, it differed from the present study in that it included studies of only healthy men, and other plant sources of isoflavones as well as complex interventions. By contrast, in one open-label study, 3 months' administration of soy isoflavones supplements (60 mg daily) decreased testosterone and DHT and increased SHBG levels in healthy men aged 30–59 years [38].

Other significant findings noted in individual studies include increased oestradiol excretion after soy supplementation, suggesting a possible mechanism for PCa risk reduction by soy [24]. Suppression of AR- but not oestrogen receptor-β expression after 6 months with isoflavone-rich soy protein compared with the control may also have relevance to the beneficial effects of soy in PCa prevention in men at high risk [25].

A clear understanding of the impact of soy isoflavones on total testosterone, free testosterone or SHBG levels cannot be derived from these data. The pooled results of several small studies looking at each of these showed no significant changes.

Only three studies assessed equol production [24,27,30]. No significant association was observed with the endpoints of PSA levels, sex hormone levels or urinary oestrogen metabolites. An association with equol-producing status was only determined for progression to cancer in at-risk men over 65 years of age in the 12-month study [30]. Elsewhere, an association has been shown between equol and reduced PCa risk in Asian [19,39,40], but not European men [41]. Because this high inter-individual variability in equol-producing capacity has the potential to affect health outcomes, it has been proposed that equol-producer status should be assessed in clinical studies on soy [17].

Findings from the studies reviewed in the present paper suggest a good safety profile for soy/soy isoflavones in these patient cohorts over study durations of up to 12 months, consistent with findings from other studies [7]. As pointed out by Messina et al. [7], isoflavone intake of up to 10–20 times the typical daily Japanese intake resulted in no evidence of toxicity and no related adverse events greater than grade I in studies conducting extensive chemical and biological analyses [7,27]. Similarly, phase I trials have demonstrated the safety of whole soy and purified isoflavones with single- and multiple-dose administration in healthy cohorts and patients with early-stage or treated cancer; doses of purified soy isoflavones ranging from 1 to 16 mg/kg body weight produced no significant clinical toxicity [29].

The strengths of the present study are its well-defined inclusion criteria, whereby it included only studies on men with PCa, or at identified risk for PCa and excluded multi-component interventions and complex dietary interventions that may confound the interpretation of results related to soy/soy isoflavones. We also included an assessment of disease progression, the impact of equol production, and adverse events. Meta-analyses were performed where possible. All the studies were of good quality, with predominantly low risk of bias. The doses used in the included trials were generally consistent with those delivered by a typical Japanese soy-based diet (25–100 mg soy isoflavones/day) [42], and estimates of daily genistein consumption delivered by soy-based diets (0.25–1.0 mg/kg) [43].

Limitations of the present study include the fact that not all the studies included all endpoints, so most of our conclusions are based on subset analyses. In addition, with the exception of surveillance patients, studies did not stratify patients according to whether they were at low or high risk; thus, the ability of soy to modify progression based on biology (aggressive or non-aggressive) could not be assessed. Publication bias cannot be excluded, especially for studies conducted before the introduction of prospective trial registration. In the meta-analyses, end-of-treatment scores rather than change scores were used, which meant differences from baseline were not captured. Heterogeneity of soy/soy isoflavone preparations, dosage regimens and study populations among

the studies suggest that the results of the meta-analyses should be interpreted with caution. Sample sizes in most studies were small; < 60 participants were retained in any of the studies except for one. The observed effects were smaller than anticipated in the three studies performing power analyses, suggesting some studies may have been underpowered. The duration of most studies was ≤6 months only the largest study continued for 12 months. This raises the question of whether the duration of most studies was sufficient to detect clinically meaningful changes in the endpoints of interest, as progression from prostatic intraepithelial neoplasia to HGPIN and early latent cancer may take 10 or more years, and clinically significant carcinoma may not occur for another 3–15 years [28], while recurrent disease may take a decade or more to become manifest [44]. Measuring PSA over short durations, as in these studies, may therefore be of limited value.

The meta-analyses performed in the present review combined studies administering soy isoflavones in a variety of forms; however, there is evidence suggesting that the type of soy product may influence outcomes. In a meta-analysis of epidemiological studies on PCa risk, significant results were obtained with non-fermented soy foods, but not with fermented soy foods or isoflavones [6]. *In vitro* evidence supports the presence of differential effects of whole soy extracts and soy isoflavones on apoptosis in PCa cells [42]. Additionally, most studies did not stratify according to equol-producer status, precluding any meaningful meta-analysis on that basis.

The results of the present systematic review support epidemiological findings of a potential role for soy/soy isoflavones in PCa risk-reduction; however, the meta-analysis on cancer-incidence was limited to data from only two studies [25,30], one of which combined at-risk men and men with early-stage PCa; no improvements in secondary outcomes were shown. Further robust RCTs are therefore warranted to validate this finding, and to determine the impact of equol-production, as well as the optimum dose and form of administration; however, given the safety profile of soy/soy-isoflavones, consumption of soy/soy isoflavones need not be discouraged.

In men with PCa, a clear understanding of the impact of soy/isoflavones could not be determined. Meta-analyses showed no significant changes on PSA or steroid hormones; however, the implications of small individual studies of short duration have already been noted. Future clinical trials on soy/isoflavones in PCa need to be adequately powered, and of sufficient duration to detect changes in clinically meaningful endpoints. Stratification according to equol-producing status is also recommended.

In conclusion, the results of the present review and meta-analyses suggest there may be a potential role for soy isoflavone supplements and soy protein in PCa risk reduction; however, whether delivered as dietary supplements or food, these substances do not affect PSA or sex hormone concentrations over the short term in men with, or at clinically-identified risk of, PCa. A good safety profile is demonstrated for soy/soy isoflavones. Further evidence is needed from robust clinical trials with adequate sample sizes and longer timeframes.

Acknowledgements

The authors thank Associate Prof. Cliff da Costa and Dr Patty Chondros for statistical support.

Conflict of Interest

K.B. works as a consultant director of Research and Development for MediHerb (Integria) Australia, who manufacture a soy tablet. K.B and D.v.D. are related to each other.

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Abbreviations: RCT, randomized controlled trial; PCa, prostate cancer; SHBG, sex hormone-binding globulin; DHT, dihydrotestosterone; AR, androgen receptor; ASAP, atypical small acinar proliferation; HGPIN, high grade prostatic intraepithelial neoplasia; MD, mean difference; GCP, genistein-combined polysaccharide.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. PRISMA 2009 checklist.
Table S1. Results of identified studies for serum PSA, testosterone, free testosterone, SHBG and oestradiol.