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Research Article

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Soy Isoflavone Intake and Bladder Cancer Risk in Japan: From the Takayama Study

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Abstract

Background: There is growing evidence suggesting that soy isoflavones play a protective role in the development of cancer. However, few epidemiological studies have investigated the association between soy isoflavone intake and bladder cancer.

Methods: We evaluated the associations of soy and isoflavone intakes with bladder cancer incidence in a population-based prospective study in Japan. Subjects were 14,233 men and 16,584 women age 35 years or older in September 1992. Soy and isoflavone intakes were assessed via a validated food-frequency questionnaire, while controlling for total energy intake. Cancer incidence was mainly confirmed through regional population-based cancer registries. Bladder cancer was defined as code C67 according to the International Classification of Diseases and Health Related Problems, 10th Revision.

Results: During mean follow-up of 13.6 years, 120 men and 41 women had developed bladder cancer. After adjustments for multiple confounders, compared with the lowest quartile of soy food intake, the estimated hazard ratios for the second, third, and highest quartiles of soy food intake were 0.74, 0.52, and 0.55, respectively, in men (*P*-trend: 0.023). The corresponding values were 0.60, 0.75, and 0.64, respectively, in women (*P*-trend: 0.43). Similar inverse associations were observed between isoflavone intake and bladder cancer risk.

Conclusions: A significant decreased risk of bladder cancer was observed among men who had higher intakes of total soy and isoflavones.

Impact: Our finding on the potential benefit of consuming soy foods against bladder cancer is promising and warrants further studies. *Cancer Epidemiol Biomarkers Prev; 27(11); 1371–5.* ©2018 AACR.

Introduction

Isoflavones have been reported to have antioxidative, anti-inflammatory, and anti-cancer properties in animal models and in vitro studies (1–3). Thus, these biologically active compounds may have favorable effects on human health (4). Epidemiological studies have demonstrated that higher consumption of isoflavones is associated with lower risks of several cancers, especially among Asian people, who consume much higher volumes of soy foods, which are a rich source of isoflavones, than Western people do (5–9).

Bladder cancer is the ninth most common cancer worldwide (10). Men are over three times more likely than women to develop bladder cancer (10). Smoking is a major and established cause of bladder cancer (11). Apart from the likelihood that arsenic in drinking water increases the risk, there is little evidence regarding dietary factors in relation to bladder cancer. Bladder cancer incidence in Japan was low in spite of a relatively high rate of smoking in men (10, 12). Considering the fact that most soy isoflavone metabolites are excreted in urine and so the lining of the bladder is exposed to them, soy-based diet might be a protective factor against bladder cancer (13). However, the association between soy or isoflavone intake and bladder cancer risk has barely been investigated (14–17).

In this study, we evaluated the associations of soy and isoflavone intakes with bladder cancer incidence after considering several lifestyle factors in a population-based prospective study in Japan. We also assessed whether or not these associations were modified by smoking status.

Materials and Methods

Participants and design

A cohort study, the Takayama study, was conducted in Takayama City, Gifu, Japan. The details of the Takayama study have been described elsewhere (18). Briefly, 36,990 residents age 35 years or older who were not hospitalized were eligible to participate in September of 1992. A total of 31,552 residents (85.3%) completed a self-administered questionnaire with items about demography, anthropometric characteristics, medical history, physical activity, smoking status, alcohol consumption, and diet. For women, menopausal status was also recorded. Smokers were defined as people who had smoked a total of at least 20 packs of cigarettes throughout life. Former and current smokers were asked to record cumulative smoking years. Physical activity was assessed by asking participants how much time on average they

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spent on the listed activities of various intensities during the previous year. The number of hours per week spent on each activity was multiplied by the corresponding energy expenditure, expressed as a metabolic equivalent (MET), and the sum of the product was counted as the physical activity score (MET·h/week). The details including the validity are described elsewhere (19).

Dietary data, including soy intake, were assessed using a 169-item semi-quantitative food frequency questionnaire (FFQ). In the FFQ, participants were asked how often on average they consumed each of the food items listed, and what the usual serving size of each item was during the previous year. Nine soy food items were included: miso soup, tofu (soy bean curd), deep-fried tofu, fried tofu, freeze-dried tofu, natto, houba-miso, soymilk, and boiled soy beans. These food items and some other dishes that contained soy products as ingredients were used to obtain estimates of the intake of soy foods. The intake of each nutrient and food was estimated from the frequency of intake and portion size using the Japanese Standard Table of Food Composition (5th Revised and Enlarged Edition), published by the Science and Technology Agency of Japan (20). Isoflavones were regarded as the sum of daidzein and genistein, and calculated on the basis of previously published data on isoflavone concentrations in soy foods (21). The validity and reproducibility of the questionnaire have been reported as reliable (22). Spearman correlation coefficients between the FFQ and 12-day diet records kept over a 1 year period for intakes of total energy, soy food, isoflavone, and alcohol were 0.44, 0.75, 0.75, and 0.72, respectively, for men. For women, the corresponding values were 0.53, 0.68, 0.62 and 0.64, respectively.

Outcomes and follow-up

After we excluded 735 people who were diagnosed with bladder cancer before the baseline, and/or reported a positive history of any cancer in the baseline questionnaire, 14,233 men and 16,584 women were included in the analyses. The follow-up was conducted until the end of March 2008. During mean follow-up period of 13.6 years, 120 men and 41 women developed bladder cancer.

Data on death and emigration were obtained from residential registers or family registers. Cause of death was identified from death certificates provided by the Legal Affairs Bureau. During the study period, 1,812 persons (5.9%) moved out of the study area. Among 242 subjects whose date of emigration was unknown (0.8%), their last date of residence in the study area was assigned as their censored date.

The incidence of cancer was mainly confirmed through two regional population-based cancer registries in Gifu. Information was also collected from a local base hospital, which played a leading role in providing medical care for the residents in the study area. The causes of cancer were coded according to the International Classification of Diseases and Health Related Problems, 10th Revision (ICD-10). Bladder cancer was defined as code C67. The mortality-to-incidence ratio for stomach cancer was 0.27, and 14.9% of patients were ascertained by death certificate-only registration. For such cases, a backward tracking review of the incidence date was conducted based on the description given in the death certificate. As a result, only 7.5% of patients had an unknown incidence date before the date of death, indicating satisfactory completeness of cancer registration in this cohort. This study was approved by the institutional review board of the Gifu University Graduate School of Medicine.

Statistical analyses

In the assessment of soy and isoflavone intakes, the residual method proposed by Willett was used to control for total energy intake (23). Study participants were categorized into quartile groups (Q1, Q2, Q3, or Q4) according to their energy-adjusted intakes of soy and isoflavones. The characteristics of the participants were calculated as the mean (standard deviation) or number (percentage) in each category, according to the quartile groups of soy intake for each sex.

Relative risks and 95% confidence intervals (CIs) for bladder cancer were estimated for the quartile groups of soy and isoflavone intake using the Cox proportional hazards regression model. The end of follow-up was determined as the date of bladder cancer diagnosis, the date of emigration from the study area, the date of death, or the end of the study, whichever came first. The reference group was set as the lowest quartile of soy and isoflavone intake. Covariates included in the models were the following potential confounders: for men, age (years, continuous), body mass index (quartiles), physical activity score (continuous), smoking status (never, past, current smoker who had smoked for 30 years or less, current smoker who had smoked for 31 years or more), alcohol consumption (g/day), and years of education ($\leq$8 y, 9–11 y, 12–14 y, $\geq$15 y) were included. For women, age, body mass index, physical activity score, smoking status (never, past, current smoker), alcohol consumption, years of education, and menopausal status (premenopausal, postmenopausal) were used. Indicator terms were specifically created for missing data on categorical covariates. Tests for a linear trend were conducted in the Cox model by using the median values of each category for soy and isoflavone intake.

Because smoking is a convincing risk factor for bladder cancer, we conducted additional analyses after dividing the subjects into ever and never smokers. Tests for interaction were performed using the likelihood ratio test.

All analyses were conducted using the SAS program, version 9.4 (SAS Institute, Cary, NC). *P* values were calculated by a two-sided test. A p value of less than 0.05 was considered statistically significant in all analyses.

Results

The characteristics of the participants are shown as the mean (standard deviation) or the percentage of each category according to the quartile groups of energy-adjusted soy food intake in Table 1. Among both men and women, participants in the higher quartile of soy intake were older at baseline. The participants among the lowest quartile of soy intake tended to be ever smokers and heavy drinkers of alcohol. Higher soy intake was associated with lower levels of education. Women with a higher soy intake tended to be postmenopausal.

In the multivariate-adjusted model, significantly decreased relative risks of bladder cancer were observed in the highest group of soy and isoflavone intake among the men (Table 2). The linear trends of the associations were statistically significant. Although similar inverse associations were observed between soy or isoflavone intake and the risk of bladder cancer in women, these associations did not reach statistically significance. The p values for interaction by sex on the association with bladder cancer were 0.97 for soy food intake and 0.91 for isoflavone intake.

Intakes of both daidzein and genistein were also inversely associated with bladder cancer risk in men. Compared with the

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Table 1. Characteristics of study subjects at baseline in Takayama study

Quartile of soy food intake[a] (range)	Men Q1 (⇐62 g)	Men Q2 (⇐87 g)	Men Q3 (⇐121 g)	Men Q4 (⇐1051 g)	*P*	Women Q1 (⇐62 g)	Women Q2 (⇐87 g)	Women Q3 (⇐121 g)	Women Q4 (⇐1001 g)	*P*
n	*3559*	*3558*	*3558*	*3558*		*4146*	*4146*	*4146*	*4146*	
Age (y)[b]	50.4 (10.8)	54.8 (12.3)	57.1 (12.6)	58.3 (12.2)	<0.001	52.7 (12.5)	56.0 (13.4)	57.7 (13.3)	58.7 (12.8)	<0.001
Body mass index (kg/m^2)[b]	22.7 (2.8)	22.5 (2.8)	22.3 (2.8)	22.4 (2.8)	<0.001	22.0 (2.9)	21.9 (2.9)	21.9 (2.9)	22.1 (3.0)	<0.001
Diet intake[b]										
Total energy (kcal/day)	2920 (854)	2411 (764)	2382 (797)	2697 (955)	<0.001	2388 (843)	1954 (693)	1969 (706)	2194 (819)	<0.001
Soy food (g/day)	54.1 (27.5)	70.1 (30.1)	99.2 (32.8)	185.2 (89.3)	<0.001	50.0 (26.3)	65.5 (26.5)	92.0 (28.5)	165.8 (79.2)	<0.001
Isoflavone (mg/day)	25.9 (14.3)	32.5 (15.8)	44.6 (18.4)	75.3 (36.4)	<0.001	24.5 (14.2)	30.8 (14.4)	42.0 (16.6)	68.5 (33.2)	<0.001
Alcohol consumption (g/day)[b]	50.5 (48.4)	38.1 (38.1)	36.2 (37.0)	39.8 (38.6)	<0.001	11.0 (22.8)	6.9 (14.1)	6.0 (13.0)	6.7 (14.8)	<0.001
Physical activity score[b] (METs·h/week)	29.1 (43.6)	26.0 (38.4)	25.6 (38.5)	28.6 (43.1)	<0.001	18.7 (28.6)	18.6 (29.2)	19.2 (28.9)	19.4 (30.0)	0.48
Smoking status[c]										
Never	531 (15.2%)	566 (16.4%)	593 (17.2%)	606 (17.7%)	<0.001	915 (76.2%)	3055 (82.1%)	3132 (85.3%)	3118 (86.4%)	<0.001
Past	826 (23.7%)	986 (28.5%)	1101 (32.0%)	1193 (34.8%)		198 (5.2%)	191 (5.1%)	145 (4.0%)	151 (4.2%)	
Current	2131 (61.1%)	1909 (55.2%)	1748 (50.8%)	1634 (47.6%)		715 (18.7%)	474 (12.7%)	396 (10.8%)	341 (9.5%)	
Length of education[c]										
≤8 years	488 (13.8%)	782 (22.3%)	920 (26.2%)	1060 (30.2%)	<0.001	781 (19.1%)	1114 (27.4%)	1262 (31.0%)	1424 (35.0%)	<0.001
9–11 years	1295 (36.7%)	1210 (34.4%)	1210 (34.5%)	1228 (35.0%)		1730 (42.2%)	1533 (37.7%)	1548 (38.0%)	1565 (38.5%)	
12–14 years	1234 (35.0%)	1120 (31.9%)	1006 (28.7%)	911 (25.9%)		1376 (33.6%)	1219 (29.9%)	1091 (26.8%)	928 (22.8%)	
≥15 years	512 (14.5%)	401 (11.4%)	374 (11.0%)	313 (8.9%)		210 (5.1%)	206 (5.1%)	177 (4.3%)	149 (3.7%)	
Menopausal status[c] (premenopausal)						2143 (52.6%)	1643 (40.7%)	1419 (35.1%)	1169 (29.1%)	<0.001

[a]Soy food intakes adjusted for total energy intake by Willett method were categorized into quartile groups.
[b]Mean (standard deviation).
[c]Number (percentage).

lowest quartile of intake, the estimated hazard ratios (HRs) of bladder cancer in Q2, Q3, and Q4 were 0.79 (95% CI: 0.48–1.32), 0.68 (95% CI: 0.41–1.15), and 0.54 (95% CI: 0.32–0.91), respectively, for daidzein (*P*-trend: 0.021) and 0.75 (95% CI: 0.45–1.24), 0.64 (95% CI: 0.38–1.06), and 0.51 (95% CI: 0.30–0.87), respectively, for genistein (*P*-trend: 0.014).

In the analyses after dividing the subjects into ever and never smokers, there was a significant association between higher soy

Table 2. Associations of soy food and isoflavone intake with bladder cancer incidence in Takayama study

	Mean intakes	No. of subjects	No. of incidence	Person-years	Age-adjusted hazard ratio (95% CI)	Multivariate-adjusted hazard ratio (95% CI)[b]
Men						
Soy food intake[a]	(g/day)					
Q1	47	3559	32	48736	1.00 (ref)	1.00 (ref)
Q2	77	3558	33	46952	0.74 (0.46–1.22)	0.74 (0.45–1.22)
Q3	107	3558	25	45791	0.51 (0.30–0.86)	0.52 (0.31–0.89)
Q4	160	3558	30	46251	0.54 (0.32–0.90)	0.55 (0.33–0.92)
linear trend *P*					0.018	0.023
Isoflavone intake[a]	(mg/day)					
Q1	21	3559	31	48973	1.00 (ref)	1.00 (ref)
Q2	35	3558	31	47040	0.76 (0.46–1.25)	0.75 (0.45–1.24)
Q3	47	3558	30	45927	0.63 (0.38–1.05)	0.64 (0.38–1.07)
Q4	69	3558	28	45789	0.51 (0.30–0.86)	0.51 (0.30–0.87)
linear trend *P*					0.011	0.014
Women						
Soy food intake[a]	(g/day)					
Q1	45	4146	12	58700	1.00 (ref)	1.00 (ref)
Q2	72	4146	8	57619	0.54 (0.22–1.33)	0.60 (0.24–1.49)
Q3	97	4146	11	57126	0.69 (0.30–1.56)	0.75 (0.33–1.74)
Q4	142	4146	10	57439	0.58 (0.25–1.36)	0.64 (0.27–1.51)
linear trend *P*					0.33	0.43
Isoflavone intake[a]	(mg/day)					
Q1	21	4146	12	58937	1.00 (ref)	1.00 (ref)
Q2	33	4146	5	57760	0.33 (0.11–0.93)	0.36 (0.13–1.04)
Q3	44	4146	15	57097	0.88 (0.41–1.90)	0.94 (0.43–2.06)
Q4	63	4146	9	57091	0.49 (0.20–1.16)	0.53 (0.22–1.28)
linear trend *P*					0.32	0.40

[a]Soy and isoflavone intakes were adjusted for total energy intake by Willet method.
[b]Estimated hazard ratio after adjustments for age (years), body mass index (quartiles), smoking status (never, past, current smoker for 30 years or less, current smoker for 31 years or more), physical activity score, alcohol consumption (g/day), and education years (⇐8 y, 9–11 y, 12–14 y,> = 15 y) for men. For women, age, body mass index, smoking status (never, past, current smoker), physical activity score, alcohol consumption, education years, and menopausal status (premenopausal, postmenopausal).

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Table 3. Associations between soy food intake and bladder cancer incidence according to smoking status

Soy food intake[a]	No. of subjects	No. of incidence	Person-years	Multivariate-adjusted hazard ratio (95% CI)[b]
Men				
Never smokers				
Q1	531	4	7241	1.00 (ref)
Q2	566	3	7625	0.54 (0.12–2.43)
Q3	593	5	7764	0.66 (0.17–2.50)
Q4	606	5	7931	0.62 (0.16–2.37)
linear trend *P*				0.65
Ever smokers				
Q1	2957	27	40493	1.00 (ref)
Q2	2895	29	38236	0.80 (0.47–1.37)
Q3	2849	20	36614	0.53 (0.29–0.96)
Q4	2827	23	36856	0.53 (0.30–0.94)
linear trend *P*				0.022
Women				
Never smokers				
Q1	2915	7	41719	1.00 (ref)
Q2	3055	5	42965	0.59 (0.19–1.87)
Q3	3132	6	43750	0.62 (0.21–1.88)
Q4	3118	7	43661	0.72 (0.25–2.09)
linear trend *P*				0.68
Ever smokers				
Q1	913	4	12678	1.00 (ref)
Q2	665	2	8869	0.94 (0.15–5.88)
Q3	541	2	7123	0.75 (0.13–4.30)
Q4	492	0	6609	0.00 (0.00, -)
linear trend *P*				0.15

[a]Soy food intakes were adjusted for total energy intake by Willet method.
[b]Estimated hazard ratio after adjustments for age (years), body mass index (quartiles), smoking status (never, past, current smoker for 30 years or less, current smoker for 31 years or more), physical activity score, alcohol consumption (g/day), and education years (⇐8 y, 9–11 y, 12–14 y,> = 15 y) for men. For women, age, body mass index, smoking status (never, past, current smoker), physical activity score, alcohol consumption, education years, and menopausal status (premenopausal, postmenopausal).

food intake and decreased risks of bladder cancer among men who had ever smoked (Table 3). The interactions by smoking status on the association between soy food intake and bladder cancer were not statistically significant in both men ($P = 0.50$) and women ($P = 0.28$).

The World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) judged the intake of tea, vegetables, and fruits as "limit-suggestive" factors in relation to a decreased risk of bladder cancer in 2015 (11). When we undertook an additional adjustment for fruit and vegetable intake, the results were not altered in men and women. For example, the estimated HRs of bladder cancer were 0.56 (95% CI: 0.33–0.95) in Q4 of soy food intake in men (*P*-trend: 0.033). In addition, an additional adjustment for the frequency of tea consumption did not substantially alter the results; the estimated HRs of bladder cancer were 0.56 (95% CI: 0.33–0.93) in Q4 of soy food intake in men (*P*-trend: 0.028).

To eliminate those who might have had undetected bladder cancer at baseline, we re-analyzed the data after excluding 10 patients who were diagnosed with bladder cancer during the first 2 years of follow-up. None of the results were substantially altered.

Discussion

To the best of our knowledge, this is the first study to find that higher intake of soy isoflavones was associated with a decreased risk of bladder cancer. However, our study might have had minimal statistical power for finding a significant association in women. The results of four previous epidemiological studies on the association between soy or isoflavone intake and the risk of bladder cancer have been inconsistent (14–17). One Japanese prospective study observed no significant difference in bladder cancer mortality between daily and non-daily consumers of soybean paste soup, although soy or isoflavone intake as a whole was not assessed (17). Another European prospective study reported no significant association between isoflavone intake and bladder cancer incidence (14); however, the amount of isoflavone intake among the majority of the subjects (mean: 1.5 mg/day) might have been too small to assess any significant association, although the estimates of dietary intake should not be compared with those based on different questionnaires. Two Chinese cohort studies among men in Singapore and men and women combined in Shanghai observed two-fold increases in the risk of bladder cancer among those with the highest intake of soy isoflavones (15, 16), which is in contrast to our finding. Differences among the types of soy foods covered in the questionnaires and the characteristics of the subjects might have caused these discordant results. Nonetheless, there is limited evidence on the impact of soy isoflavone intake on bladder cancer, thus the association needs to be further evaluated.

The effect of genistein on the inhibition of bladder cancer development was observed in a randomized placebo-controlled trial (24). In 59 patients with urothelial bladder cancer before surgery, a significantly greater reduction in epidermal growth factor receptor phosphorylation staining in bladder cancer tissue was observed in the treatment group receiving oral daidzein than in the placebo group. Experimental studies have shown that genistein in the range of concentrations in human urine excretion inhibits the growth and proliferation of bladder cancer cells by inducing cell cycle arrest and apoptosis (25, 26). In another study, genistein was found to inhibit tumor angiogenesis (27). Daidzein also reduces cell viability and induces apoptosis in bladder cancer cells (28). In addition, treatment with soy phytochemical concentrates inhibit lung metastases of bladder cancer cells (29).

One merit of our study was its prospective design, in which information on various factors including soy intake was collected before a diagnosis of bladder cancer occurred. Thus, recall bias would not systematically occur at baseline between subjects with bladder cancer and those without. A good participation rate, long follow-up, the use of a validated FFQ, and the consideration of several confounding factors were the other strengths of our study. The validated FFQ that listed various types of soy foods enabled precise estimates and greater variations in the intake of soy or isoflavone foods. The FFQ was designed to measure an individual's relative intake of foods and nutrients, rather than absolute values. The data presented in the tables may have been overestimated by the questionnaire; the estimated values of soy food intake obtained from the FFQ were 35% higher than the estimates based on 12-day dietary records.

One limitation of our study was that the information on exposures was collected at baseline only and changes in lifestyle habits were not evaluated during the follow-up period. The consumption of soy foods in Japan had decreased after this study started (30). Dietary patterns or lifestyle habits might have changed due to preclinical signs or underlying disease. However, the exclusion of participants with cancer that occurred during the first two years of follow-up did not change the results. Although

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several lifestyle factors were adjusted in the analyses, we could not fully exclude the possibility of residual confounders. In addition, we could not have detected the modifying effect of smoking on the association between soy intake and bladder cancer due to the low rates of male never smokers and female ever smokers among subjects.

In conclusion, this prospective study conducted in Japan demonstrated a decreased risk of bladder cancer in men who had higher intakes of total soy and isoflavones. Our finding on the potential benefit of consuming soy foods against bladder cancer is intriguing, and warrants further studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: K. Wada, C. Nagata
Development of methodology: C. Nagata
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Wada, A. Hori, S. Tanabashi, S. Matsushita, N. Tokimitsu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K. Wada, M. Tsuji, T. Tamura, K. Konishi, Y. Goto, F. Mizuta, S. Koda, T. Uji
Writing, review, and/or revision of the manuscript: K. Wada, C. Nagata
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Wada

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