Short Communication

Soy Isoflavones Do Not Modulate Prostate-Specific Antigen Concentrations in Older Men in a Randomized Controlled Trial

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Abstract

Mortality rates for prostate cancer are low in Asia but high in the West. One explanation is the high level of soy consumption in Asia. Soy isoflavones reduce prostate tumor growth in many, but not all, animal models. Elevated levels of serum prostate-specific antigen (PSA) are a marker of prostate tumor growth. Our objective was to determine whether 12-month soy isoflavone supplementation would alter serum PSA concentrations in healthy, older men. The parent study was a double-blinded, parallel-arm, randomized trial in which participants were assigned to consume either a soy protein drink providing 83 mg/day isoflavones (+ISO) or a similar drink with isoflavones removed (−ISO). Participants in the parent study were 85% men. Of the 128 men enrolled in the trial, 112 completed. These men were later contacted for consent to allow their stored sera to be analyzed for PSA and 81 men consented. We measured PSA in serum collected at 0 and 12 months using a commercial radioimmunometric assay. Serum PSA concentrations increased in both groups over the 12-month intervention, but the changes were similar: Geometric mean PSA concentration increased 0.5% more in the +ISO group than in the −ISO group (P = 0.94; 95% confidence interval = −17.3 to 22.2). The proportion of participants having a serum PSA velocity greater than 1 ng/ml/year was similar in the +ISO and −ISO groups (17.6% *versus* 12.8%; P = 0.54). We found no evidence that a 12-month 83 mg/day isoflavone treatment alters serum PSA concentration or velocity in seemingly healthy men aged 50–80 years. (Cancer Epidemiol Biomarkers Prev 2004;13(4):644–648)

Introduction

Differences in prostate cancer mortality between Asia and the West suggest an environmental cause. Prostate cancer mortality is low in Asia but high in the United States and Europe (1–3) and migrants from Asia to the United States have higher mortality than their counterparts remaining in Asia (4). Although some of the difference in mortality between East and West may be due to underreporting in Asian countries, a substantial portion appears to be real (5). Differences in mortality have been proposed to be due to differences between Western and Asian diets. For example, men in Asia consume substantial amounts of soy, while men in the United States consume very little. Soy contains isoflavones, which are naturally occurring, biologically active compounds. The predominant isoflavones in soy are genistein and daidzein. Circulating levels of these isoflavones are much higher in Japanese men than in Western men due to high soy intake in this population (6, 7). One hypothesis is that a traditional Asian diet, high in soy isoflavones, protects against development of prostate cancer by inhibiting growth of existing small cancers (8).

Isoflavones bind to and modulate the estrogen receptor (9). In addition, isoflavones have several effects independent of the estrogen receptor, including inhibition of tyrosine kinases and topoisomerases (10). Several animal studies have suggested that soy phytochemicals have the ability to slow the growth of prostate tumors and prevent their occurrence (reviewed in Refs. 11, 12). In mice experimentally implanted with human prostate cancer cells, soy protein with isoflavones reduced tumor growth and inhibited angiogenesis (13). In Lobund-Wistar rats having high spontaneous incidence of prostate cancer, soy protein with isoflavones decreased the incidence of prostate tumors (14). However, in a

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Copenhagen rat model, isoflavone-rich isolated soy protein increased prostate tumor volume (15). Analytical epidemiological studies have been equivocal (16–22). In the most promising of these, an inverse association with prostate cancer incidence was found for Seventh Day Adventists who consumed soy milk (20). Three previous, relatively short-term interventions evaluated the effects of isoflavones on serum prostate-specific antigen (PSA), but none found an effect (7, 23, 24). Whether a longer exposure would influence PSA is unknown.

PSA is a protein serine protease produced in the prostate. It is secreted into seminal fluid, where it breaks down the gel surrounding the semen, resulting in liquefaction of the seminal fluid (25). PSA is produced by prostate tumors. Prostate tumors can break down barriers to allow PSA to escape into the blood (26). In men with prostate tumors, serum PSA concentration is proportional to prostate tumor volume (27), making it a useful marker of tumor growth. However, PSA is not always elevated in prostate cancer and is also elevated by benign prostatic hyperplasia, prostatic inflammation, and other prostate conditions (28).

The objective of our study was to determine whether soy isoflavone supplementation alters serum PSA concentrations. Our study involved a substantially longer intervention and a larger sample size than previously evaluated by others (7, 23). Specifically, we hypothesized that 83 mg/day isoflavone supplementation would slow the rate of increase in serum PSA relative to the control condition in a randomized, controlled, double-blinded 12-month intervention.

Methods

Subjects and Design. We conducted an ancillary study testing the effects of soy isoflavones on serum PSA among men enrolled in a randomized intervention trial. The parent study, called the Soy Isoflavone Prevention Trial (SIP), was a randomized, double-blinded, placebo-controlled, dietary intervention evaluating the effects of soy isoflavones on markers of colon cancer risk in colonic epithelium. This ancillary study measured PSA concentration from stored serum from men who had participated in SIP. We compared change in PSA concentration over the intervention between isoflavone (+ISO) and control (−ISO) groups.

Participants were recruited from patients who were undergoing colonoscopy at two gastroenterology clinics at a large managed care organization. The parent study recruited men and women, aged 50–80 years, who were not hormone (*e.g.*, hormone replacement therapy) users and who had adenomatous polyps detected on colonoscopy. Exclusions included various gastrointestinal and other medical conditions and high soy food intake. Participants were block randomized to intervention groups by sex, clinic, and nonsteroidal anti-inflammatory drug (NSAID) use.

The study design has been described previously (29). Participants were randomly allocated to one of two treatment groups and provided 58 g/day soy drink powder (2 packets/day, 29 g/packet SUPRO brand isolated soy protein powder; Protein Technologies International, St. Louis, MO), which they were asked to consume for 12 months. The powder provided 40 g protein and 200 kcal energy/day. Under the +ISO condition, the powder provided 45.6 mg genistein, 31.7 mg daidzein, and 5.5 mg glycitein (aglycone equivalents; ~90% glycoside conjugates), while the −ISO powder, the same product as +ISO but extracted with ethanol, provided only small quantities of these isoflavones (3 mg/day). In addition to containing isoflavones, soy protein isolate contains saponins, phytates, and protease inhibitors (30). Many of these alcohol-soluble constituents are also removed during the alcohol wash, such that isoflavone content is not the sole difference between +ISO and −ISO (31, 32). The 83 mg/day isoflavone dose was chosen to be comparable with the intake of Asians consuming a traditional diet (33) and an amount that motivated persons in the West could attain by adding soy foods to their diets. Participants were encouraged to substitute the soy drink, which was suitable as a milk substitute, into their typical diets. Fasting blood was collected at 0-, 4-, 8-, and 12-month clinic visits, spun down, and frozen at −70°C. Adherence to treatment was assessed by packet count. Soy beverage packets were distributed to participants at 0-, 4-, and 8- month clinic visits and participants were instructed to return unused packets at 4-, 8-, and 12-month visits. Participants (n = 70) who returned fewer than 20% of packets over the 12-month intervention were considered adherent.

Because PSA is used clinically to screen for prostate cancer, and the original consent did not include PSA measurement, we reconsented participants for the PSA analysis. Study activities were approved by the institutional review boards of the Fred Hutchinson Cancer Research Center (Seattle, WA) and Group Health Cooperative (Seattle, WA) and informed written consent was obtained from all study participants.

Measurements. Serum samples from SIP study participants were assayed in duplicate for serum PSA using radioimmunometric assay (Diagnostic Systems Laboratories, Webster, TX). Baseline and 12-month treatment samples from the same individuals were included in each batch of assays. Assay performance was monitored by standard curve parameters and quality control samples. Three Diagnostic Systems Laboratories kit controls and one Bio-Rad Immunoassay Plus Control (Hercules, CA) were assayed at the beginning and end of each batch of 34 samples. Westgard QC multirules were used to accept or reject a run. In addition, duplicate samples with coefficient of variation (CV) > 10% were reassayed. Intra-assay CVs for the quality control samples were 4.0% at 0.24 ng/ml, 1.9% at 3.91 ng/ml, 1.6% at 20.71 ng/ml, and 2.5% at 4.64 ng/ml. Interassay CVs were 9.0% at 0.18 ng/ml, 2.7% at 3.99 ng/ml, 1.6% at 19.15 ng/ml, and 2.8% at 4.41 ng/ml. The detection limit was 0.2 ng/ml. We measured genistein in serum samples using a modified version of the gas chromatography-mass spectrometry method as described previously (29).

Analysis. Statistical analysis was a comparison of mean change in PSA concentration from baseline to 12 months, between the intervention and the control groups, using a linear regression model. PSA measurements were log transformed to more closely approximate a normal distribution. The primary analysis was by

intention-to-treat, with adjustment for baseline response and stratification variables (clinic and NSAID use) and robust SE estimates to account for unequal variances. Differences in proportions of participants with a PSA velocity (PSAV) > 1 ng/ml/day were tested using a two-sample test of proportions. Analyses were carried out using Stata statistical software (version 7.0; Stata Corporation, College Station, TX). An α level of 0.05 was used.

Results

One hundred and twelve men completed the SIP intervention, providing serum samples at the 12-month clinic visit. Of these, 34 of the 51 men who completed the intervention in the +ISO group consented to PSA analysis (67%) compared with 47 of 61 from the −ISO group (77%; $P = 0.2$). Of the 31 men who did not consent, 24 did not respond to our repeated contacts, 3 explicitly refused, and 4 were lost to follow-up (no forwarding address, death, or illness). Baseline characteristics of participants, including serum PSA levels, were similar in the +ISO and −ISO groups (Table 1). Five PSA sample measurements were below the detection limit and were assigned a concentration of 0.1 ng/ml (one-half the detection limit). Serum genistein concentrations, a marker for isoflavone consumption, were similar in the +ISO and −ISO groups at baseline. At 4, 8, and 12 months, genistein concentrations were significantly elevated in the +ISO group compared with the −ISO group (Fig. 1). This analysis is limited to participants who completed the parent study; by definition, none of the participants withdrew. Participants were considered adherent if they returned fewer than 20% of packets over the course of the study. By this measure, 27 (79%) participants were adherent in the +ISO group compared with 43 (91%) in the −ISO group.

Geometric mean PSA concentration increased by about 16% in both groups over the 12-month intervention (Table 2). PSA changed on average 0.5% more [95% confidence interval (95% CI) = −17.3 to 22.2; $P = 0.97$] for a person in the +ISO group than it did for a person in the −ISO group, a difference of very small magnitude and not statistically significant. Overall, the median increase in PSA was 0.13 ng/ml/year, and 12 participants had a rate greater than 1 ng/ml/year. The proportion of men with a PSAV [$(PSA_{12} - PSA_0)$/year on study] greater than 1 ng/ml/year was 17.6% in the +ISO group compared with 12.8% in the −ISO group ($P = 0.54$).

Table 1. Baseline characteristics of PSA study participants

	Treatment group	
	−ISO (n = 47)	+ISO (n = 34)
Age (yr)	63.9 ± 7.2	64.9 ± 7.7
Body mass index (kg/m^2)	29.1 ± 4.8	28.3 ± 4.1
Race (%)		
White	89.4	88.2
Asian	6.4	2.9
Black	0.0	2.9
Other	4.3	5.9
College graduate (%)	53.2	67.6
Smoking (%)		
Never	36	38
Former	53	53
Current	11	9
Alcohol (drinks/wk)	3.4 ± 3.1	3.4 ± 3.2
Exercise (h/wk)	5.5 ± 4.6	4.1 ± 2.6
Protein intake (g/day)	61 ± 22	64 ± 26
Carbohydrate intake (g/day)	170 ± 68	171 ± 62
Energy intake (kcal/day)	1528 ± 529	1545 ± 593
Energy from fat (%)	37 ± 8	36 ± 7

Note: Arithmetic mean ± SD unless indicated to be proportion.

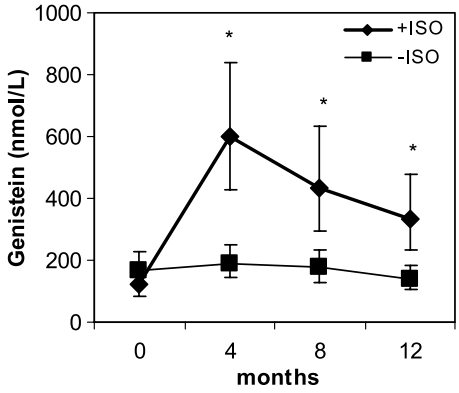

Fig. 1. Fasting serum genistein concentrations (nmol/l) in PSA study participants. *Points,* geometric mean; *bars,* 95% CI. *, Statistically significant differences between +ISO and −ISO groups.

In secondary analyses, statistical adjustment for age, body mass index, alcoholic drinks/day, smoking status, exercise, or baseline dietary intake of fat, protein, or energy did not change these null results. Similarly, restricting the analysis to subjects who returned fewer than 20% of packets did not affect the results. In addition, we found no association between serum PSA and serum genistein concentration, a marker for consumption of isoflavones. In an analysis restricted to men with baseline PSA > 1 ng/ml (+ISO n = 23, −ISO n = 32), geometric mean PSA concentrations in the +ISO group increased 16.7% compared with 6.7% in the −ISO group (for the 9.4% difference, 95% CI = −13.8 to 38.7; $P = 0.5$).

Discussion

In this study, a soy isoflavone intervention did not slow the increase of serum PSA over a 12-month intervention in older men. Geometric mean serum PSA concentrations increased by about 15% in both the active treatment (+ISO) and the control (−ISO) groups, but there was no difference between treatment groups. These results did not change when we adjusted for other factors that could influence PSA levels, restricted our analysis to adherent participants only, or examined observational associations between a serum marker of isoflavone intake and PSA concentrations. Rates of PSA change or PSAV were similar in both treatment groups.

Three smaller human studies of shorter duration also have found no effect of isoflavones on PSA. No effect of soy isoflavones (69 mg/day) on serum PSA was observed in a 6-week intervention in men having initial PSA concentrations > 4 ng/ml (7). Similarly, a 6-week, nonrandomized intervention in prostate cancer patients using red clover-derived isoflavones (160 mg/day)

Table 2. Serum PSA concentrations in SIP study participants before and after 12-month intervention

	Treatment group		
	−ISO (n = 47)	+ISO (n = 34)	Relative difference between +ISO and −ISO groups (95% CI)
PSA concentration (ng/ml)			
Baseline	1.7 (2.9)[b]	1.7 (3.1)	
12 months	2.0 (3.5)	2.0 (3.2)	
Δ (%)	16.3	15.4	0.5 (−17.3 to 22.2)

Note: Geometric mean (geometric SD).
[b]Relative difference in geometric mean PSA in +ISO group compared with −ISO group, adjusted for baseline serum PSA concentration, clinic, and NSAID use.

found no difference in pretreatment *versus* posttreatment PSA (23). However, this study did report higher levels of apoptosis in resected prostate tissue from isoflavone-treated men compared with levels measured in historical controls. In contrast, an abstract not yet published reported that consumption of isoflavones for 6 months improved PSA in cancer patients with uncontrolled prostate cancer (presented in Ref. 12). A fourth study pooled 44 participants from four relatively short-term cross-over interventions, three of which were 3–4 weeks in duration and one was 3 months in duration, and found no effect of soy protein and isoflavones on PSA (24). Because prostate tumors tend to grow slowly, our expectation was that an intervention substantially longer than 6 weeks would be necessary for isoflavones to affect PSA. We believe our study was long enough for isoflavones to exert an effect on PSA, if there is one.

Unlike previous interventions (7, 23), we did not select our study population based on elevated serum PSA levels or the presence of prostate cancer. Possibly, isoflavones only modulate PSA in men with elevated levels, although other published studies generally do not support this. Another possibility is that soy isoflavones slow prostate tumor growth without affecting serum PSA concentrations. Evidence for this is the finding of Jarred *et al.* that prostate cancer patients who consumed isoflavones prior to surgery had higher levels of apoptosis in resected tissue than men who did not consume isoflavones, while PSA in men who consumed isoflavones did not change pretreatment *versus* posttreatment (23). Nevertheless, given the high prevalence of latent prostate cancer in men in this age group (34), and the fairly high rate of change in PSA in participants over the 12-month intervention, we considered our study population to be at increased risk and therefore potentially benefiting from the intervention.

The strengths of this study are the randomized, controlled, parallel-arm design, the blinding of investigators and participants, the relatively long (12-month) duration of the intervention, and the larger sample size than previous studies. The limitations include participant dropout and measurement of a serum marker rather than prostate cancer itself. Statistical power is lost due to participant withdrawal from the study and incomplete adherence. Participant withdrawal could bias the study if PSA levels were related to levels of participation in the two treatment arms. However, withdrawal from the intervention for health-related reasons was similar in the two treatment groups (29). Furthermore, it is not clear how PSA levels (which are not symptomatic and would not be known by most participants) would affect participants' choice to complete the soy isoflavone intervention or willingness later to give consent to the PSA analysis. Finally, there is no hint of a difference in PSA levels between groups among the participants who completed the trial *versus* those who did not, suggesting that isoflavones in soy protein at the level we employed truly have no effect on PSA. We calculated PSAV from two PSA measurements instead of the recommended three measurements, at least 1 year apart (the duration recommended for clinical applications; Ref. 35). Possibly, a longer intervention, with additional PSA measurements, would show an effect of isoflavones on PSAV. This study was conducted in participants with colon adenomatous polyps: it may not be generalizable to the general male population, although we find no reason to suspect a connection between colon polyps and PSA. The men were not selected based on PSA levels (*e.g.*, baseline PSA > 4 ng/ml), so it could also be argued that they were not at high enough risk to benefit from the treatment. However, the rate of increase in PSA in our population (median 0.13 ng/ml/year) was substantial. By comparison, for 65-year-old men, Carter *et al.* reported average rates of change of 0.04 ng/ml/year for normal controls and 0.11 ng/ml/year for men with benign prostatic hyperplasia (35). This suggests that men in our study were in a position to benefit from the treatment.

In summary, a 12-month isoflavone supplementation did not alter serum PSA concentration in a population of men aged 50–80 years. While our study found that an isoflavone intervention has no effect on circulating PSA, an intermediate marker of tumor growth, it is nevertheless possible that isoflavones affect earlier stages in the cancer process or have other effects on tumor growth not reflected in PSA levels. Our study suggests that an isoflavone intervention does not slow tumor growth or other prostate conditions that affect circulating PSA concentration.

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References

1. Muir CS, Nectoux J, Staszewski J. The epidemiology of prostatic cancer. Geographical distribution and time-trends. Acta Oncol, 1991;30:133–40.

2. Boyle P, Maisonneuve P, Napalkov P. Geographical and temporal patterns of incidence and mortality from prostate cancer. Urology, 1995;46:47–55.
3. Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. Int J Cancer, 2000;85:60–7.
4. Haenszel W, Kurihara M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst, 1968;40:43–68.
5. Hsing AW, Devesa SS. Trends and patterns of prostate cancer: what do they suggest? Epidemiol Rev, 2001;23:3–13.
6. Adlercreutz H, Markkanen H, Watanabe S. Plasma concentrations of phyto-estrogens in Japanese men. Lancet, 1993;342:1209–10.
7. Urban D, Irwin W, Kirk M, et al. The effect of isolated soy protein on plasma biomarkers in elderly men with elevated serum prostate specific antigen. J Urol, 2001;165:294–300.
8. Adlercreutz H. Western diet and Western diseases: some hormonal and biochemical mechanisms and associations. Scand J Clin Lab Invest Suppl, 1990;201:3–23.
9. Setchell KD. Soy isoflavones—benefits and risks from nature's selective estrogen receptor modulators (SERMs). J Am Coll Nutr, 2001;20:354S–62S; discussion 381S–3S.
10. Barnes S, Peterson TG, Coward L. Rationale for the use of genistein-containing soy matrices in chemoprevention trials for breast and prostate cancer. J Cell Biochem Suppl, 1995;22:181–7.
11. Barnes S. Role of phytochemicals in prevention and treatment of prostate cancer. Epidemiol Rev, 2001;23:102–5.
12. Messina MJ. Emerging evidence on the role of soy in reducing prostate cancer risk. Nutr Rev, 2003;61:117–31.
13. Zhou JR, Gugger ET, Tanaka T, Guo Y, Blackburn GL, Clinton SK. Soybean phytochemicals inhibit the growth of transplantable human prostate carcinoma and tumor angiogenesis in mice. J Nutr, 1999;129:1628–35.
14. Pollard M, Wolter W. Prevention of spontaneous prostate-related cancer in Lobund-Wistar rats by a soy protein isolate/isoflavone diet. Prostate, 2000;45:101–5.
15. Cohen LA, Zhao Z, Pittman B, Scimeca J. Effect of soy protein isolate and conjugated linoleic acid on the growth of Dunning R-3327-AT-1 rat prostate tumors. Prostate, 2003;54:169–80.
16. Oishi K, Okada K, Yoshida O, et al. A case-control study of prostatic cancer with reference to dietary habits. Prostate, 1988;12:179–90.
17. Severson RK, Nomura AM, Grove JS, Stemmermann GN. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. Cancer Res, 1989;49:1857–60.
18. Mills PK, Beeson WL, Phillips RL, Fraser GE. Cohort study of diet, lifestyle, and prostate cancer in Adventist men. Cancer, 1989;64:598–604.
19. Lee MM, Wang RT, Hsing AW, Gu FL, Wang T, Spitz M. Case-control study of diet and prostate cancer in China. Cancer Causes & Control, 1998;9:545–52.
20. Jacobsen BK, Knutsen SF, Fraser GE. Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study (United States). Cancer Causes & Control, 1998;9:553–7.
21. Villeneuve PJ, Johnson KC, Kreiger N, Mao Y. Risk factors for prostate cancer: results from the Canadian National Enhanced Cancer Surveillance System. The Canadian Cancer Registries Epidemiology Research Group. Cancer Causes & Control, 1999;10:355–67.
22. Kolonel LN, Hankin JH, Whittemore AS, et al. Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. Cancer Epidemiol Biomarkers & Prev, 2000;9:795–804.
23. Jarred RA, Keikha M, Dowling C, et al. Induction of apoptosis in low to moderate-grade human prostate carcinoma by red clover-derived dietary isoflavones. Cancer Epidemiol Biomarkers & Prev, 2002;11:1689–96.
24. Jenkins DJ, Kendall CW, D'Costa MA, et al. Soy consumption and phytoestrogens: effect on serum prostate specific antigen when blood lipids and oxidized low-density lipoprotein are reduced in hyperlipidemic men. J Urol, 2003;169:507–11.
25. Lilja H. A kallikrein-like serine protease in prostatic fluid cleaves the predominant seminal vesicle protein. J Clin Invest, 1985;76:1899–903.
26. Partin AW, Hanks GE, Klein EA, Moul JW, Nelson WG, Scher HI. Prostate-specific antigen as a marker of disease activity in prostate cancer. Oncology (Huntington), 2002;16:1218–24; discussion 1224, 1227–8 passim.
27. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med, 1987;317:909–16.
28. Crawford ED, DeAntoni EP, Ross CA. The role of prostate-specific antigen in the chemoprevention of prostate cancer. J Cell Biochem Suppl, 1996;25:149–55.
29. Adams KF, Newton KM, Chen C, et al. Soy isoflavones do not modulate circulating insulin-like growth factor concentrations in an older population in an intervention trial. J Nutr, 2003;133:1316–9.
30. Fournier DB, Erdman JW Jr, Gordon GB. Soy, its components, and cancer prevention: a review of the *in vitro,* animal, and human data. Cancer Epidemiol Biomarkers & Prev, 1998;7:1055–65.
31. Anderson RL, Wolf WJ. Compositional changes in trypsin inhibitors, phytic acid, saponins and isoflavones related to soybean processing. J Nutr, 1995;125:581S–8S.
32. Erdman JW Jr. AHA Science Advisory: Soy protein and cardiovascular disease: a statement for healthcare professionals from the Nutrition Committee of the AHA. Circulation, 2000;102:2555–9.
33. Messina M. Isoflavone intakes by Japanese were overestimated. Am J Clin Nutr, 1995;62:645.
34. Yatani R, Chigusa I, Akazaki K, Stemmermann GN, Welsh RA, Correa P. Geographic pathology of latent prostatic carcinoma. Int J Cancer, 1982;29:611–6.
35. Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA, 1992;267:2215–20.