

# Soy Product and Isoflavone Consumption in Relation to Prostate Cancer in Japanese Men

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## Abstract

The incidence of prostate cancer is much lower in Asian than Western populations. Environmental factors, such as dietary habits, may play a major role in the causation of prostate cancer. Although isoflavones have been suggested to show a preventive effect against prostate cancer in animal experiments, the results of epidemiologic studies are inconsistent. Here, we conducted a population-based prospective study in 43,509 Japanese men ages 45 to 74 years who generally have a high intake of isoflavones and low incidence of prostate cancer. Participants responded to a validated questionnaire, which included 147 food items. During follow-up from 1995 through 2004, 307 men were newly diagnosed with prostate cancer, of which 74 cases were advanced, 220 cases were organ localized, and 13 cases were of an undetermined stage. Intakes of genistein,

daidzein, miso soup, and soy food were not associated with total prostate cancer. However, these four items decreased the risk of localized prostate cancer. In contrast, positive associations were seen between isoflavones and advanced prostate cancer. These results were strengthened when analysis was confined to men ages >60 years, in whom isoflavones and soy food were associated with a dose-dependent decrease in the risk of localized cancer, with relative risks for men in the highest quartile of genistein, daidzein, and soy food consumption compared with the lowest of 0.52 [95% confidence interval (95% CI), 0.30-0.90], 0.50 (95% CI, 0.28-0.88), and 0.52 (95% CI, 0.29-0.90), respectively. In conclusion, we found that isoflavone intake was associated with a decreased risk of localized prostate cancer. (Cancer Epidemiol Biomarkers Prev 2007;16(3):538–45)

## Introduction

The incidence of prostate cancer is much lower in Asian than in Western populations (1). However, Japanese migrants to the United States and Brazil have an increased incidence (2, 3), and the incidence of latent or clinically insignificant prostate cancer in autopsy studies among men from Asian countries and the United States is similar (4, 5). It has therefore been suggested that environmental factors may play an important role in the progression of prostate cancer. Asian populations consume large quantities of soy food that contained isoflavones such as genistein and daidzein (6). Mean serum or plasma concentrations of isoflavones in Japanese men are 10 to 100 times higher than those in men from the United Kingdom (7) and Finland (8). Moreover, Morton et al. (9) reported a higher concentration of daidzein in the prostatic fluid of Asian men than in Western men. Genistein and daidzein exhibit anticarcinogenic properties and estrogenic activity *in vitro* and have shown a protective effect against prostate cancer development in some animal studies (6). On these bases, isoflavones have been recognized as key substances that may decrease the incidence of prostate cancer in Asia. However, previous findings from epidemiologic studies

regarding isoflavone or soy food intake and prostate cancer are equivocal (10-17).

This inconsistency may be due to errors in exposure measurement and limited variation in soy intake. Some of the previous epidemiologic studies investigated association between prostate cancer and a single soy food only, such as tofu or soy milk, and most were conducted in Western countries, in which physiologically meaningful amounts of soy are not consumed (10-12). Here, we investigated the association between isoflavone intake and risk of prostate cancer in a prospective study in Japanese who consume large amounts of soy.

## Materials and Methods

**Study Population.** The Japan Public Health Center–Based Prospective Study was initiated in 1990 for cohort I and in 1993 for cohort II. The study design has been described in detail previously (18). Cohort I included those residents ages 40 to 59 years who had registered their addresses in five public health center areas (Iwate, Akita, Nagano, Okinawa, and Tokyo). Cohort II included those residents ages 40 to 69 years who had registered in six public health center areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka). The Tokyo subjects were not included in the data analysis because incidence data were not available. This study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan. The initial cohort consisted of 68,557 men.

**Food Frequency Questionnaire.** At baseline, participants completed a self-administered questionnaire that assessed information on lifestyle factors, medical, and smoking histories. The food frequency questionnaire (FFQ) in the baseline survey had 44 food items for cohort I and 52 food items for cohort II with four (cohort I) or five (cohort II) frequency categories but without standard portions/units. In contrast, the 5-year follow-up survey included a self-administered FFQ, which included lifestyle factors, medical history, and 147 food

Received 6/28/06; revised 12/5/06; accepted 12/21/06.

**Grant support:** Grants-in-aid for Cancer Research (16shi-2), 3rd Term Comprehensive 10-Year-Strategy for Cancer Control (H16-sanjigan-010), and Research on Risk of Chemical Substances (H17-kagaku-014) from the Ministry of Health, Labour and Welfare of Japan and grant-in-aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology (17015049).

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**Note:** N. Kurahashi received a Research Resident Fellowship from the Foundation for Promotion of Cancer Research (Japan) for the 3rd Term Comprehensive 10-Year-Strategy for Cancer Control. Study Group members are listed in Appendix A.

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doi:10.1158/1055-9965.EPI-06-0517

and beverage items with standard portions/units and nine frequency categories. Owing to this greater detail, the present study therefore used the 5-year follow-up survey as baseline and followed the subjects from 1995 for cohort I and from 1998 for cohort II until 2004. After the 5-year follow-up survey, 128 subjects were found to be ineligible and were excluded because of non-Japanese nationality ( $n = 28$ ), late report of emigration occurring before the start of the follow-up period ( $n = 97$ ), incorrect birth data ( $n = 3$ ), and subjects with self-reported prostate cancer ( $n = 21$ ), leaving 58,427 men eligible for participation. Among eligible subjects, 46,001 men (79%) returned valid responses to the 5-year follow-up FFQ.

We dealt with two item groups: consumption of miso soup and soy food. Soy food referred to the consumption of "Tofu, Yushidofu (pre-drained tofu), Koyadofu (freeze-dried tofu), Aburaage (deep-fried tofu), Natto (fermented soybean), and soy milk," for which the major ingredient is soybeans. The questionnaire asked about the usual consumption of 147 foods and beverages during the previous year. The frequency of miso soup consumption was divided into six categories (almost never, 1-3 days/mo, 1-2 days/wk, 3-4 days/wk, 5-6 days/wk, and daily). Portion sizes were specified, and the amounts provided in three categories (less than half, same, and more than 1.5 times). One bowl of miso soup was calculated as 150 mL. Nine frequency categories were used for soy foods (almost never, 1-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, once a day, 2-3 times per day, 4-6 times per day, and  $\geq 7$  times per day). Portion sizes were specified, and the amounts were determined in three categories (less than half, same, and more than 1.5 times). Ten frequency categories were used for soy milk (almost never, 1-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, 1 glass per day, 2-3 glasses per day, 4-6 glasses per day, 7-9 glasses per day, and  $>9$  glasses per day). The total consumption of miso soup (mL/d) and soy food (g/d) was calculated from these responses, whereas that of isoflavones (daidzein and genistein) was calculated using values in a specially developed food composition table for isoflavones in Japanese foods (19, 20).

Validity was assessed among subsamples using 14- or 28-day dietary records. Spearman's correlation coefficients between the energy-adjusted intake of miso soup and soy food consumption from the questionnaire and from dietary records were 0.54 and 0.53 for cohort I and 0.48 and 0.52 for cohort II, respectively, whereas those for energy-adjusted intake of daidzein and genistein were 0.65 and 0.65 for cohort I and 0.49 and 0.48 for cohort II, respectively. Moreover, Spearman's correlation coefficients for daidzein and genistein between energy-adjusted intakes from FFQ and those from serum concentration were 0.26 and 0.40, respectively, and with those from creatinine-adjusted urinary excretion were 0.22 and 0.33, respectively (21). These correlation coefficients are considered acceptable (22). With regard to the reproducibility of estimations between two questionnaires administered 1 year apart, respective correlation coefficients for the energy-adjusted intake of miso soup, soy food, daidzein, and genistein were 0.80, 0.64, 0.75, and 0.75 for cohort I and 0.75, 0.57, 0.53, and 0.51 for cohort II (23-25).

Among the 46,001 men who responded to the questionnaire, 2,492 who reported extreme total energy intake ( $<800$  or  $>4,000$  kcal) were excluded, leaving 43,509 men for analysis.

**Follow-up.** Subjects were followed from the 5-year follow-up survey until December 31, 2004. Changes in residence status, including survival, were identified annually through the residential registry in each area or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Generally, mortality data for residents included in the residential registry are forwarded to the Ministry of Health, Labour, and Welfare and coded for

inclusion in the national Vital Statistics. Residency and death registration are required by the Basic Residential Register Law and Family Registry Law, respectively, and the registries are believed to be complete. Here, information on the cause of death was based on death certificates from the respective public health center for those who had not moved out of the original area. Among questionnaire respondents to the 5-year follow-up FFQ, 3,855 men (8.4%) died, 1,492 men (3.2%) moved out of the study area, and 66 men (0.1%) were lost to follow-up during the study period.

The occurrence of cancer was identified by active patient notification from major local hospitals in the study area and data linkage with population-based cancer registries, with permission from the local governments responsible for the cancer registries. Cases were coded using the International Classification of Diseases for Oncology, Third Edition (26). Death certificate information was used as a supplementary information source. The proportion of cases of prostate cancer first notified by death certificate was 0.9%. The ratio of incidence to mortality was 7.7. The registration rate as introduced by Parkin et al. (27) was 94.3%. The proportion of case patients with prostate cancer ascertained by death certificate only was 0.6%. These ratios were considered satisfactory for the present study. A total of 307 newly diagnosed prostate cancer cases were identified by December 31, 2004.

Finally, a population-based cohort of 43,509 men (18,105 in cohort I and 25,404 in cohort II) was established for analysis. During the 325,371 person-years of follow-up (167,611 in cohort I and 157,760 in cohort II), 307 cases of prostate cancer were newly diagnosed (156 in cohort I and 151 in cohort II).

**Statistical Analysis.** Person-years of follow-up were calculated for each man from the date of completion of the 5-year follow-up FFQ to the date of prostate cancer diagnosis, the date of emigration from the study area, or the date of death, whichever came first; or if none of these occurred, follow-up was through to the end of the study period (December 31, 2004). Men who were lost to follow-up were censored at the last confirmed date of presence in the study area. The crude incidence rate for prostate cancer was calculated by dividing the number of prostate cancer cases by the number of person-years. The relative risks (RR) of prostate cancer were calculated in quartile for the categories of miso soup consumption, soy food consumption, and isoflavone intake, with the lowest consumption category as the reference. RRs and 95% confidence intervals (95% CI) were calculated by the Cox proportional hazards model, adjusting for age at 5-year follow-up survey and study area (10 public health center areas) according to the SAS PHREG procedure (version 9.1; SAS Institute, Inc., Cary, NC). For further adjustment, additional possible confounders were incorporated into the model: smoking status (never, former, and current); alcohol intake (almost never,  $<3-4$  days/wk, and  $>5$  days/wk); marital status (yes/no); body mass index; and consumption of dairy foods, vegetables, fruit, and total fatty acids.

We conducted additional analyses according to the stage of prostate cancer. Advanced cases were defined by a diagnosis of extraprostatic or metastatic cancer involving lymph nodes or other organs. If this information was not available, advanced cases were defined as those with a high Gleason score (8-10) or poor differentiation. These criteria were selected to allow the identification of advanced cases with a high likelihood of poor prognosis. The remaining cases were organ localized. In this study, there were 74 advanced cases, 220 localized cases, and 13 (4% of total) cases of undetermined stage.

The trend was assessed by assigning ordinal values for categorical variables. All  $P$ s were two sided, and statistical significance was determined at the  $P < 0.05$  level.

## Results

Distribution of subject characteristics at the 5-year follow-up survey according to quartile of energy-adjusted isoflavone consumption is shown in Table 1, in which the results for genistein were used as a surrogate for isoflavones owing to the high correlation among results for genistein, daidzein, miso soup, and soy food. Men with high genistein consumption were slightly older. Body mass index was higher in the highest category than in the other categories. The proportion of current smokers increased as genistein intake increased, whereas alcohol intake decreased. The proportion of men who live with their wife was lower in the lowest category than in the other categories. Screening-detected prostate cancer accounted for >40% of cases in all categories. Dairy food, fruit, vegetable, and total fatty acid consumption were positively correlated with genistein intake. As expected, soy food and miso soup increased as genistein intake increased and were highly correlated with it ( $P < 0.0001$ ).

Table 2 shows age- and area-adjusted and multivariable RRs and 95% CIs for total prostate cancer by each quartile of genistein, daidzein, miso soup, and soy food consumption. Genistein, daidzein, and soy food consumption slightly decreased the risk of total prostate cancer. Multivariable RRs for the highest versus lowest quartile of genistein, daidzein, and soy food consumption were 0.71 (95% CI, 0.48-1.03), 0.77 (95% CI, 0.52-1.13), and 0.82 (95% CI, 0.57-1.19), respectively. Tests for linear trends were not statistically significant. No statistically significant association was seen between miso soup consumption and total prostate cancer risk (highest versus lowest: RR, 1.04; 95% CI, 0.72-1.50).

We next classified the data according to prostate cancer stage (Table 3). Consumption of genistein decreased the risk of localized prostate cancer in a statistically significant manner (RR, 0.59; 95% CI, 0.38-0.93), although  $P_{\text{trend}}$  was not statistically significant. Men in the highest quartile of daidzein also had a decreased the risk of localized prostate cancer, although with only marginal significance (RR, 0.66; 95% CI, 0.42-1.04). Miso soup and soy foods tended to decrease the risk of localized prostate cancer, with respective multivariable RRs for the highest versus lowest quartile of 0.78 (95% CI, 0.51-1.20) and 0.77 (95% CI, 0.50-1.19). In contrast, genistein and daidzein increased the risk of advanced prostate cancer, with respective RRs for men with the highest versus lowest consumption of genistein and daidzein of 1.26 (95% CI, 0.56-2.83) and 1.43 (95% CI, 0.63-3.28). Miso soup was dose-dependently increased the risk of advanced prostate cancer, with multivariable RR for the highest versus lowest quartile of 2.79 (95% CI, 1.19-6.55;

$P_{\text{trend}} = 0.02$ ). Consumption of soy food was not associated with advanced cancer.

Table 4 shows multivariable RRs and 95% CIs for prostate cancer by stage categorized according to age. We found that the negative association with genistein, daidzein, and soy food and localized prostate cancer became clear when we analysis was restricted to men ages >60 years. Genistein, daidzein, and soy food were dose-dependently associated with a decreased risk of localized prostate cancer, with multivariable RR for the highest versus lowest quartile of 0.52 for genistein (95% CI, 0.30-0.90;  $P_{\text{trend}} = 0.03$ ), 0.50 for daidzein (95% CI, 0.28-0.88;  $P_{\text{trend}} = 0.04$ ), and 0.52 for soy food (95% CI, 0.29-0.90;  $P_{\text{trend}} = 0.01$ ). Miso soup also decreased the risk of localized prostate cancer, although without statistical significance. In contrast, RRs of daidzein and miso soup showed an increased risk of advanced prostate cancer in men ages >60 years old. In particular, miso soup was positively associated with advanced cancer, with a multivariable RR for the highest versus lowest quartile of 2.86 (95% CI, 1.01-8.11). Daidzein tended to increase the risk of advanced cancer (highest versus lowest: RR, 1.49; 95% CI, 0.55-4.03). Genistein was not associated with advanced cancer. Soy food tended to be negatively associated with advanced cancer in men ages >60 years. In men ages  $\leq 60$  years, genistein, daidzein, and soy food increased the risk of both localized and advanced prostate cancer. Multivariable RR for the highest versus lowest quartile was 1.18 for genistein, 1.38 for daidzein, and 1.38 for soy food in localized prostate cancer and 2.00 for genistein, 2.46 for daidzein, and 1.48 for soy food in advanced prostate cancer. Miso soup was not associated with localized prostate cancer (RR, 0.82) but was associated with an increased risk of advanced prostate cancer (RR, 2.65). However, none of these values was statistically significant.

To weaken the influence of localized prostate cancer detected by prostate-specific antigen screening, we also analyzed the association between prostate cancer and the four items after excluding screening-detected tumors by stage in men ages >60 years, notwithstanding that screening information was available for only 70% of subjects (Table 5). Results in both localized and advanced prostate cancer were similar to those in Table 4 when screening-detected prostate cancer was included, although the statistical significance in these results was lost. Genistein, daidzein, and miso soup tended to decrease the risk of localized prostate cancer (highest versus lowest: RRs of genistein, daidzein, miso soup, and soy food of 0.52, 0.49, 0.73, and 0.51, respectively) but without statistical significance. In advanced prostate cancer, multivariable RR for the highest versus lowest quartile was 0.85 for genistein,

**Table 1. Characteristics of study subjects according to genistein consumption**

	Genistein consumption				$P_{\text{difference}}^*$
	Lowest	Second	Third	Highest	
Age $\pm$ SD (y)	56.2 $\pm$ 8.2	56.5 $\pm$ 7.9	56.7 $\pm$ 7.7	57.7 $\pm$ 7.6	<0.0001
Body mass index $\pm$ SD (kg/m <sup>2</sup> )	23.6 $\pm$ 3.0	23.6 $\pm$ 2.9	23.6 $\pm$ 2.8	23.7 $\pm$ 2.9	0.009
Current smoker (%)	49.8	52.3	54.5	58.8	<0.0001
Alcohol intake, $\geq 5$ d/wk (%)	49.1	49.7	49.5	46.2	<0.0001
Men who live with their wife (%)	81.1	83.9	83.8	83.2	<0.0001
Screening-detected tumors (%)	40.4	43.9	47.4	42.6	0.97
Dairy food (g/d)	161.2 $\pm$ 260.1	159.5 $\pm$ 215.1	164.7 $\pm$ 200.4	170.1 $\pm$ 188.5	0.002
Fruits (g/d)	152.3 $\pm$ 169.5	175.7 $\pm$ 168.2	193.5 $\pm$ 177.6	201.4 $\pm$ 177.2	<0.0001
Vegetables (g/d)	163.9 $\pm$ 141.6	192.0 $\pm$ 143.2	209.5 $\pm$ 146.1	225.2 $\pm$ 159.7	<0.0001
Total fatty acids (g/d)	48.7 $\pm$ 26.9	48.9 $\pm$ 23.8	51.0 $\pm$ 24.2	51.6 $\pm$ 23.0	<0.0001
Soy food (g/d)	33.0 $\pm$ 18.8	62.4 $\pm$ 26.4	92.3 $\pm$ 39.6	164.5 $\pm$ 144.6	<0.0001
Miso soup (mL/d)	51.3 $\pm$ 39.6	167.4 $\pm$ 57.3	301.8 $\pm$ 74.2	449.6 $\pm$ 139.0	<0.0001
Genistein (mg/d)	8.5 $\pm$ 4.3	17.0 $\pm$ 5.7	26.8 $\pm$ 9.1	49.1 $\pm$ 30.9	<0.0001
Daidzein (mg/d)	5.4 $\pm$ 2.8	10.8 $\pm$ 3.5	16.8 $\pm$ 5.5	29.9 $\pm$ 17.8	<0.0001

NOTE: Results for genistein are reported as isoflavones because the intake estimates for genistein and daidzein were highly correlated ( $P < 0.0001$ ).

\* $P_{\text{difference}}$  values of characteristics between categories of genistein consumption were calculated by ANOVA and the  $\chi^2$  test for homogeneity.

**Table 2. RRs and 95% CIs for total prostate cancer according to quartile of energy-adjusted intake of genistein, daidzein, miso soup, and soy food**

	Intake by quartile				<i>P</i> <sub>trend</sub>
	Lowest (<13.2 mg/d)	Second (13.2-21.2 mg/d)	Third (21.3-32.7 mg/d)	Highest (≥ 32.8 mg/d)	
<b>Genistein</b>					
No. cases	75	76	91	65	
Person-years of follow-up	78,439	81,443	83,208	82,282	
Age/area-adjusted RR (95% CI)	1.00	0.92 (0.67-1.27)	1.16 (0.84-1.59)	0.80 (0.56-1.14)	0.48
Multivariate RR (95% CI)	1.00	0.81 (0.62-1.23)	1.13 (0.81-1.57)	0.71 (0.48-1.03)	0.22
	Intake by quartile				<i>P</i> <sub>trend</sub>
	Lowest (<8.5 mg/d)	Second (8.5-13.4 mg/d)	Third (13.5-20.3 mg/d)	Highest (≥ 20.4 mg/d)	
<b>Daidzein</b>					
No. cases	70	79	93	65	
Person-years of follow-up	78,260	81,548	83,193	82,370	
Age/area-adjusted RR (95% CI)	1.00	1.01 (0.73-1.40)	1.25 (0.91-1.72)	0.87 (0.61-1.25)	0.77
Multivariate RR (95% CI)	1.00	0.95 (0.67-1.33)	1.21 (0.87-1.70)	0.77 (0.52-1.13)	0.43
	Intake by quartile				<i>P</i> <sub>trend</sub>
	Lowest (<110.0 mL/d)	Second (110.0-225.9 mL/d)	Third (226.0-355.9 mL/d)	Highest (≥ 356.0 mL/d)	
<b>Miso soup</b>					
No. cases	58	79	85	85	
Person-years of follow-up	75,651	79,621	84,403	85,696	
Age/area-adjusted RR (95% CI)	1.00	1.11 (0.79-1.57)	1.10 (0.78-1.56)	1.06 (0.75-1.51)	0.82
Multivariate RR (95% CI)	1.00	1.10 (0.77-1.58)	1.08 (0.75-1.55)	1.04 (0.72-1.50)	0.94
	Intake by quartile				<i>P</i> <sub>trend</sub>
	Lowest (<46.6g/d)	Second (46.6-71.8 g/d)	Third (71.9-107.3 g/d)	Highest (≥ 107.4 g/d)	
<b>Soy food</b>					
No. cases	66	88	79	74	
Person-years of follow-up	77,756	81,557	83,116	82,941	
Age/area-adjusted RR (95% CI)	1.00	1.18 (0.85-1.63)	1.05 (0.75-1.47)	0.91 (0.65-1.29)	0.43
Multivariate RR (95% CI)	1.00	1.10 (0.78-1.54)	0.95 (0.67-1.36)	0.82 (0.57-1.19)	0.18

NOTE: Multivariate RRs were adjusted for age, area, smoking status, drinking frequency, marital status, body mass index, and intake of total fatty acids, dairy, vegetables, and fruits.

1.10 for daidzein, 1.97 for miso soup, and 0.73 for soy food; however, these results were not statistically significant. Results in subjects ages ≤60 years were similar to those which included screening-detected cancers. Multivariable RR for the highest versus lowest quartile was 1.28 (95% CI, 0.33-4.97) for genistein, 1.55 (95% CI, 0.42-5.78) for daidzein, and 1.94 (95% CI, 0.58-6.52) for soy food in localized prostate cancer and 2.22 (95% CI, 0.50-9.91) for genistein, 2.93 (95% CI, 0.53-16.29) for daidzein, and 1.82 (95% CI, 0.33-9.91) for soy food in advanced prostate cancer. However, these values were not statistically significant (data not shown).

## Discussion

In the present study, we observed a dose-dependent decrease in the risk of localized prostate cancer with isoflavone consumption. Men with the highest intake of isoflavones (as genistein, ≥32.8 mg/d) had a decreased risk of prostate cancer compared with those with the lowest intake of isoflavones (as genistein, <13.2 mg/d). To our knowledge, this is the first prospective study to report an inverse association between isoflavone and localized prostate cancer in Japanese, whose intake of soy food is high.

Our results support previous studies, which reported that soy food is protective for prostate cancer. Among case-control studies, Sonoda et al. (17) reported that *natto* (fermented soy) consumption showed a significantly decreasing linear trend for risk of prostate cancer in Japanese; Lee et al. (13) found that the highest intake of tofu and genistein had a statistically

significant association with a decreased risk of prostate cancer in Chinese compared with the lowest intake; and Strom et al. (11) reported an inverse association between daidzein intake and prostate cancer risk in American men. Soy foods were also inversely related to prostate cancer in a large multicenter case-control study (12). In prospective studies, Jacobson et al. (10) reported that frequent consumption of soy milk was associated with a decreased risk of prostate cancer in Californian Adventist men. However, no association was seen between tofu consumption and a decreased risk of prostate cancer in Japanese men living in Hawaii (16), nor was tofu or miso soup significantly associated with prostate cancer risk in native Japanese (14). The reason these studies did not show a protective effect of soy foods on prostate cancer may have been due to their evaluation of a single soy food only or their failure to assess specific nutrients such as genistein or daidzein.

Studies *in vivo* and *in vitro* experiments have also shown a protective effect of isoflavones against prostate cancer development. Isoflavones possess weak estrogen activity, inhibit tyrosine protein kinases and angiogenesis, and reduce serum testosterone levels (6, 28, 29). Isoflavones also inhibit 5 $\alpha$ -reductase, an enzyme that metabolizes testosterone to dihydrotestosterone (30). Any or all of these mechanisms may explain the inverse association between isoflavones and localized prostate cancer seen here. Moreover, our results are plausible because the incidence of prostate cancer in Japanese is much lower than in Western men (1).

However, when the data were analyzed by stage, we found that the results differed between advanced and localized

cancer. These results suggest that the effects of isoflavone may differ according to stage. One mechanism by which isoflavones reduce the risk of prostate cancer seems to involve estrogen receptor  $\beta$  in prostate tissue (31), but cancer with higher metastatic potential is associated with the complete or partial loss of estrogen receptor  $\beta$  expression (32-34). Moreover, animal studies in rats showed that the beneficial effects of a soy diet play a role in the early stages of tumor development but have no effect in invasive prostate cancer (35, 36). On this basis, isoflavones may prevent the early stages of prostate cancer development only. Clinically significant localized prostate cancer likely arises from latent cancer and then develop to advanced cancer with high mortality (4, 37). Given that the incidence of latent prostate cancer in Japanese men is the same as in Western men despite a lower incidence of prostate cancer (1, 4, 5), isoflavone may delay the progression of latent prostate cancer.

When we limited analysis to men ages >60 years, the association between isoflavone and localized prostate cancer was strengthened. Hoffman et al. (38) reported that men with cancers detected by prostate-specific antigen screening were more often younger than those men in whom cancer was clinically diagnosed. Our study also showed that the proportion

of screening-detected cancers was higher (54.6%) in those men ages  $\leq 60$  years than in those ages >60 years (28.1%), although prostate-specific antigen screening information was available for only 70% of subjects. However, although we analyzed the association between localized prostate cancer and isoflavones after excluding screening-detected tumors, results did not change. Isoflavone may be protective for localized prostate cancer only in men ages >60 years and may not have a protective effect in the early stage of prostate cancer in younger men.

Our study has several methodologic strengths. First, it was a prospective design, which diminishes the probability of recall bias that is inherent to case-control studies. Second, we evaluated isoflavone intake using a validated questionnaire, and participants had a large variation in isoflavone consumption. One reason for the inconsistent findings for the association between soy food and prostate cancer in previous studies may be errors in exposure measurements and the small exposure variation in Western subjects. Third, we adjusted possible confounding factors to remove associations with other substances. It is also possible that a lifestyle associated with a high intake of soy food may have contributed to the risk of prostate cancer. In this study, the associations between isoflavones and prostate cancer were strengthened after

**Table 3. RRs and 95% CIs for prostate cancer according to quartile of energy-adjusted intake of genistein, daidzein, miso soup, and soy food by stage**

	Intake by quartile				<i>P</i> <sub>trend</sub>
	Lowest	Second	Third	Highest	
<i>Localized prostate cancer</i>					
Genistein					
No. cases	54	51	73	42	
Person-years of follow-up	78,329	81,340	83,086	82,219	
Age/area-adjusted RR (95% CI)	1.00	0.81 (0.55-1.20)	1.21 (0.84-1.74)	0.67 (0.44-1.03)	0.31
Multivariate RR (95% CI)	1.00	0.77 (0.52-1.15)	1.16 (0.79-1.69)	0.59 (0.38-0.93)	0.15
Daidzein					
No. cases	51	54	71	44	
Person-years of follow-up	78,150	81,441	83,686	82,296	
Age/area-adjusted RR (95% CI)	1.00	0.90 (0.61-1.32)	1.22 (0.84-1.77)	0.75 (0.49-1.15)	0.50
Multivariate RR (95% CI)	1.00	0.86 (0.57-1.28)	1.20 (0.82-1.76)	0.66 (0.42-1.04)	0.27
Miso soup					
No. cases	44	55	65	56	
Person-years of follow-up	75,540	79,526	84,287	85,620	
Age/area-adjusted RR (95% CI)	1.00	0.96 (0.65-1.43)	0.99 (0.67-1.46)	0.83 (0.55-1.25)	0.40
Multivariate RR (95% CI)	1.00	0.95 (0.63-1.43)	0.98 (0.65-1.46)	0.78 (0.51-1.20)	0.29
Soy food					
No. cases	46	64	58	52	
Person-years of follow-up	77,644	81,454	83,017	82,857	
Age/area-adjusted RR (95% CI)	1.00	1.17 (0.80-1.72)	1.05 (0.70-1.55)	0.88 (0.58-1.32)	0.38
Multivariate RR (95% CI)	1.00	1.06 (0.71-1.57)	0.93 (0.61-1.40)	0.77 (0.50-1.19)	0.17
<i>Advanced prostate cancer</i>					
Genistein					
No. cases	16	23	15	20	
Person-years of follow-up	78,416	81,440	83,193	82,264	
Age/area-adjusted RR (95% CI)	1.00	1.46 (0.77-2.78)	1.02 (0.49-2.11)	1.32 (0.65-2.67)	0.69
Multivariate RR (95% CI)	1.00	1.60 (0.78-3.30)	1.11 (0.50-2.48)	1.26 (0.56-2.83)	0.88
Daidzein					
No. cases	14	23	18	19	
Person-years of follow-up	78,243	81,537	83,185	82,347	
Age/area-adjusted RR (95% CI)	1.00	1.66 (0.85-3.25)	1.40 (0.68-2.88)	1.47 (0.70-3.09)	0.45
Multivariate RR (95% CI)	1.00	1.67 (0.79-3.52)	1.39 (0.63-3.10)	1.43 (0.63-3.28)	0.58
Miso soup					
No. cases	11	18	18	27	
Person-years of follow-up	75,639	79,620	84,382	85,671	
Age/area-adjusted RR (95% CI)	1.00	1.51 (0.70-3.23)	1.58 (0.72-3.44)	2.21 (1.05-4.66)	0.04
Multivariate RR (95% CI)	1.00	1.73 (0.73-4.12)	1.65 (0.67-4.04)	2.79 (1.19-6.55)	0.02
Soy food					
No. cases	16	20	19	19	
Person-years of follow-up	77,736	81,557	83,096	82,923	
Age/area-adjusted RR (95% CI)	1.00	1.21 (0.62-2.35)	1.15 (0.58-2.27)	1.07 (0.53-2.15)	0.92
Multivariate RR (95% CI)	1.00	1.36 (0.65-2.85)	1.19 (0.55-2.56)	1.05 (0.47-2.34)	0.92

NOTE: Multivariate RRs were adjusted for age, area, smoking status, drinking frequency, marital status, body mass index, and intake of total fatty acids, dairy, vegetables, and fruits.

**Table 4. RRs and 95% CIs for prostate cancer according to quartile of energy-adjusted intake of genistein, daidzein, miso soup, and soy food by stage categorized according to age**

	Intake in quartile				<i>P</i> <sub>trend</sub>
	Lowest	Second	Third	Highest	
<i>&gt;60 y</i>					
Localized prostate cancer					
Genistein					
No. cases	42	37	38	27	
Person-years of follow-up	24,531	25,312	25,859	25,538	
Multivariate RR (95% CI)	1.00	0.81 (0.51-1.29)	0.79 (0.49-1.28)	0.52 (0.30-0.90)	0.03
Daidzein					
No. cases	41	36	42	25	
Person-years of follow-up	24,475	25,398	25,790	25,576	
Multivariate RR (95% CI)	1.00	0.80 (0.50-1.28)	0.90 (0.56-1.45)	0.50 (0.28-0.88)	0.04
Miso soup					
No. cases	34	32	44	34	
Person-years of follow-up	23,842	24,855	26,264	26,279	
Multivariate RR (95% CI)	1.00	0.72 (0.43-1.18)	0.87 (0.54-1.41)	0.65 (0.39-1.11)	0.22
Soy food					
No. cases	35	47	37	25	
Person-years of follow-up	24,270	25,488	25,866	25,616	
Multivariate RR (95% CI)	1.00	1.12 (0.71-1.79)	0.76 (0.46-1.27)	0.52 (0.29-0.90)	0.01
Advanced prostate cancer					
Genistein					
No. cases	15	15	11	12	
Person-years of follow-up	24,585	25,381	25,924	25,572	
Multivariate RR (95% CI)	1.00	1.16 (0.51-2.64)	0.82 (0.33-2.07)	1.03 (0.41-2.59)	0.87
Daidzein					
No. cases	11	19	11	12	
Person-years of follow-up	24,536	25,465	25,852	25,611	
Multivariate RR (95% CI)	1.00	1.97 (0.83-4.66)	1.16 (0.43-3.12)	1.49 (0.55-4.03)	0.75
Miso soup					
No. cases	9	15	13	16	
Person-years of follow-up	23,915	24,904	26,314	26,329	
Multivariate RR (95% CI)	1.00	2.01 (0.74-5.45)	1.79 (0.63-5.13)	2.86 (1.01-8.11)	0.07
Soy food					
No. cases	14	18	11	10	
Person-years of follow-up	24,332	25,539	25,933	25,659	
Multivariate RR (95% CI)	1.00	1.49 (0.66-3.34)	1.06 (0.43-2.54)	0.70 (0.25-1.95)	0.38
<i>≤60 y</i>					
Localized prostate cancer					
Genistein					
No. cases	14	19	24	19	
Person-years of follow-up	53,645	55,739	57,270	57,080	
Multivariate RR (95% CI)	1.00	1.10 (0.55-2.22)	1.51 (0.76-2.98)	1.18 (0.57-2.45)	0.49
Daidzein					
No. cases	14	21	20	21	
Person-years of follow-up	53,555	55,728	57,310	57,310	
Multivariate RR (95% CI)	1.00	1.17 (0.58-2.39)	1.44 (0.71-2.93)	1.38 (0.67-2.83)	0.32
Miso soup					
No. cases	14	20	24	18	
Person-years of follow-up	51,470	54,766	57,743	59,756	
Multivariate RR (95% CI)	1.00	0.96 (0.48-1.92)	1.02 (0.52-2.00)	0.82 (0.40-1.68)	0.62
Soy food					
No. cases	13	20	22	21	
Person-years of follow-up	52,997	55,845	57,205	57,687	
Multivariate RR (95% CI)	1.00	1.17 (0.58-2.39)	1.44 (0.71-2.93)	1.38 (0.67-2.83)	0.32
Advanced prostate cancer					
Genistein					
No. cases	4	5	3	9	
Person-years of follow-up	53,692	55,772	57,296	57,102	
Multivariate RR (95% CI)	1.00	1.05 (0.28-4.00)	0.44 (0.08-2.53)	2.00 (0.53-7.51)	0.32
Daidzein					
No. cases	3	5	5	8	
Person-years of follow-up	53,598	55,772	57,339	57,153	
Multivariate RR (95% CI)	1.00	1.42 (0.33-6.05)	1.21 (0.26-5.75)	2.46 (0.57-10.60)	0.23
Miso soup					
No. cases	2	4	6	9	
Person-years of follow-up	51,506	54,800	57,775	59,781	
Multivariate RR (95% CI)	1.00	1.66 (0.30-9.14)	1.78 (0.34-9.43)	2.65 (0.54-12.89)	0.20
Soy food					
No. cases	3	5	6	7	
Person-years of follow-up	53,044	55,871	57,239	57,708	
Multivariate RR (95% CI)	1.00	1.27 (0.30-5.42)	1.15 (0.26-5.05)	1.48 (0.35-6.20)	0.63

NOTE: Multivariate RRs were adjusted for age, area, smoking status, drinking frequency, marital status, body mass index, and intake of total fatty acids, dairy, vegetables, and fruits.

**Table 5. RRs of prostate cancer according to quartile of energy-adjusted intake of genistein, daidzein, miso soup, and soy food after excluding screening-detected tumors by stage in men aged more than 60 years old**

	Intake in quartile				<i>P</i> <sub>trend</sub>
	Lowest	Second	Third	Highest	
<i>&gt;60 y</i>					
<i>Localized prostate cancer</i>					
Genistein					
No. cases	32	42	23	17	
Person-years of follow-up	24,457	25,225	25,766	25,455	
Multivariate RR (95% CI)	1.00	0.73 (0.41-1.29)	0.71 (0.39-1.29)	0.52 (0.27-1.03)	0.07
Daidzein					
No. cases	31	22	28	15	
Person-years of follow-up	24,401	25,313	25,699	25,490	
Multivariate RR (95% CI)	1.00	0.69 (0.39-1.24)	0.92 (0.52-1.61)	0.49 (0.24-1.00)	0.13
Miso soup					
No. cases	25	17	30	24	
Person-years of follow-up	23,766	24,780	26,160	26,196	
Multivariate RR (95% CI)	1.00	0.58 (0.30-1.10)	0.95 (0.54-1.70)	0.73 (0.39-1.38)	0.67
Soy food					
No. cases	25	29	26	16	
Person-years of follow-up	24,199	25,383	25,782	25,538	
Multivariate RR (95% CI)	1.00	1.02 (0.58-1.81)	0.79 (0.43-1.46)	0.51 (0.26-1.01)	0.04
<i>Advanced prostate cancer</i>					
Genistein					
No. cases	18	14	10	11	
Person-years of follow-up	24,501	25,276	25,826	25,474	
Multivariate RR (95% CI)	1.00	0.97 (0.46-2.03)	0.62 (0.25-1.50)	0.85 (0.35-2.05)	0.50
Daidzein					
No. cases	13	19	11	10	
Person-years of follow-up	24,449	25,360	25,759	25,509	
Multivariate RR (95% CI)	1.00	1.69 (0.79-3.63)	0.96 (0.39-2.39)	1.10 (0.43-2.87)	0.85
Miso soup					
No. cases	12	14	10	17	
Person-years of follow-up	23,817	24,819	26,218	26,224	
Multivariate RR (95% CI)	1.00	1.32 (0.55-3.16)	1.10 (0.43-2.84)	1.97 (0.80-4.86)	0.18
Soy food					
No. cases	14	20	9	10	
Person-years of follow-up	24,246	25,427	25,835	25,569	
Multivariate RR (95% CI)	1.00	1.82 (0.86-3.86)	0.92 (0.37-2.30)	0.73 (0.27-2.00)	0.31

NOTE: Multivariate RRs were adjusted for age, area, smoking status, drinking frequency, marital status, body mass index, and intake of total fatty acids, dairy, vegetables, and fruits.

adjustment for several confounding factors. Fourth, response rate was high (~80%), and the proportion of subjects lost to follow-up was relatively low (0.1%).

On the other hand, the present study had several limitations. One was our inability to distinguish screening-detected cancer from total prostate cancer. It is possible that men who have health check-ups are more health conscious and may consume more soy food. However, such misclassification, if present, would lead to increase the risk of localized prostate cancer. Therefore, this inability to distinguish would not account for the decreased risk of localized prostate cancer. Another limitation was that the number of advanced prostate cancer cases was small. A larger sample size may have detected the positive effects of isoflavones on advanced prostate cancer with greater precision. Moreover, misclassification of exposure due to changes in isoflavone consumption during the study period might have occurred because we used information on consumption obtained at one point only. If present, however, such misclassification would underestimate the true relative risk.

In summary, we found that isoflavone intake was associated with a decreased risk of localized prostate cancer but tended to be associated with an increased risk of advanced prostate cancer. Recent interest has focused on whether isoflavones have chemopreventive effects. Given that Japanese consume isoflavones regularly throughout life, we do not yet know the period during which the effects of isoflavones on prostate cancer are preventive. Further research is required, including well-designed clinical trials in humans.

## Appendix A

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