Short Communication

Soy and Isoflavone Consumption in Relation to Prostate Cancer Risk in China[1]

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Abstract

This case-control study in China evaluated the effect of soy food consumption and isoflavones (genistein and daidzein) on the risk of prostate cancer. One hundred and thirty-three cases and 265 age- and residential community-matched controls between the ages of 50 and 89 years were interviewed in person between 1989 and 1992. Usual consumption of soy foods and isoflavones was assessed using a food frequency questionnaire developed in China and a nutrient database developed and validated in Asian-American populations. The age- and total calorie-adjusted odds ratio (OR) of prostate cancer risk comparing the highest tertile of tofu intake to the lowest tertile was 0.58 [95% confidence interval (CI), 0.35–0.96]. There were also statistically significant associations comparing the highest quartile of intake of soy foods (OR, 0.51; 95% CI, 0.28–0.95) and genistein (OR, 0.53; 95% CI, 0.29–0.97) with the lowest quartiles. There was also an indication of a reduced risk associated with intake of daidzein (OR, 0.56; 95% CI, 0.31–1.04 for the highest *versus* lowest quartile). Our results indicate a reduced risk of prostate cancer associated with consumption of soy foods and isoflavones. These findings should be confirmed in longitudinal follow-up studies in populations with varying risk of prostate cancer.

Introduction

Prostate cancer is the second most commonly diagnosed cancer among Chinese-American males, contributing to 16% of the overall cancer burden in this population (1–3); however, very little is known regarding the etiology of prostate cancer. The average annual incidence rate of prostate cancer between 1988 and 1992 among Chinese men in the United States was 15 times higher than that of their counterparts living in Shanghai and Tianjin (45.8 *versus* 3.2 per 100,000; Ref. 1). These observed differences in prostate cancer incidence led to the hypothesis that the Westernization of lifestyle and diet may play a role in prostate cancer etiology.

Recently, researchers have focused on the protective effect of phytoestrogens in the etiology of hormone-dependent cancers, including breast and prostate cancer, and some epidemiological studies have examined the relationship between soy and prostate cancer (4–7). This study examined the association between intake of soy-based foods and isoflavones and the risk of prostate cancer in a case-control study conducted in 12 cities in China.

Materials and Methods

The methods of the study have been published in detail elsewhere (8, 9). In brief, case patients were newly diagnosed with pathologically confirmed prostate cancer [International Classification of Diseases (ICD)-9 code 185] between 1989 and 1992 from 12 cities throughout China. Cases were identified through major teaching hospitals in these cities. For each index case, two control subjects matched to the case by 5-year age group were randomly selected from the registry roster of the residential community of the case by physical examination patient. Control subjects were screened for prostate cancer, and only those with negative results were invited to participate in the study. The overall response rate was 80% (79% for cases and 80% for controls). The final study sample for this report consisted of 133 case patients and 265 control subjects.

Information on demographic characteristics, marital and occupational history, weight and height, dietary habits, physical activity, medical history, and family history of cancer was ascertained from the subjects by face-to-face interviews. The reference period for assessing diet and other lifestyle factors was between 1980 and 1985. The development of the food frequency questionnaire has been described in detail elsewhere (9–11).

Combined soy foods was defined as a summation of six food items: soy bean milk; tofu (bean curd); dried/fried bean curd; fermented beans; dry bean milk cream; and fermented bean milk. Daily consumption of all soy items (in grams) and genistein and daidzein (in milligram) was calculated using a nutrient database developed by colleagues (12). The Wilcoxon rank-sum test was used to compare the levels of these food items and nutrients between cases and controls. ORs[3] and 95% CIs associated with each tertile of tofu and each quartile of combined soy foods, genistein, and daidzein adjusted for age and total calories were modeled by unconditional logistic regression (13). We included a measure for total fiber in our initial models to assess the possible confounding effect of fruits

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[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 Characteristics of subjects by case-control status, China, 1989–1992

	Cases (N = 133) (%)	Controls (N = 265) (%)	P
Age (yrs)			
40–59	9.4	10.5	0.97
60–69	40.0	40.4	
≥70	50.0	49.1	
Education			
Illiterate	13.0	10.3	0.99
Primary school	32.6	39.0	
High school	29.7	27.6	
College	24.6	22.7	
Marital status			
Currently married	91.3	90.9	0.88
Divorced/widowed	8.7	9.1	
Socioeconomic status			
Low	51.5	46.6	0.12
Medium	43.4	51.2	
High	5.1	2.2	
Body mass index, kg/cm^2 (mean)	22.8	22.8	1.00
Ever smoked cigarettes	60.9	62.1	0.90
Ever used alcohol	67.2	57.0	0.07
Ever had benign prostate hyperplasia	48.3	13.6	<0.001
Ever had prostatitis	24.3	6.1	<0.001

Table 2 Mean and median consumption of tofu (daily gram units), combined soy foods (daily gram units), genistein (daily milligram units), and daidzein (daily milligram units) by case-control status, China, 1989–1992

	Cases (N = 133)		Controls (N = 265)		P^a
	Mean	Median	Mean	Median	
Tofu (g/day)	26.9	15.6	31.3	28.5	0.024
Combined soy foods (g/day)	70.1	49.9	83.8	52.9	0.190
Genistein (mg/day)	40.7	30.0	47.9	35.2	0.137
Daidzein (mg/day)	24.0	17.5	27.8	19.2	0.155

[a] Wilcoxon rank-sum test comparing the median consumption levels between cases and controls.

and vegetables, but left it out in the final models because its inclusion did not change the magnitudes of the ORs for soy foods or isoflavones.

Results

The distributions of age, educational, marital status, socioeconomic index, body mass index, and smoking habits were similar between cases and controls; however, cases were more likely to report ever using alcohol, history of benign prostatic hyperplasia, and prostatitis (Table 1).

Table 2 shows that case patients consumed lower levels of tofu, combined soy foods, genistein, and daidzein than control subjects; however, only the difference in tofu consumption was statistically significant (P = 0.024).

The adjusted ORs for each level of nutrient and phytoestrogen intake are presented in Table 3. The highest tertile of tofu was associated with a >40% decrease in the risk of prostate cancer compared with the lowest tertile (OR, 0.58; $P <$ 0.05). The trend for the reduction in risk of each level of tofu consumption was also statistically significant. The highest quartiles of combined soy food, genistein, and daidzein were also associated with a 50% decrease in risk compared with the lowest quartile (OR, 0.51–0.56), although the dose-response trends were not statistically significant.

Discussion

Our study is the first study in an Asian population to examine the association of prostate cancer risk with isoflavones in soy-based products. Our results support previous investigations showing a reduced risk of prostate cancer with consumption of soy and isoflavones (4–7). In addition to epidemiological studies, many *in vitro* and *in vivo* studies have concurred on the protective effects of phytoestrogen against prostate cancer (14–19).

Several limitations may affect the results of our study. Misclassifications of soy intake may have occurred due to measurement error associated with the dietary instrument or to the reference period (1980–1985); however, such misclassification was likely nondifferential, which would have biased our results toward null. Differential recall bias is possible because cancer patients, regardless of any dietary changes made after the diagnosis, may recall differently from the controls; however, the information regarding soy foods and prostate cancer was not widespread among the general public in China, and it is unlikely that the case patients would have altered the amount of soy consumed after the cancer diagnosis. If we assumed that case patients had somehow learned that soy may slow the progression of prostate cancer and had increased the consumption of soy after diagnosis of cancer, our results would have been biased toward null. Longitudinal follow-up studies would help to clarify the effects of phytoestrogen on prostate cancer risk without the potential bias of the differential recall. Another limitation is that, depending on which nutrient database is used, the values of phytoestrogen calculated may be different. The nutrient values of the same food may be different in different databases due to the variability in laboratory techniques, food sources, growing methods, and so forth. Lastly, we examined the association between soy foods or isoflavones and the risk of prostate cancer without adjusting for all other possible nutrients; therefore, the reduced risk of prostate cancer may not be entirely attributable to soy foods or isoflavones.

Studies with well-quantified soy product or isoflavone consumption such as ours and the study by Kolonel *et al.* (6) show that the level of isoflavone is related to its association with reduced prostate cancer risk. If the risk-lowering effect of soy only occurs at a certain level, the studies of homogeneous populations with low levels of soy consumption would not have the capability to detect the protective effect. For example, the study by Strom *et al.* (7), which comprised only Caucasian subjects (83 cases and 107 controls), showed a protective trend of genistein and daidzein against prostate cancer, although neither was statistically significant. Similarly, another study by Horn-Ross *et al.* (20) in non-Asian breast cancer patients (1326 cases and 1657 controls) found that phytoestrogens had little protective effect against breast cancer. In both studies of Western subjects, the mean daily levels of isoflavones (sum of genestein, daidzein formononetin, and biochanin A) were extremely low (<3 mg), even though both studies used recently developed phytoestrogen databases tailored to capture the phytoestrogen levels of the Western diet (12, 21). In contrast, a Japanese study reported a mean daily total isoflavone consumption of 47.2 mg (22). Although our study only measured the mean daily levels of two major isoflavones (genestein and daidzein), the combined total of the two (76 mg) already far exceeded the total isoflavones in the studies with Western subjects. Future studies should include subjects with wide var-

Table 3 ORs and 95% CIs for prostate cancer in relation to tofu, combined soy foods, genistein, and daidzein, China, 1989–1992

	Cases (*n*)	Controls (*n*)	OR[a]	95% CI
Tofu (g/day)[b]				
<14.3	51	98	1.00	
14.3–34.5	26	62	0.77	0.45–1.29
>34.5	31	76	0.58	0.35–0.96
			(*P* for linear trend = 0.032)	
Combined soy foods (g/day)[c]				
<27.5	32	57	1.00	
27.5–52.9	25	62	0.64	0.36–1.16
52.9–111.8	31	59	0.77	0.44–1.37
>111.8	20	58	0.51	0.28–0.95
			(*P* for linear trend = 0.061)	
Genistein (mg/day)[c]				
<17.9	32	55	1.00	
17.9–34.5	20	55	0.60	0.33–1.01
34.5–62.0	27	58	0.70	0.40–1.23
>62.0	21	57	0.53	0.29–0.97
			(*P* for linear trend = 0.058)	
Daidzein (mg/day)[c]				
<10.0	29	54	1.00	
10.0–19.1	21	56	0.67	0.37–1.21
19.1–36.3	29	58	0.79	0.45–1.38
>36.3	21	57	0.56	0.31–1.04
			(*P* for linear trend = 0.116)	

[a] Adjusted for total calories and age.
[b] ORs calculated by tertile.
[c] ORs calculated by quartile.

iation in the levels of soy consumption to capture the potential protective effect of soy or isoflavones.

In summary, our results suggested that consumption of soy foods is associated with reduced risk of prostate cancer among men in China. These findings should be confirmed in longitudinal follow-up studies in different populations. Concurrent evaluation of other nutrients is also needed to assess the independent contribution of soy foods to the reduced risk of prostate cancer. In addition to the epidemiological evidence, several biological mechanisms through which soy phytoestrogen reduces the risk of prostate cancer have been proposed, including inhibition of angiogenesis (18), inhibition or stimulation of regulatory proteins in the cell cycle (23), and inhibition of signal transduction pathway involving epidermal growth factor (24). Future studies, especially prospective studies, are needed to confirm the role of isoflavones and the underlying mechanisms involved.

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