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Inverse Association of Soy Product Intake With Serum Androgen and Estrogen Concentrations in Japanese Men

Chisato Nagata, Shizuyo Inaba, Norito Kawakami, Tadao Kakizoe, and Hiroyuki Shimizu

Abstract: *The cross-sectional relationships of soy product intake and serum testosterone, estrone, estradiol, sex hormone-binding globulin, and dihydrotestosterone were examined in 69 Japanese men. Soy product intake was estimated from a semiquantitative food frequency questionnaire. Serum estradiol concentration was significantly inversely correlated with soy product intake (*r = *–0.32,* p = *0.009), and serum estrone concentration was nonsignificantly inversely correlated with soy product intake (*r = *–0.24,* p = *0.05) after controlling for age, body mass index, smoking status, and ethanol intake. Total and free testosterone concentrations were inversely correlated with soy product intake after controlling for the covariates, but these correlations were of borderline significance (*r = *–0.25,* p = *0.05 and* r = *–0.25,* p = *0.06, respectively). Similar correlations were observed for these hormones with isoflavone intake from soy products. The data suggest that soy product intake may be associated with the endogenous hormone levels in Japanese men.*

Introduction

There is increasing evidence that isoflavones, which mainly occur in soy products, can influence the risk of prostate cancer. A soy diet lowered the incidence of prostate-seminal vesicle tumors in animals (1). Genistein could have an inhibitory effect on growth of benign prostatic hypertrophy and prostate cancer tissue in histoculture (2). In comparison with animal as well as cell culture data, there are few analytic epidemiological studies on dietary soy and prostate cancer. International comparisons indicate an inverse association between soy product consumption or urinary excretion of isoflavones and prostate cancer mortality rate (3).

Isoflavones are classified as phytoestrogens; the structure of phytoestrogens is similar to that of steroid estrogens, and they possess some estrogenic activities (4). Dietary soy isoflavones may influence the initiation or promotion of prostate cancer through mechanisms including the endocrine system.

Although the relationships between endogenous hormones and prostate cancer have not been established, testosterone and its metabolite dihydrotestosterone (DHT) have been strongly implicated in the etiology of prostate cancer (5). Estrogens may also have a role in carcinogenesis of the prostate (6).

Several studies have evaluated the relationships between diet and serum androgens and estrogens in men (7–17), but none of the studies have assessed the association of the hormones with dietary soy. Here we present a study of the cross-sectional relationships of soy product intake to serum androgens and estrogens in Japanese men.

Materials and Methods

The study subjects were among the participants in the Takayama Study (18), designed to evaluate the role of diet and lifestyle in subsequent development of cancer. About 92% of all residents ≥35 years old in Takayama City, Gifu, Japan, participated in the study in 1992.

In 1995, we invited 256 men randomly selected from 14,427 male participants in the Takayama Study to participate in the present study. A total of 97 men agreed to take part in the study, which was approved by the local institutional review board, and all the participants provided written informed consent. A blood sample was collected from each subject. The time of blood collection and hours since the last meal were recorded. Samples were centrifuged within three hours after collection, and the serum was stored at –80°C. Radioimmunoassay kits were used to measure serum estradiol and total and free testosterone (Diagnostic Products, Chiba, Japan), estrone (Eiken Chemical, Tokyo, Japan), DHT (Medical System Service, Kanagawa, Japan), and sex hormone-binding globulin (SHBG) (Pharmacia & Upjohn, Tokyo, Japan). The intra-assay coefficients of variation, derived from routine quality control procedures, were 10.8% for estrone, 15.4% for estradiol, 6.1% for total testosterone, 4.9% for free testosterone, 11.7% for DHT, and 7.8% for SHBG.

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We used information on diet and other lifestyle factors previously obtained by a self-administered questionnaire at the beginning of the Takayama Study. The questionnaire included basic demographic information; past medical history; diet, smoking, and drinking habits; and exercise.

Dietary history was obtained by a semiquantitative food frequency questionnaire. The men were asked to indicate the average frequency of intake of 169 food items during the year before the study and the usual serving size of each food item. We included nine food items for soy products (miso soup, tofu, deep-fried tofu, fried bean curd, dried bean curd, fermented soy beans, houba-miso, soy milk, and boiled soybeans). The total intake of soy products was calculated as the sum of these nine food items. We also estimated isoflavone intake contained in these soy products (19). Individual nutrient intake was estimated from frequency of intake and portion size by use of the *Standard Tables of Food Composition in Japan* (19a). Detailed information on the questionnaire, including validity and reproducibility tests, has been described elsewhere (19,20). The Spearman correlation coefficient comparing soy product intake estimated from the questionnaire and from 12 daily diet records at about one-month intervals over a one-year period was 0.71 (p = 0.0003), and that comparing the estimates from the questionnaires with a three-year interval was 0.42 (p = 0.046).

Exercise was assessed by asking the average hours per week spent performing various kinds of activities during the past year. The details are described elsewhere (21).

The information on body size, smoking status, and medical history were renewed by the interview at the time of blood collection in 1995.

We excluded men from the present analysis who reported a history of prostate surgery (n = 2), prostatic hypertrophy (n = 4), diabetes mellitus (n = 8), chronic liver disease (n = 1), and cardiovascular diseases (ischemic heart diseases and thrombosis, n = 6), inasmuch as these conditions may affect testosterone or estrogen levels (22–24). We further excluded seven men because the volume of the serum sample was too small for hormone measurement.

The associations of soy product intake with hormone concentrations were determined using the Spearman rank correlation coefficient. Age, body mass index (BMI), smoking status (never, current, or ex-smoker), and estimated ethanol intake were used as confounders in the models. Intake of fat, cholesterol, carbohydrate, and vitamins B-1 and D, which were significantly correlated with any of the androgens measured, was additionally included in the models for androgens. Adjustment for these potential confounders of these associations was done by regressing the hormone and nutrient values separately on the confounders. The Spearman rank correlation coefficients between these residuals were then calculated. The nutrient and soy product intake was logarithmically transformed and adjusted for total energy by the method proposed by Willett (25). Inasmuch as serum estrone and estradiol were not detectable (<10 pg/ml) in 14 and 11 men, respectively, we used minimum values (i.e., 10 pg/ml) for them in the analysis. All statistical analyses were performed using SAS programs (26).

Results

The descriptive characteristics of 69 subjects are shown in Table 1.

Serum estradiol was inversely correlated with soy product intake in age-adjusted (r = –0.24, p = 0.04) or age + other covariate (BMI, smoking status, and ethanol intake)-adjusted analysis (r = –0.32, p = 0.009; Table 2). Adjustment for age, BMI, smoking status, and ethanol intake strengthened the negative correlation between estrone and soy product intake (r = –0.24, p = 0.05), although this was not statistically significant. Serum total and free testosterone was inversely correlated with soy product intake after further controlling for nutrient intake, but these correlations were of borderline significance (r = –0.25, p = 0.05, and r = –0.25, p = 0.06, respectively). The ratio of DHT to testosterone was not significantly correlated with soy product intake. The correlation coefficients of these hormone concentrations with isoflavone intake from soy products did not differ greatly from those with soy product intake. Additional adjustments for exercise and intake of other nutrients, such as protein, crude fiber, and vitamins, did not alter the results substantially.

Table 1. Characteristics of Study Subjects[a]

Variable	Value
Age, yr	60.5 ± 10.7
Height, cm	163.3 ± 6.5
Weight, kg	60.4 ± 9.8
Body mass index, kg/m^2	22.6 ± 3.0
No. of children	2.1 ± 1.0
Exercise,[b] METs·h·wk^{-1}	25.2 ± 37.1
Food and nutrient intake per day	
Soy products, g	51.0 ± 21.5
Isoflavone from soy products, mg	21.9 ± 8.7
Energy, kcal	2421 ± 616
Fat, g	57.7 ± 20.8
Protein, g	89.3 ± 26.0
Ethanol, ml	37.6 ± 36.0
Hormone concentration	
Total testosterone, ng/dl	432.3 ± 137.0
Free testosterone, pg/ml	14.3 ± 4.3
Estrone,[c] pg/ml	19.4 ± 9.2
Estradiol,[d] pg/ml	17.1 ± 6.4
Sex hormone-binding globulin, nmol/l	49.7 ± 20.3
Dihydrotestosterone, ng/ml	0.75 ± 0.28
Smoking[e]	
Current	28 (40.6)
Past	28 (40.6)
Never	13 (18.8)

a: Values are means ± SD for 69 subjects.
b: MET, metabolic equivalents.
c: 10 pg/ml was allotted to 14 men with undetectable level (<10 pg/ml).
d: 10 pg/ml was allotted to 11 men with undetectable level (<10 pg/ml).
e: Values represent number of subjects, with percentage in parentheses.

Table 2. Spearman Correlation Coefficients Between Soy Product and Isoflavone Intake and Serum Estrogen and Androgen Concentrations[a,b]

	Soy Products[c]		Isoflavone[c]	
	Age-adjusted	Adjusted[d]	Age-adjusted	Adjusted[d]
Estrone[e]	–0.13	–0.24	–0.08	–0.23
Estradiol[f]	–0.24*	–0.32†	–0.24	–0.32†
Total testosterone	–0.22	–0.25	–0.23	–0.18
Free testosterone	–0.16	–0.25	–0.13	–0.20
DHT	–0.11	–0.17	–0.12	–0.09
DHT-to-testosterone ratio	0.13	0.10	0.05	0.03
SHBG	–0.17	–0.08	–0.21	–0.05

a: Abbreviations are as follows: DHT, dihydrotestosterone; SHBG, sex hormone-binding globulin.
b: Statistical significance is as follows: *, $p < 0.05$; †, $p < 0.01$.
c: Adjusted for total energy.
d: For estrogens and SHBG: adjusted for age, body mass index, smoking status, and ethanol intake. For androgens: adjusted for above variables and intake of fat, carbohydrate, cholesterol, and vitamins B-1 and D.
e: 10 pg/ml was allotted to 14 men with undetectable level (<10 pg/ml).
f: 10 pg/ml was allotted to 11 men with undetectable level (<10 pg/ml).

Discussion

We found a significant inverse association between soy product intake and serum estradiol concentration in Japanese men. The relationship between dietary soy and endogenous hormones has not been investigated in men but has been studied in women. Although the results from these studies (27–32) were inconsistent, we recently noted a significant negative correlation between soy product intake and serum estradiol concentration in premenopausal Japanese women (19). We further demonstrated that women supplemented with 400 ml of soy milk (109 mg of isoflavones) over a two-month period had lower estrone concentrations than women who continued their usual diet, although the difference was of borderline statistical significance (33). The result from the present study does not contradict those from our previous studies in women.

The negative correlations between soy product or isoflavone intake and total and free testosterone were of borderline significance in the present study. Shultz and co-workers (34) observed no significant change in total and free testosterone and SHBG in six men after six weeks of flaxseed supplementation (13.5 g/day). Flaxseed contains another type of plant estrogen, lignan. A significant negative correlation between free testosterone and urinary excretion of enterolactone, a metabolite of lignan, was reported in an observational study of Finnish women (35).

The likely mechanism by which soy intake may influence serum estrogen and androgen concentrations is unclear. However, several known properties of isoflavones may have important roles. Isoflavones inhibit key steroidogenic enzymes, such as aromatase and 17β-hydroxysteroid oxidoreductase, which may lead to a decrease in estradiol concentration (36,37). Isoflavones also inhibit cytochrome *P*-450 isozymes responsible for estrogen hydroxylations (38). Estrogenicity of soy may exert an effect on the hypothalamic-pituitary-gonadal axis to downregulate estrogen and androgen synthesis. The inhibition effect of isoflavones on binding of estradiol and testosterone to SHBG may also accelerate steroid metabolism (39). It is also possible that isoflavones may affect intestinal reabsorption of biliary estrogens by modifying the activity of fecal bacteria (40).

Epidemiological studies on serum estrogens and androgens and prostate cancer risk have yielded varying results (41–45). The possibility that soy product intake may influence prostate cancer risk mediated by altered hormone metabolism needs to be investigated.

The mean estimate of soy product intake presented in Table 1 may be underestimated by our questionnaire. In the validity test, the soy product intake estimated from the 12 daily diet records over one year was about 40% higher than that estimated from the questionnaire.

Although we had a single serum sample, sex steroid hormone concentrations in men are relatively stable for a long interval (46). It was desirable that we should determine the time of blood collection, because there is circadian variation in testosterone concentration. However, additional adjustment for the time of blood collection as categorized before 10 AM, between 10 AM and 2 PM, and after 2 PM did not change the results substantially: the correlation coefficients of soy product intake with estrone, estradiol, testosterone, free testosterone, DHT, and DHT-to-testosterone ratio were –0.25, –0.31, –0.26, –0.25, –0.17, and 0.10, respectively; values for isoflavone intake were –0.23, –0.31, –0.17, –0.18, –0.09, and 0.02, respectively.

The assessment of diet and blood collection was nearly three years apart. However, according to the results from the reproducibility test, dietary change during the three years might not be great.

In conclusion, our data suggest a relationship between soy product intake and serum estradiol concentration in men, although cross-sectional studies cannot prove causality.

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