Clinical studies show no effects of soy protein or isoflavones on reproductive hormones in men: results of a meta-analysis

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Objective: To determine whether isoflavones exert estrogen-like effects in men by lowering bioavailable T through evaluation of the effects of soy protein or isoflavone intake on T, sex hormone–binding globulin (SHBG), free T, and free androgen index (FAI) in men.

Design: PubMed and CAB Abstracts databases were searched through July 1, 2008, with use of controlled vocabulary specific to the databases, such as *soy, isoflavones, genistein, phytoestrogens, red clover, androgen, testosterone,* and *SHBG*. Peer-reviewed studies published in English were selected if [1] adult men consumed soy foods, isolated soy protein, or isoflavone extracts (from soy or red clover) and [2] circulating T, SHBG, free T, or calculated FAI was assessed. Data were extracted by two independent reviewers. Isoflavone exposure was abstracted directly from studies.

Main Outcome Measure(s): Fifteen placebo-controlled treatment groups with baseline and ending measures were analyzed. In addition, 32 reports involving 36 treatment groups were assessed in simpler models to ascertain the results.

Result(s): No significant effects of soy protein or isoflavone intake on T, SHBG, free T, or FAI were detected regardless of statistical model.

Conclusion(s): The results of this meta-analysis suggest that neither soy foods nor isoflavone supplements alter measures of bioavailable T concentrations in men. (Fertil Steril® 2010;94:997–1007. ©2010 by American Society for Reproductive Medicine.)

Key Words: Soy, isoflavones, testosterone, SHBG, red clover, phytoestrogens

Soy foods have played an important role in the diets of many East Asian countries for centuries. They are especially valued for their versatility and protein content. More recently, these foods have become quite popular among health-conscious consumers in Western countries because of reports suggesting that soy intake is associated with a variety of health benefits. Noteworthy in this regard is the health claim for soy foods and coronary heart disease awarded by the U.S. Food and Drug Administration in 1999 on the basis of the cholesterol-lowering properties of soy protein (1). Although there continues to be much interest in soy protein, most of the soy-related research in recent years has been conducted because the soybean is essentially the only commonly consumed food to contain biologically relevant amounts of isoflavones. Each gram of soy protein in traditional soy foods is associated with approximately 3.5 mg isoflavones (expressed as the aglycone weight), and mean daily soy protein and isoflavone intake among Japanese adults ranges from approximately 6 to 11 g and 25 to 50 mg, respectively (2).

Isoflavones are diphenolic compounds that bind to estrogen receptors and exert some estrogen-like effects under certain experimental conditions; for this reason they are classified as phytoestrogens (3, 4). The two primary isoflavones in soybeans are genistein and daidzein. Not surprisingly, there has been considerable investigation of the effects of isoflavones on the health of menopausal women. These studies suggest that isoflavones are classified more accurately as selective estrogen receptor modulators (5, 6), because in clinical trials they have no effects on many biologic processes known to be affected by estrogen (7–9) while at the same time in many studies inhibiting bone resorption (10, 11) and alleviating hot flashes (12–14). The selectivity of isoflavones, and especially genistein, may be attributed at least in part to their preferential binding to estrogen receptor beta in

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comparison with estrogen receptor alpha (15–17). Yet, classifying isoflavones as selective estrogen receptor modulators is still an incomplete characterization because in addition to hormonal effects they exert nonhormonal effects that are potentially relevant to cancer prevention and treatment (18, 19).

In comparison with research in women, much less isoflavone-related research has been performed in men although there is considerable interest in establishing the impact of soy foods and isoflavones on prostate cancer risk (20, 21). Because lower T concentrations are associated with a decreased risk of prostate cancer in some epidemiologic studies (22, 23) (although a recent analysis of prospective studies indicates there is no relationship [24]), it has been suggested that lowering bioactive T concentrations is one mechanism by which soy foods decrease prostate cancer risk. In theory, the estrogen-like effects of isoflavones might lower T levels in men, and some animal studies in fact have shown that isoflavones act as endocrine disruptors. Some studies in adult male rodents treated with soy protein or genistein have found reduced serum T concentrations (25, 26) although others have found unchanged (27–29) and increased (30) T concentrations. Low bioavailable T in men has been associated with a loss of energy, depressed mood, decreased libido, erectile dysfunction, decreased muscle mass and strength, increased fat mass, frailty, osteopenia, and osteoporosis (31, 32) and may even increase risk of coronary heart disease (33).

Because of the increasing popularity of soy foods and the availability of isoflavone supplements, there is an important public health need to understand the impact of soy isoflavones on reproductive hormone levels in men. To this end, a meta-analysis of clinical studies was conducted. The objective of this research was to evaluate the effects of isoflavone consumption on circulating concentrations of T, sex hormone–binding globulin (SHBG), and free T or free androgen index (FAI) in men. The analytic approach was to examine the data from randomized placebo-controlled trials reporting baseline and study end measures and then to compare the results within the context of all identified clinical interventions. Secondary analysis was planned to evaluate whether parameters thought to influence isoflavone effects on circulating hormones explained the heterogeneity of the data. The rationale of these approaches was to highlight the data from the higher-quality studies, to support the findings with all data unrestricted by study design, and to suggest which influential parameters should be considered in the design of future trials.

MATERIALS AND METHODS

Study Identification

To identify appropriate intervention trials, PubMed (National Library of Medicine, Bethesda, MD) and CAB Abstracts databases were searched through July 1, 2008, using the keywords *soy, isoflavones, genistein, phytoestrogens, red clover, diet-vegetarian, dietary supplements, therapeutic use of soybeans, androgen, hormones, testosterone,* and *sex hormone–binding globulin (SHBG).* References within identified articles, as well as peer-reviewed articles that had come to the attention of the authors through other means, also were examined for suitability. Neither abstracts nor articles not published in English were considered for review. When sufficient details regarding the study design or results were not provided in the article, the authors were contacted for the missing information. Studies were selected for analysis if they met the following criteria: [1] men consumed soy foods, isolated soy protein (by definition isolated soy protein is $\geq$90% protein), or isoflavone extracts (derived from soy or red clover) and [2] circulating T, SHBG, free T, or calculated FAI was assessed. Clinical trials (parallel or crossover) and single-group studies were included. Although findings must be interpreted with caution given the absence of a control group, data from single-group pre-post design studies were considered useful because of the limited number of well-controlled studies. Single-group studies were analyzed separately from two-group comparisons and were included only to ascertain results obtained from placebo-controlled trials.

Analyzed Studies and Outcome Measures

Data were extracted and tabulated onto an Excel (Microsoft, Redmond, WA) spreadsheet. Outcomes tabulated included means and variability measures of T, SHBG, free T, and FAI. Units were standardized and converted to molar concentrations. Authors were contacted to confirm that correct units were published.

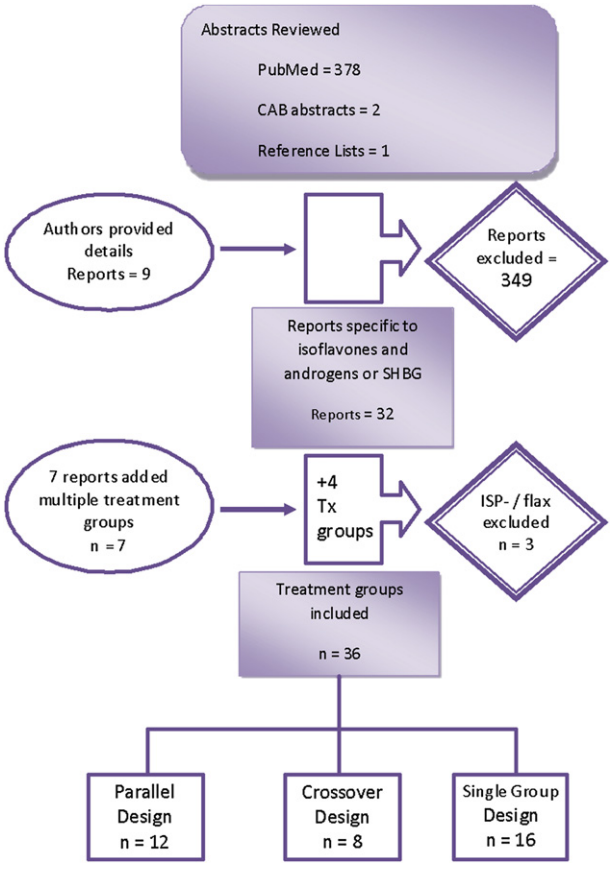
Study characteristics tabulated included publication year, study design, and number of participants per group. Participant characteristics assessed were age and prostate cancer status. Treatment characteristics assessed were duration of intervention, intake of soy protein (grams per day) and isoflavones (milligrams per day expressed as the aglycone weight), isoflavone source (red clover or soy), and treatment vehicle (isolated isoflavones, isolated soy protein, or food). To address whether the effects were attributable to isoflavones from food sources or isoflavones from commercially prepared extracts, isolated soy protein, tofu, and soy milk, soy grits, and soy flour were coded as soy foods and compared with the effects of isoflavone extracts given in pills or tablets. Given the wide range in isoflavone exposure among the trials, doses were classified as low (<10 mg/d), medium (10–65 mg/d), high (66–150 mg/d), or very high (>150 mg/d). Similarly, soy protein doses varied by protocol; therefore, exposure was categorized as low (<5 g/d), medium (5–20 g/d), high (21–45 g/d), or very high (>45 g/d). Last, duration of intervention was characterized as short (<1 month), medium (5 weeks–4 months), or long term (>4 months).

Meta-analysis and Statistical Analysis

Data were analyzed with the use of STATA for meta-analysis (Stata Statistical Software, release 9; StataCorp LP, College Station, TX). Effect size was computed by comparing the difference in change of baseline and ending values between the treatment arm and the control arm of parallel and crossover

FIGURE 1

Flow diagram of systematic review of literature. Tx = treatment; ISP− = isolated soy protein depleted of isoflavones; n = number of treatment groups.



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trials. In addition, effect size was calculated by comparing ending with baseline values in the treatment arms of parallel, crossover, and single-group studies and by comparing ending values in the treatment arms versus the control arms of parallel and crossover trials. These last two models were used solely for context to confirm the results.

Standard deviations were generated from different measures of variability (SD, range, SE, confidence intervals [CIs]) or, if missing, were imputed with the pooled SD (geometric mean of SD) and use of information available from studies reporting at the same intervention time for the same outcome. Intraclass correlation was generated from studies with individual data and was used to adjust the SEs for the change of posttreatment and pretreatment estimates.

Coefficients of variation were generated to assess whether the relation of SD to mean was similar in all studies. To preserve all data but not skew the analysis, a standardized mean difference was calculated for each comparison on each available outcome. The standardized mean difference is the difference between the group means divided by the pooled SD. The purpose of expressing the standardized mean difference is to express the effect irrespective of the units in which the outcome was measured. We used a random effects model to calculate the pooled standardized mean difference and 95% CIs. I^2 was used to describe heterogeneity between studies (34). Forest plots for analyses were created by outcome and treatment intervention. Heterogeneity was investigated by comparing subgroups of studies defined by population (healthy vs. cancer, older vs. younger) and treatment study characteristics (soy protein dose, isoflavone dose, isoflavones derived from soy vs. red clover, and isoflavones derived from soy foods vs. pill or tablet) with use of univariate approach (test of heterogeneity between subgroups, Q statistic) and multivariate approach with metaregression (35). We also calculated the pooled effect on the hormone profile, T and SHBG, using the mixed-effects model (36). Publication bias was assessed with use of the trim and fill method (37). Effect size estimates were assessed for overinfluential studies.

RESULTS

Study Selection

On the basis of the inclusion and exclusion criteria, 32 articles were identified (7, 38–68). Nine of the studies from the reports did not publish means and variability measures of all hormones assessed (41, 44, 45, 54, 59, 63–66). The authors of these articles were contacted. In response, either the means and variability of T (44, 54, 63–66), SHBG (59, 64), or free T (44, 64), or the raw data of T (41, 45), SHBG (41), or free T (45) were sent. The article by Higashi et al. (51) contained data from two experiments; the first experiment was a crossover with a control, whereas the second experiment had two soy groups and no control. We analyzed the second study as two single-group studies; therefore, this article contributed data from three separate treatment groups.

Although 32 articles were identified, some articles presented data in which multiple arms could be included in the meta-analysis; therefore, the number of treatment groups analyzed was greater than the number of trials reviewed. The parallel trial by Kalman et al. (64) included an isolated soy protein arm and a soy protein concentrate arm; both treatment groups were analyzed. The crossover trial by Goldin et al. (39) included an isolated soy protein arm and an isoflavone extract arm; both treatment groups were analyzed. The article by van Veldhuizen et al. (58) contained data from three patient cohorts. Because raw data were reported in the article, we averaged the data from the 168 mg/d isoflavone–supplemented group and the 224 mg/d isoflavone–supplemented group. The 112 mg/d isoflavone–supplemented group from this study was kept in its separate cohort, because this dose was more comparable with the isoflavone dose of studies that intervened with isolated soy protein and/or soy foods. The parallel trial by Dalais et al. (43) included a soy grits arm and a soy grits plus flax arm; only the soy grits treatment group was analyzed because of hormonal properties of flax. Given that isoflavone-depleted

TABLE 1

Characteristics of studies included in the meta-analysis.

Author (reference)	Trial location	Length	Outcomes	Patient with prostate cancer	Age (y) (mean ± SD or range)	Intervention product/ (n per group)	Exposure	
							IF[a] (mg/d)	Soy protein (g/d)
Parallel-arm studies								
Dalais et al., 2004 (43)[,b]	Australia	25 d	T, FAI, SHBG	Yes	62 ± 5	Soy grits (8)	117	9
					61 ± 5	Placebo (8)	0	0
DiSilvestro et al., 2006 (61)[,b]	United States	4 wk	T	No	22 (18–30)	ISP (10)	97.6	41.5
					22 (18–30)	Whey (10)	0	0
Hamilton-Reeves et al., 2007 (62)[,b]	United States	6 mo	T, FT, SHBG	No	68 ± 8	ISP (20)	107	40
					68 ± 7	Placebo (19)	0	0
Kalman et al., 2007 (64)[,b]	United States	12 wk	T, FT, SHBG	No	31 (18–40)	ISP (5)	58	50
						SPC (5)	154	50
						Whey (5)	2	50
Kumar et al., 2004 (42)[,b]	United States	3 mo	T, FT, SHBG	Yes	73 ± 5	ISP (29)	120	60
					71 ± 5	Placebo (30)	0	0
Kumar et al., 2007 (67)[,b]	United States	12 wk	FT, SHBG	Yes	72 ± 6	Soy IF (22)	80	0
					72 ± 6	Placebo (27)	0	0
Li et al., 2007 (59)[,b]	United States	4 y	T, SHBG[c]	Yes	60 ± 1	ISP and low-fat diet (26)[d]	80	40
					63 ± 2	Placebo and USDA diet (14)[d]	0	0
Nagata et al., 2001 (63)[,b]	Japan	2 mo	T, FT, SHBG	No	33 ± 8	Soy milk (17)	60.2[e]	17.2[e]
					32 ± 8	Placebo (17)	14.4[e]	4.4[e]
Ornish et al., 2005 (38)[,b]	United States	1 y	T	Yes	65 ± 7	Tofu and ISP (44)	133	51
					67 ± 8	Placebo (49)	0	0
Rannikko et al., 2006 (55)[,b]	Finland	2 wk	T, FT, SHBG	Yes	64 (52–72)	Red clover IF (20)	240	0
					64 (54–73)	Placebo (20)	0	0
Teede et al., 2001 (7)[,b]	Australia	3 mo	T	No	63 (50–75)	ISP (48)	84	40
					63 (50–75)	Placebo (48)	0	0
Crossover studies								
Dillingham et al., 2005 (40)[,b]	United States	2 mo	T, FT, SHBG	No	28 ± 6	ISP (35)	62	32
					28 ± 6	Placebo (35)	0	0
Goldin et al., 2005 (39)	United States	6 wk	T	No	61	ISP (15)	139	71
					61	Soy IF (15)	156	0
					61	Animal protein (15)	0	0
Habito et al., 2000 (53)	Australia	4 wk	T, FAI, SHBG	No	49 (35–62)	Tofu (42)	123	35
					49 (35–62)	Animal protein (42)	0	0
Higashi et al., 2001 (51)[,b]	Japan	4 wk	T	No	31 ± 4	ISP (14)	20	20

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TABLE 1

Continued.

Author (reference)	Trial location	Length	Outcomes	Patient with prostate cancer	Age (y) (mean ± SD or range)	Intervention product/ (n per group)	Exposure	
							IF[a] (mg/d)	Soy protein (g/d)
					31 ± 4	Nothing (14)	0	0
Kranse et al., 2005 (57)	The Netherlands	6 wk	T, FAI, SHBG	Yes	68	Soy IF (32)	100	0
					68	Placebo (32)	0	0
Maskarinec et al., 2006 (56)[,b]	United States	3 mo	T	No	59 ± 7	High soy diet (23)	40	16
					59 ± 7	Low soy diet (23)	0.2	<1
Schroder et al., 2005 (41)[,b]	The Netherlands	10 wk	T, SHBG	Yes	70 ± 7	Soy IF (42)	62.5	0
					70 ± 7	Placebo (42)	0	0
Single-group studies								
Celec et al., 2007 (65)	Slovak Republic	1 wk	T, FT	No	21 ± 6	Soybeans (7)	74[f]	21
deVere White et al., 2004 (45)	United States	6 mo	T, FT	Yes	74	Soy IF (42)	900	0
Fischer et al., 2004 (44)	United States	3 mo	T, FT	Yes	69 ± 7	Soy IF (20)	449[g]	0
Gardner-Thorpe et al., 2003 (46)	United Kingdom	6 wk	T, SHBG	No	36 ± 11	Soy flour (19)	120	30.7
Goodin et al., 2007 (60)	United States	4 wk	T	No	32	ISP (12)	54	56
Grainger et al., 2008 (66)[,h]	United States	4 wk	T	Yes	70 ± 7	ISP (21)	80	40
Higashi et al., 2001[i] (51)	Japan	3 wk	T	No	30 ± 2	ISP (12)	20	20
Higashi et al., 2001[i] (51)	Japan	3 wk	T	No	30 ± 2	ISP and vitamin E (12)	20	20
Hussain et al., 2003 (48)	United States	5 mo	T	Yes	73	Soy IF (39)	120	0
Jarred et al., 2002 (50)	Australia	20 d	T	Yes	61	Red clover IF (19)	160	0
Lewis et al., 2002 (49)	New Zealand	4 wk	T, SHBG	No	50 (40–53)	Red clover IF (6)	40	0
Mackey et al., 2000 (54)	Australia	3 mo	T, SHBG	No	52	ISP (27)	65	28
Mitchell et al., 2001 (52)	United Kingdom	2 mo	T	No	27 (18–35)	Soy IF (14)	40	0
Pendleton et al., (68)	United States	12 mo	T	Yes	72 ± 6	Soy milk (20)	141	21
Spentzos et al., 2003 (47)	United States	2 mo	T, FT	Yes	71 (59–81)	ISP (15)	68	33.5
van Veldhuizen et al., 2006 (58)	United States	4 wk	T	Yes	63	Soy IF (11)	112–224	0

Note: FT = free testosterone; IF = isoflavones; ISP = isolated soy protein; SPC = soy protein concentrate; USDA = U.S. Department of Agriculture.

[a] Isoflavone dose is presented in aglycone equivalents.

[b] Denotes studies analyzed in primary difference of change model.

[c] SHBG provided by Li et al. for baseline and 6 months only.

[d] Sample sizes were control (n = 6) and treatment (n = 19) at 12 and 42 months for T and control (n = 12) and treatment (n = 19) at 0 and 6 months for SHBG.

[e] Background diet added into total obtained from Nagata (personal communication).

[f] Protein and isoflavone estimated with use of USDA database for boiled soybeans.

[g] Days 0–28, 449 mg IF; days 28–84, 898 mg IF.

[h] Study design originally parallel but reclassified as single-group study for the meta-analysis.

[i] Study designs originally crossovers but reclassified as single-group studies for the meta-analysis.

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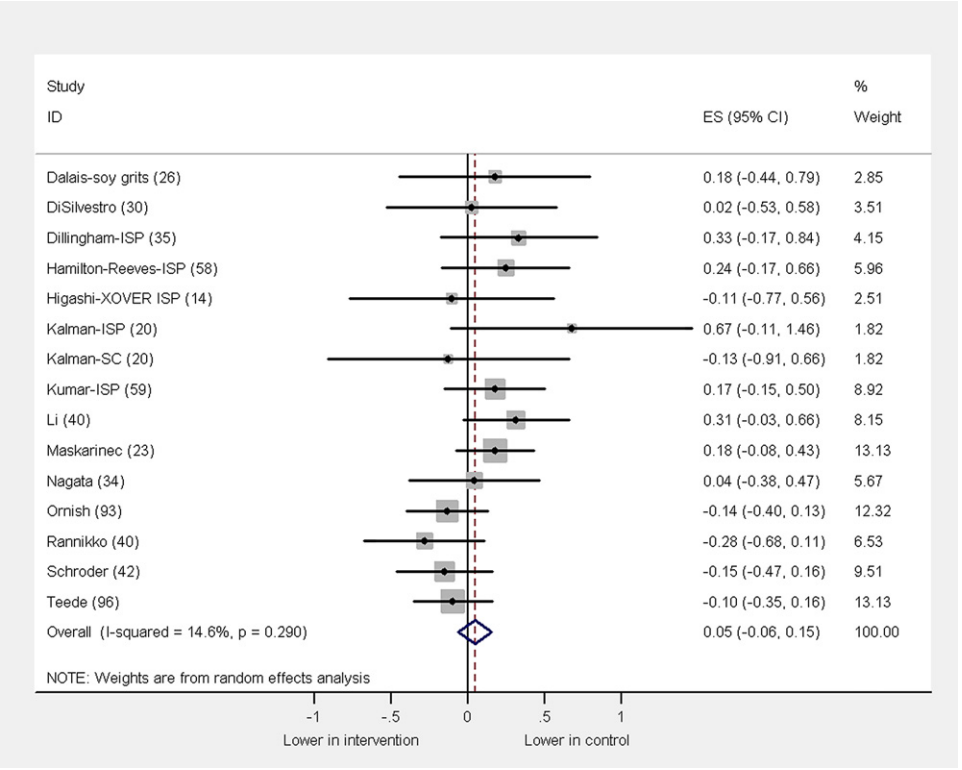
FIGURE 2

Mean change difference per SD of testosterone.



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isolated soy protein is not commercially available and the composition of the product is altered by the ethanol-washed processing used to extract isoflavones, the isoflavone-depleted isolated soy protein treatment groups used in three studies (39, 40, 62) were excluded from all analyses except the subgroup analysis of the effects of soy protein dose. Therefore, including the studies with multiple soy or isoflavone treatment groups but excluding the isoflavone-depleted isolated soy protein treatment groups and the flax group, a total of 36 treatment groups were analyzed as shown in Figure 1 (7, 38–63).

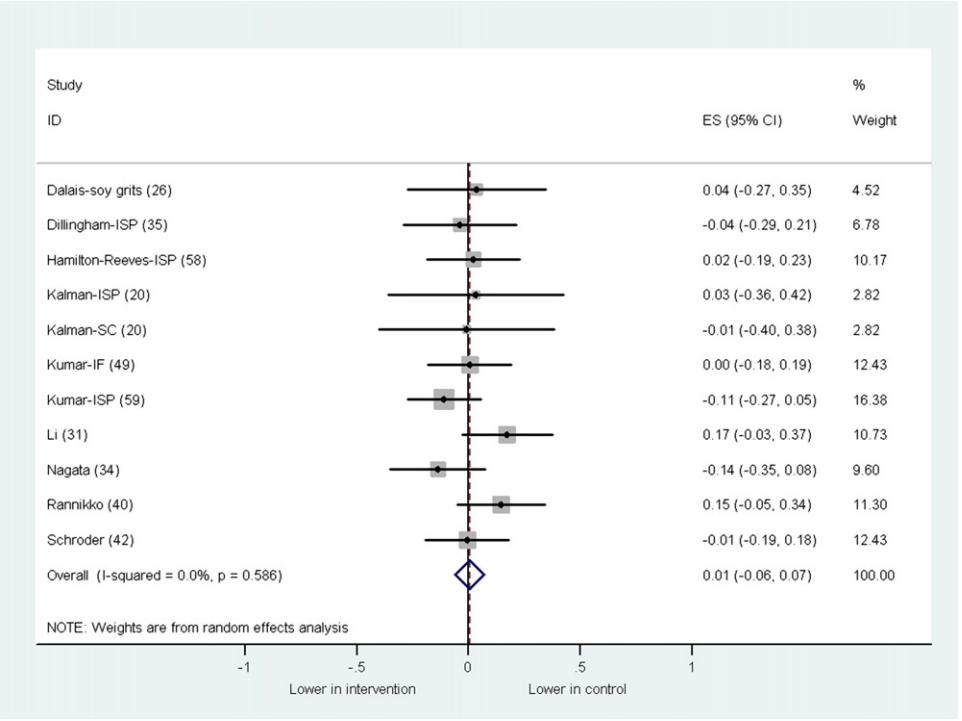
Characteristics of the Studies

Table 1 lists the 32 articles included in this meta-analysis. Eleven articles used a parallel design (7, 38, 42, 43, 55, 59, 61–64, 67) and seven a crossover design (39–41, 51, 53, 56, 57). To test our hypothesis accurately several studies were reclassified as single-group studies. As previously noted, the second experiment in the article by Higashi et al. (51) used a crossover design but did not have a control; therefore the soy arms were classified as two separate single-group studies. In addition, although Gardner-Thorpe et al. (46) used a crossover design, this study was classified as a single-group study because of a lack of hormone concentration assessment during the placebo period. Last, although Grainger et al. (66) used a parallel design, this study was classified as a single-group study because of a lack of a protein-matched placebo. Including these reclassifications, there were 16 single-group treatment groups (44–52, 54, 58, 60, 65, 66, 68). Sixteen of the 32 articles were limited to men with prostate cancer (38, 41–45, 47, 48, 50, 55, 57, 58, 59, 66–68). The average age of study participants ranged from 21 years (65) to 74 years (45). Study length ranged from 1 week (65) to 4 years (59). However, for the purpose of the meta-analysis, the 1-year instead of the 4-year data from the study by Li et al. (59) were used to be comparable with the other long-term studies (38, 45, 62) although the 4-year data were similar to the 1-year time point. Isoflavone intake in aglycone equivalents ranged from 20 mg/d (51) to 900 mg/d (45), and soy protein ranged from 0 g/d (39, 41, 44, 45, 48–50, 52, 55, 57, 58) to 71 g/d (39). In soy food studies, subjects in the control groups consumed similar amounts of a nonsoy protein. The reported mean baseline values for T (data not shown in Table 1) ranged from 4.8 nmol/L (48) to 58 nmol/L (54), for free T from 29 pmol/L (62) to 284 pmol/L (55), for FAI from 34 (43) to 50 (53), and for SHBG from 21 nmol/L (40) to 100 nmol/L (59). Three studies reported values that were out of the normal range, one reported abnormally high T (54), another abnormally low T (48), and another abnormally high free T (55).

In regard to intervention products, six studies used soy foods including soy milk (63, 68), soy grits (43), soy flour (46), tofu only (53), tofu and isolated soy protein (38), or

FIGURE 3

Mean change difference per SD of SBHG.



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a combination of traditional and processed soy foods (56). Two studies intervened with a comprehensive dietary approach; the subjects in the study by Ornish et al. (38) consumed a vegan diet and dietary supplements, whereas subjects in the study by Li et al. (59) followed a low-fat diet in addition to the soy protein supplement. Finally, two studies from the same institution used a mixed supplement that provided isoflavones, as well as other nutrients and phytochemicals (41, 57).

Circulating Hormones and SHBG

No significant effects of soy protein or isoflavone intake on T or SHBG were detected (data shown in Figs. 2 and 3). In addition, no significant effects of soy protein or isoflavone intake on bioavailable T as indicated by free T (Table 2) or FAI (data not shown) were observed. Table 2 presents the effect size per SD and clinical units for each measured outcome. The simpler statistical models, which included single-group studies and placebo-controlled treatment groups lacking baseline measures, also exhibited null results (Table 2).

Overall Effect

There was no significant pooled effect of isoflavone consumption on the hormonal profile, T and SHBG (P=.58). The overall estimated effect per SD of the mixed-effect model was 0.02 (CI −0.05, 0.09).

Heterogeneity and Association of Study Level Characteristics with Treatment Effect

I^2 indicators of heterogeneity are shown in Table 2. Of the study level characteristics explored, product type (soybean or red clover), isoflavone dose, soy protein dose, study duration, participant age, cancer status, or treatment vehicle (pill or tablet or soy food), only treatment vehicle (pill or tablet or soy food) contributed to some of the heterogeneity found in the T data (P value = .03). Pill or tablet consumption showed a slight decrease in T with a standardized mean effect of −0.2 (CI −0.4, 0.04).

Publication Bias and Overinfluential Studies

No publication bias was detected in the funnel plots with use of the trim and fill method. There were no overinfluential studies detected when studies were removed one at a time and models reestimated.

DISCUSSION

The objective of this meta-analysis was to evaluate in men the effects of soy protein or isoflavone intake on T and other indicators of bioavailable T, such as SHBG, free T, and FAI as reported in clinical trials. The results indicate that neither soy protein nor isoflavone intake significantly alters any of these measures.

TABLE 2

Estimated hormonal effects of isoflavone intake by statistical model.

Outcome/model	No. of groups	Effect size (standardized mean) (95% CI)	Clinical units (95% CI)	*P* value	I^2 (%)
T (nmol/L) (SD = 6)					
Difference in change[a]	15	0.05 (−0.1, 0.2)	0.26 (−0.4, 0.9)	.41	15
Tx versus control[b]	19	0.12 (−0.03, 0.3)	0.68 (−0.2, 1.5)	.12	42
Change over time[c]	32	−0.03 (−0.1, 0.1)	−0.17 (−0.7, 0.3)	.49	82
SHBG (nmol/L) (SD = 18)					
Difference in change	11	0.01 (−0.1, 0.1)	0.11 (−1.1, 1.3)	.87	0
Tx versus control	13	−0.05 (−0.2, 0.05)	−0.96 (−2.8, 0.9)	.31	84
Change over time	14	−0.04 (−0.1, 0.02)	−0.72 (−1.8, 0.4)	.21	78
Free T (pmol/L) (SD = 32)					
Difference in change	8	−0.006 (−0.2, 0.2)	−0.19 (−8, 7)	.96	7
Tx versus control	8	0.21 (−0.1, 0.5)	6.64 (−2, 15)	.14	0
Change over time	13	−0.01 (−0.1, 0.1)	−0.42 (−5, 4)	.85	56

Note: Standardized mean = difference between the group means divided by the pooled SD.

[a] Comparing the difference in change of baseline and ending values between the treatment arm and the control arm of parallel and crossover trials.

[b] Comparing ending values in the treatment arms versus the control arms of parallel and crossover trials.

[c] Comparing ending with baseline values in the treatment arms of parallel, crossover, and single-group studies.

Hamilton-Reeves. Meta-analysis of soy and hormones in men. Fertil Steril 2010.

It is not surprising given the results of this meta-analysis that few individual trials included in the analysis found statistically significant effects of either soy protein or isoflavones on T levels. One study reported that in response to 56 g/d of isolated soy protein serum T levels were markedly decreased over a 4-week period (60). However, there were only 12 subjects in this study, it did not include a control group, and it did not describe the method used to assess hormones. Furthermore, the study included one subject whose baseline T levels exceeded the normal upper range and whose T levels continued to decline well after discontinuation of isolated soy protein intake; the change in this one subject markedly influenced the group mean percent change reported. Although the decreased percent change was statistically significant with a nonparametric inferential test, the trial was not placebo controlled and was a small, short-term study. Another study found that in response to 120 mg/d isoflavones from soy flour, serum T significantly decreased by approximately 5% over a 6-week period; however, baseline and final T values for the control group fed wheat flour were not presented. Therefore, as noted previously, this study was classified as a single-group study (46). Without these data it is not possible to know whether the change in T levels that occurred in the soy flour group was significantly different from the change in the wheat flour group.

One difficulty in interpreting the soy intervention data in general is that the intervention product often is described inadequately. It is essential to have an accurate understanding of isoflavone content for hormone-related health outcomes. Isoflavone content varies not only among different types of soy products but among the same types of products and from batch to batch among the same soy product. For the purpose of this meta-analysis, we contacted the authors to obtain accurate product information. Unfortunately, many investigators relied on the product manufacturer for this information rather than having the product directly analyzed. Moreover, the isoflavone information included in the published article often lacks specifics about the form in which the isoflavones occur. Furthermore, information on other biologically active components of soy, such as saponins, is often lacking. Relatively little is known about the possible physiologic effects of these other components and, importantly, whether they interact with or affect the biologic actions of isoflavones.

Increasingly, it is recognized that genetic polymorphisms may determine the efficacy of drugs and nutrients. In the case of isoflavones, there is a vast interindividual variation in isoflavone metabolism that leads to disparate circulating levels of parent isoflavones and their metabolites. For example, Wiseman et al. (69) found that among the 38 individual subjects who consumed approximately 110 mg/d isoflavones for 10 weeks, when comparing the highest with the lowest circulating levels, genistein and daidzein levels varied >30- and 1,500-fold, respectively. In addition, levels of equol, a bacterially derived metabolite of the isoflavone daidzein, also varied >1,000-fold (69). This finding is not surprising because only approximately 25% to 35% of Westerners possess the intestinal bacteria capable of producing equol (62, 70–72). Equol is more biologically active than its parent isoflavone and has properties that differ from those of genistein. Thus, it has been proposed (the equol hypothesis) that equol

producers respond to isoflavone-containing products differently than nonproducers (73).

Although the equol hypothesis remains just that, certainly, investigators should be encouraged to analyze the results of isoflavone interventions according to the isoflavone metabolism of each participant. One may find subsets of individuals responding to isoflavones that would otherwise be missed. Related to this, it is possible that because of a chance preponderance of subjects with atypical isoflavone metabolism, studies especially with small numbers of subjects may provide results different from those of the literature overall.

Limitations

The quality of studies included in a meta-analysis largely determines the utility of the findings. Only 15 studies were placebo controlled and included baseline and ending analyte concentrations, yet results were consistent with all clinical studies conducted to date. In all, most studies were short-term, with an average study duration of about 74 days. In addition, several studies measured T without also assessing SHBG concentrations. The major limitation of these findings is that most of the studies were designed for primary endpoints other than bioavailable T assessment.

Conclusion

The results of this meta-analysis indicate that neither soy protein nor isoflavones affect reproductive hormone concentrations in men regardless of age or cancer status. Although the duration of most trials was <6 months, soy protein and isoflavone intake greatly exceeded typical dietary Japanese intake (2). These results suggest that consumption of soy foods or isoflavone supplements would not result in the adverse effects associated with lower T levels (31–33). Conversely, these data also suggest that lowering either free T or T is not a likely mechanism for the proposed role of soy in reducing prostate cancer risk.

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