Effect of Soymilk Consumption on Serum Estrogen and Androgen Concentrations in Japanese Men[1]

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Abstract

Soy consumption has been associated with a reduced risk of prostate cancer. The mechanism for this association may involve the effect of soy on the endocrine system. We conducted a randomized dietary intervention study to determine the effects of soy consumption on serum levels of steroid hormones in men. Thirty-five men were randomly assigned to either a soymilk-supplemented group or a control group. The men in the soy-supplemented group were asked to consume 400 ml of soymilk daily for 8 weeks. The men in the control group maintained their usual diet. Blood samples were obtained just before the initiation of the dietary period and thereafter every two weeks for 12 weeks. Changes in hormone concentrations were analyzed and compared between the two groups using the mixed linear regression model against weeks from the start of the dietary period. The mean (SD) soymilk intake estimated from dietary records during the dietary study period was 342.9 (SD, 74.2) ml in the soymilk-supplemented group. There was a significant difference between the two groups in terms of changes in serum estrone concentrations, which tended to decrease in the soy-supplemented group and increase in the control group over time. None of the other hormones measured (estradiol, total and free-testosterone, or sex hormone-binding globulin) showed any statistical difference between the two groups in terms of patterns of change. The results of the study indicate that soymilk consumption may modify circulating estrone concentrations in men.

Introduction

Several lines of investigation suggest that isoflavones, which are present mainly in soy products, can influence the risk of prostate cancer. Soy consumption and urinary excretion of isoflavones are high in a population with a low prostate cancer mortality rate (1). A cross-national study showed a significant inverse correlation between consumption of soy products and prostate cancer mortality rate (2). Severson *et al.* (3) found in a prospective study of Japanese men in Hawaii that those who ate tofu five times or more a week were at reduced risk (0.35) of prostate cancer compared with those who ate tofu once or less a week. A recent case-control study conducted by Jacobson *et al.* (4) showed that frequent intake of soymilk (more than once a day) was associated with a 70% reduction in the risk of prostate cancer. Additional supports come from experimental studies. A soy diet lowered the incidence of prostatic dysplasia or tumors in animals (5–8). Genistein, one of isoflavones, could inhibit the proliferation of human prostate cancer cells (9–11).

Studies have shown that isoflavones inhibit several enzymes or growth factors involved in signal transduction, such as tyrosine protein kinase and transforming growth factor β (12, 13). In addition, isoflavones have estrogenic properties (14). The mechanism by which dietary soy can influence prostate cancer development may include the endocrine system, although the literatures on hormone levels and prostate cancer risk is controversial (15–20). In our previous cross-sectional study, we found inverse associations of soy product intake with serum estrone, estradiol, and free-testosterone concentrations in Japanese men (21). Dietary soy may affect serum estrogen and androgen concentrations in men. In this study, we conducted a dietary intervention trial to assess the effect of soymilk consumption on the hormonal status of Japanese men.

Materials and Methods

The participants were teachers and students in a nurse school affiliated with the Japan Self-Defense Forces; 35 of 37 men, 22–50 years of age, participated in the study. Each man signed an informed consent statement. The protocol of this study was approved by the local institutional review board. Criteria for exclusion from the study were current use of hormonal medication, diagnosis of prostatic disease, diabetes mellitus, chronic liver disease, or any endocrine disease. Each man provided information on demographic characteristics, smoking and drinking habits, past medical history, use of medication, and other lifestyle variables before the initiation of the dietary study period.

The participants were randomly assigned to either a soymilk-supplemented group or a control group. The soymilk-supplemented group was required to consume 400 ml (408 g) of soymilk daily for 8 weeks. The soymilk used for the study was provided by Kibun Food Chemifa, Tokyo and was supplied to the participants by the study during the dietary study period. One hundred grams of soymilk contains 0.6 mg of daizein, 7.8 mg of daidzin, 0.6 mg of genistein, and 13.0 mg of genistin. The energy and protein contribution were 58 kcal and 3.9 g/100 g of soymilk, respectively. The men in the soymilk-supplemented group did not consume soymilk from any source other than

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what was provided to them. The control group maintained their previous dietary habits. Both groups were asked to maintain their usual lifestyle.

We assumed that relationships between soy isoflavone intake and serum estrogen and androgens in our previous cross-sectional study were applicable for the prediction of changes in serum estrogen and testosterone after 2 months of dietary intervention. We expected a 38.2% decrease in estrone, a 36.2% decrease in estradiol, and a 28% decrease in testosterone by isoflavone intake available from 400 ml of soymilk. We determined that at least 16 subjects in each group were required to have a power of 80% to detect the difference with type I error = 0.05.

Changes in diet were assessed using two 7-day dietary records kept before the dietary study period and during the last week of the dietary study period. In addition, the men in the soymilk-supplemented group recorded their soymilk consumption throughout the dietary study period.

The intake of soy products and macro- and micronutrients were estimated from the dietary records using the Standard Tables of Food Composition in Japan, 4th Revised Edition. Isoflavone intake from soy products was estimated using data summarized by Wakai *et al.* (22).

Blood samples were drawn from nonfasting subjects early in the morning just before the initiation of the dietary study period. Thereafter, samples were drawn every 2 weeks for 12 weeks (at 2, 4, 6, 8, 10, and 12 weeks). The men were weighed at each blood sampling.

The blood samples were centrifuged at 1300 × *g* for 10 min at room temperature within 3 h of sample collection, and the serum was separated. The samples were stored at −80°C until assayed. RIA kits were used to measure serum estradiol and total and free-testosterone (Diagnostic Products Cooperation, Chiba, Japan), estrone (Eiken Chemical Co., Ltd., Tokyo, Japan) and SHBG[3] (Pharmacia & Upjohn Co., Ltd., Tokyo, Japan). The intra-assay coefficients of variation based on control pools were 10.8% for estrone, 8.4% for estradiol, 6.1% for testosterone, 4.9% for free-testosterone, and 7.8% for SHBG. The inter-assay coefficients of variation were 12.5% for estrone, 16.4% for estradiol, 8.3% for testosterone, 7.8% for free-testosterone, and 7.1% for SHBG.

For statistical analyses, log-transformation was used for dietary and hormone values to normalize the distribution. We used a standard *t* test and a paired *t* test to compare the dietary values between the two groups at baseline and changes in those values over the study period. Group differences in anthropometric measurements were calculated by a standard *t* test.

The longitudinal data for each hormone concentration were analyzed by mixed linear regression models against the weeks from the start of the dietary study period. We included in the model first-order and/or second-order terms for time (week). If the effect of the second-order term was not statistically significant, we proceeded to fit a linear regression. Compound symmetric covariance structure was used to model the correlation among the repeated measurements over the study period. To determine the appropriate type of covariance structure for each model of hormone concentration, we compared compound symmetric, autoregressive of order 1, and unstructured covariances objectively using goodness-of-fit criteria, including the Akaike information criteria and the Schwarz Bayesian criterion (23). Our main interest was to test the difference in changes of each hormone level over time between the soymilk-supplemented group and the control group. This was examined in the model by the effect of the interaction term for time and group. We used the Procedure Mixed in SAS (24).

Serum estrone was not detectable (<10pg/ml) in some of the samples obtained from three men in the soymilk-supplemented group after the dietary study period started (at 2, 8, and 2 and 6 weeks for them, respectively). We used minimum values (*i.e.,* 10 pg/ml) for them in the analysis. Although we had explained to potential participants that the study could not include those who were soymilk-intolerant, one participant in the soymilk-supplemented group dropped out on the first day of the dietary study period because he felt sick. He was excluded from the present analyses.

Table 1 Demographic characteristics before the dietary study period

	Soymilk-supplemented (n = 17)	Control (n = 17)
Age (yr)	32.0 (8.4)[a]	32.8 (8.3)[a]
Height (cm)	169.6 (5.9)[a]	169.1 (4.7)[a]
Weight (kg)	67.1 (9.9)[a]	68.9 (9.6)[a]
Body mass index (kg/m^2)	23.3 (3.2)[a]	23.8 (2.9)[a]
Married	9 (52.9)[b]	13 (76.5)[b]
Parous	9 (52.9)[b]	10 (58.8)[b]
Current smoker	11 (64.7)[b]	11 (64.7)[b]
Past smoker	1 (5.9)[b]	2 (11.8)[b]

[a] Mean (SD).
[b] No. (%).

Results

The soymilk-supplemented and control groups did not differ significantly with respect to age and anthropometric and lifestyle variables at baseline (Table 1). The mean intake of soy products and nutrients measured were also similar between the two groups at baseline (Table 2).

In the soymilk-supplemented group, the mean intake of soymilk estimated from the dietary records for the last 7 days of the dietary study period was 342.9 ml (SD, 74.2 ml; Table 2). According to the records, the daily intake of soymilk throughout the dietary study period was 360.0 ml (SD, 41.0 ml). Significant increases in vitamin B1, iron, and phosphate were observed during the dietary study period in the soymilk-supplemented group. Significant decreases in retinol, vitamin A [retinol plus precursors (carotene)], and salt were observed in this group during the same period. There were no significant changes in intake of nutrients and soy products in the control group. The estimates of protein intake from soymilk during the dietary study period were 13.4 g (SD, 2.9 g) in the soymilk-supplemented group and 0 g (SD, 0.0 g) in the control group. Protein intake from soy products other than soymilk were 26.3 g (SD, 17.1 g) and 26.1 g (SD, 15.1 g) before and during the dietary study period, respectively, in the soymilk-supplemented group. Corresponding values for the control group were 30.7 g (SD, 20.4 g) and 30.5 g (SD, 19.8 g), respectively.

None of the hormone values at baseline differed between the two groups (Table 3). Fig. 1 shows the changes in the mean concentrations of each hormone over the course of the study. The concentrations of free-testosterone and estradiol fit a quadratic rather than a linear equation. When we analyzed data at 0, 2, 4, 6, and 8 weeks, none of the hormone measured showed any statistical difference in changing patterns between the two groups. On the basis of data at 0, 2, 4, 6, 8, 10, and 12 weeks, the interaction term for time and group was statistically signif-

[3] The abbreviation used is: SHBG, sex hormone-binding globulin.

Table 2 Food and nutrient consumption[a] before and following the dietary study period

	Soymilk supplemented (n = 17)		Control (n = 17)	
	Initial	Final	Initial	Final
Soymilk				
Total amount (ml)	0.0 (0.0)	342.9 (74.2)[b]	0.0 (0.0)	0.0 (0.0)
Isoflavones (mg)	0.0 (0.0)	76.8 (16.6)[b]	0.0 (0.0)	0.0 (0.0)
Other soy products				
Total amount (g)	30.1 (18.0)	31.0 (17.5)	38.6 (26.0)	39.3 (30.5)
Isoflavones (mg)	16.1 (10.4)	16.0 (8.2)	18.2 (13.3)	17.8 (11.4)
Nutrient				
Energy (kcal)	2,244 (613)	2,214 (261)	2,030 (597)	2,046 (481)
Protein (g)	73.6 (18.9)	86.7 (15.3)	72.7 (24.6)	71.5 (17.6)
Fat (g)	77.3 (29.6)	76.0 (16.9)	63.5 (24.8)	62.2 (16.3)
Cholesterol (mg)	279 (74)	326 (96)	290 (106)	312 (105)
Carbohydrate (g)	287 (75)	272 (52)	262 (81)	262 (61)
Crude fiber (g)	3.4 (1.3)	3.5 (0.7)	3.0 (1.5)	3.2 (1.8)
Retinol (μg)	265 (162)	150 (59)[c]	412 (597)	156 (73)
Carotene (μg)	1,687 (789)	1,380 (532)	1,556 (696)	1,781 (2,131)
Vitamin A (IU)	1,491 (694)	1,029 (316)[c]	1,830 (1,700)	1,230 (1,107)
Vitamin B1 (mg)	0.71 (0.22)	2.56 (0.57)[b]	0.68 (0.25)	0.64 (0.23)
Vitamin B2 (mg)	0.95 (0.37)	0.97 (0.27)	0.97 (0.40)	0.89 (0.30)
Vitamin C (mg)	81.5 (109)	66.8 (66.5)	33.7 (31.5)	30.1 (21.3)
Vitamin D (mg)	182 (100)	127 (69)	191 (131)	198 (132)
Vitamin E (mg)	8.1 (2.6)	7.5 (2.2)	7.1 (2.8)	6.8 (1.9)
Phosphate (mg)	1,051 (267)	1,230 (213)[b]	1,039 (370)	1,011 (260)
Calcium (mg)	406 (167)	401 (148)	393 (197)	372 (146)
Iron (mg)	9.5 (2.8)	11.1 (2.0)[b]	9.5 (3.7)	9.7 (5.6)
Salt (g)	12.0 (3.5)	10.6 (2.6)[c]	10.6 (4.2)	10.5 (3.0)
Alcohol (g)	12.6 (19.4)	11.1 (15.1)	18.3 (19.8)	24.2 (33.5)

[a] Mean (SD).
[b] $P < 0.01$ for the difference between initial and final.
[c] $P < 0.01$ for the difference between initial and final.

Table 3 Serum concentrations of sex hormones and SHBG before the dietary study period[a]

	Soymilk-supplemented (n = 17)	Control (n = 17)
Total testosterone (ng/dl)	470.9 (145.4) [188.0–741.0]	449.5 (134.0) [234.0–714.0]
Free testosterone (pg/ml)	16.2 (6.2) [7.8–27.3]	14.9 (4.5) [8.9–23.1]
Estrone (pg/ml)	29.5 (11.4) [11.7–51.3]	27.8 (9.7) [14.1–50.6]
Estradiol (pg/ml)	33.6 (15.2) [16.6–82.4]	29.6 (5.3) [18.8–36.1]
SHBG (nmol/liter)	33.5 (14.0) [12.0–61.0]	34.8 (14.0) [12.0–60.0]

[a] Mean (SD). Ranges are given in brackets.

icant for estrone ($P = 0.04$), which means that the slopes for time were significantly different between the two groups. Estrone concentration tended to decrease in the soymilk-supplemented group [regression parameter β (SE) = -0.003352 (0.00226)] and increase in the control group [β (SE) = 0.003228 (0.00223)] over the study period. None of the other hormones measured showed any statistical difference in changing patterns between the two groups. Adjustment for baseline values did not alter the results substantially. For estrone, the slopes were still significantly different between the soymilk-supplemented and the control groups ($\beta = -0.003241$ and $\beta = 0.003228$, respectively; $P = 0.04$) after controlling for baseline value.

Weight changes over the study period were not great in both groups. The means of 0–8 week change were 1.0 kg (SD, 1.35 kg) and 0.23 kg (SD, 1.45 kg) in the soymilk-supplemented and the control groups, respectively. The means of 0–12 week change were -0.07 kg (SD, 1.14 kg) and 0.03 kg (SD, 1.34 kg) in the soymilk-supplemented and the control groups, respectively. In the regression analysis for the 12-week period, adjustment for weight, which was measured every 2 weeks, also did not alter the results substantially; $\beta = -0.003640$ in the soymilk-supplemented group, $\beta = 0.003053$ in the control group, and $P = 0.04$ for the difference in the slopes.

When we simply compared the 0 to 8 week change as well as 0 to 12 week change of estrone between the two groups, the differences were not statistically significant ($P = 0.13$ and $P = 0.10$, respectively). The means of 2–12 week values for estrone were 29.5 and 29.6 pg/ml in the soymilk-supplemented and the control groups, respectively. The changes of these mean values from baseline values did not differ significantly between the two groups ($P = 0.15$).

We repeated the analysis after excluding the three subjects with nondetectable estrone levels. The results were not altered substantially. In the estrone model, the interaction term for group and time (concerned from 0 until 12 weeks) remained statistically significant ($P = 0.02$), and slope for time in the soymilk-supplemented group was somewhat strengthened ($\beta = -0.004478$).

Discussion

We observed a significant difference between the soymilk-supplemented group and the control group in terms of changes

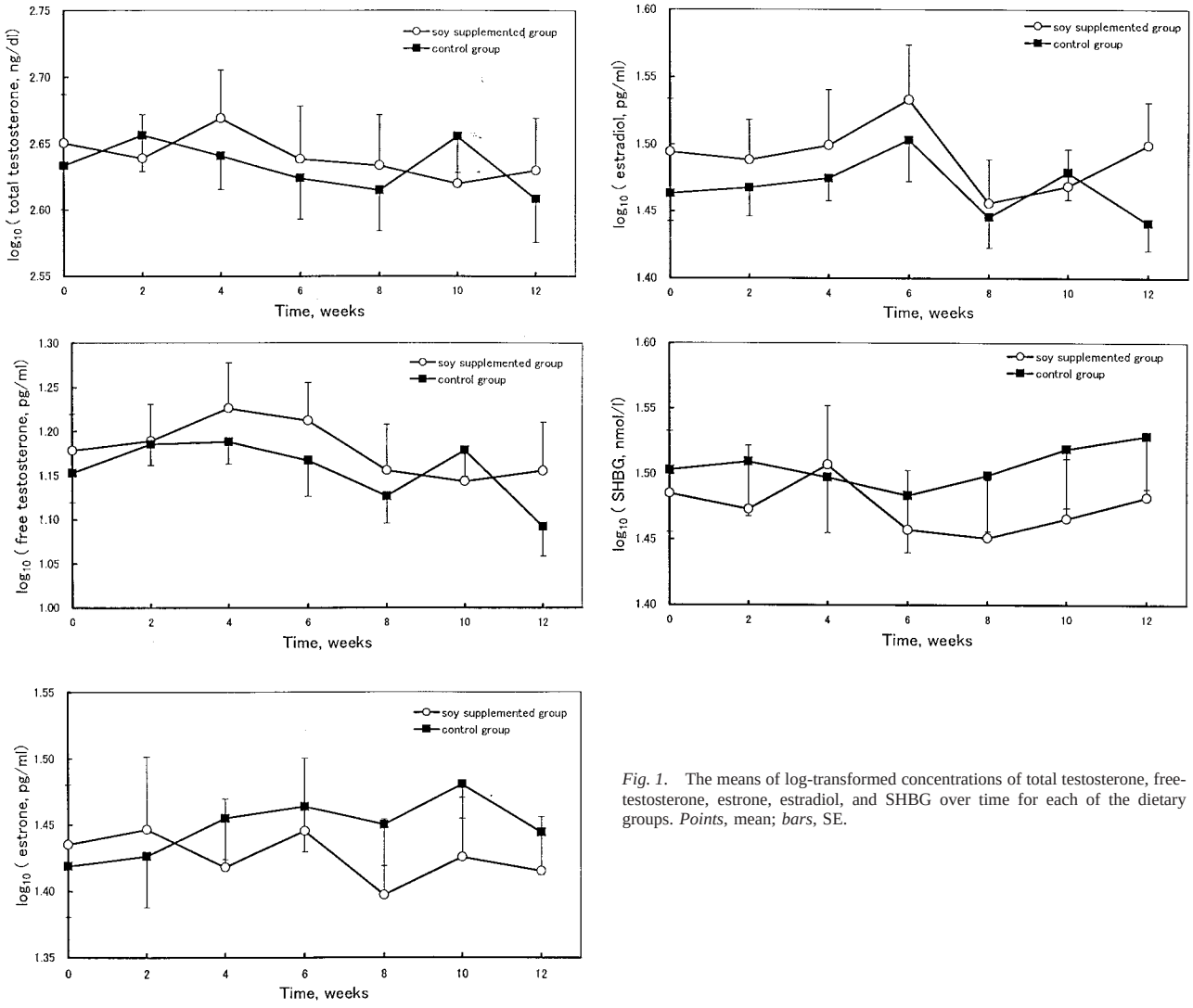

Fig. 1. The means of log-transformed concentrations of total testosterone, free-testosterone, estrone, estradiol, and SHBG over time for each of the dietary groups. *Points*, mean; *bars*, SE.

in serum estrone concentrations over the study period (12 weeks). Soymilk supplementation may affect circulating estrone concentrations. The intervention was conducted for 8 weeks. Although we could not attain statistical significance in the analysis for the 8-week period, estrone concentration also tended to decrease in the soymilk-supplemented group ($\beta = -0.004211$; SE, 0.00411) and increase in the control group ($\beta = 0.004991$; SE, 0.00405; $P = 0.11$ for the difference in the slopes). The results from the analysis for the 12-week period should include a reflection of a delayed effect of the intervention. However, we cannot exclude the possibility that the participants in the soymilk-supplemented group made some change during the 4 weeks after the intervention that affected the results.

It is difficult to interpret the increase in serum estrone concentrations over time in the control group, although this increase was not statistically significant. Because a positive association between alcohol intake and serum estrogen concentration has been reported (25, 26), one might argue that a nonsignificant increase in alcohol intake in the control group may be responsible for the difference between the two groups in the changes in serum estrone. However, when we included alcohol intake estimated from the dietary records both before and after the dietary study period or the difference in these values as covariates into the model for estrone, the effect of interaction term remained statistically significant ($P = 0.04$). We had asked the subjects to maintain their usual lifestyle, but we could not control or monitor their activities during the study period. However, considering that nutrient intakes were similar before and after the dietary study period in the control group, it is unlikely that the subjects changed their lifestyle substantially as a result of assignment to the control group. Although it is unclear which factor caused the moderate increase in serum estrone concentration observed in the control group, it is likely that exposure to this factor occurred in both groups.

It is also possible that the decrease in serum estrone over time in the soymilk-supplemented group may be attributable to a change in diet or lifestyle variables other than soymilk intake. However, the main dietary change was the intake of nutrients rich in soymilk in the soymilk-supplemented group. In addition,

several known properties of soy isoflavones suggest the mechanism by which soy intake can modify serum estrogen concentrations. Isoflavones inhibit key steroidogenic enzymes, such as aromatase enzyme (27) and 17β-hydroxysteroid oxidoreductase (28). Isoflavones also inhibit cytochrome P-450 isozymes responsible for estrogen hydroxylations (29). Estrogenicity of soy may exert an effect on the hypothalamic-pituitary-gonadal axis and ultimately down-regulate the estrogen synthesis. The inhibition effect of isoflavones on binding of estrogen to SHBG may also accelerate steroid metabolism (30).

The reason for the lack of change in estradiol concentration is not clear. The rate of peripheral formation derived from the aromatization of androgen is greater in estrone than in estradiol (31), which may be related in part to the differential effects of the soymilk consumption.

It is not clear whether decreased estrone concentrations lead to a reduction in the risk of prostate cancer. Estrogens have been suggested to be involved in the development of prostate cancer. However, epidemiological studies on serum estrogen concentrations and the risk of prostate cancer have yielded varying results. Higher estrogen concentrations in cases than those in controls have been reported in some studies (32, 33) but not in others (15, 16, 18).

Testosterone has been strongly implicated in the etiology of prostate cancer (34). In the present study, we did not find any differences in changes of total and free-testosterone concentrations between the two groups. Lu *et al.* (35) reported no change in serum testosterone in six men after 1 month of 12-oz soymilk supplementation. To our knowledge, there has been no other dietary intervention study that has investigated the effect of soy consumption on serum androgens in men. Furthermore, our study is the first based on a randomized design.

We assessed previously the effect of soy intake on serum estrogens in premenopausal women in a cross-sectional study (36) and an intervention study (37). In the intervention study, supplementation of 400 ml of soymilk daily for about 2 months decreased serum estradiol concentrations by 33.2%, when we expected a 38% decrease based on the result from the cross-sectional study. In the present study, the observed changes in estrogen and androgen concentrations in the soymilk-supplemented group were much less than were expected from the results of our previous cross-sectional study of men. The duration of soymilk-supplementation may have been too short to bring about the substantial changes in hormone concentrations in men. Larger and longer-term soy intervention studies are needed to investigate the effect of soy intake on endogenous hormone concentrations in men.

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