Short Communication

Dietary Soy and Increased Risk of Bladder Cancer: the Singapore Chinese Health Study[1]

Can-Lan Sun,[2] Jian-Min Yuan, Kazuko Arakawa, Siew-Hong Low, Hin-Peng Lee, and Mimi C. Yu

USC/Norris Comprehensive Cancer Center, University of Southern California Keck School of Medicine, Los Angeles, California 90089 [C-L. S., J-M. Y., K. A., M. C. Y.], and Department of Community, Occupational and Family Medicine, National University of Singapore, Singapore [S-H. L., H-P. L.]

Abstract

The association between soyfood consumption and subsequent bladder cancer risk was investigated in a population-based cohort study, the Singapore Chinese Health Study. As of December 31, 2000, 329,848 person-years of follow-up were accrued. Sixty-one histologically confirmed incident bladder cancer cases were identified. Information on soyfood consumption at baseline was obtained through in-person interviews using a validated dietary questionnaire. Relative risks and 95% confidence intervals were calculated using the Cox proportional hazard regression method. High intake of soyfood was statistically significantly related to an elevated risk of bladder cancer. Relative to the lowest quartile of energy-adjusted total soy intake (<36.9 g/1000 Kcal), the highest quartile of total soy intake (≥92.5 g/1000 Kcal) was associated with a 2.3-fold increase in bladder cancer risk (95% confidence interval = 1.1–5.1) after adjustment for cigarette smoking and level of education. Similar results were obtained for intakes of soy protein and soy isoflavones. The soyfood-bladder cancer risk association did not differ significantly between men and women and was not explained by other dietary factors. The soy-cancer relationship became stronger when the analysis was restricted to subjects with longer (≥3 years) duration of follow-up. To our knowledge, this is the first epidemiological report on the effect of dietary soy on bladder cancer risk.

Introduction

The correlation between high consumption of soyfoods and low incidence rates of cancers of the breast, prostate, and colon in Asian populations, particularly among Japanese and Chinese, suggests that soyfoods may exert protective effects in the development of these malignancies (1). On the other hand, two recent studies have raised concerns that soy intake may adversely impact on risks of cognitive impairment and infant leukemia (2, 3).

To our knowledge, there are no epidemiological data on the relationship between dietary soy and bladder cancer risk. There are limited data from *in vitro* and nonhuman *in vivo* studies suggesting that soy isoflavones may protect against bladder cancer development (4, 5). In this study, we examined adult soy intake in relation to bladder cancer risk within a prospective cohort study of Singapore Chinese whose intake levels of soy are among the highest in the world.

Subjects and Methods

The design of the Singapore Chinese Health Study has been described in detail elsewhere (6). Briefly, 63,257 Chinese men (27,959) and women (35,298) ages 45–74 years were recruited into the population-based residential cohort between April 1993 and December 1998. Eighty-five percent of eligible subjects participated in the study. At recruitment, each participant was interviewed in-person by a trained interviewer using a subsequently validated 165-item food frequency questionnaire. The structured questionnaire also requested demographic information, lifetime use of tobacco, current alcohol drinking pattern, current physical activity profile, reproductive history (women only), occupational exposures, medical history, and family history of cancer.

There are seven common soyfoods (all are nonfermented) in the Singapore Chinese diet, including plain tofu, taupok, taukwa, foopei, foojook, tofu-far, and soybean drink. Taupok is taukwa plus oil and tofu-far is tofu plus syrup. We used the following algorithm to estimate an overall soy intake for each study subject: water accounts for 89% of cooked plain-tofu by weight; 69% of cooked taukwa; 58% of cooked foopei; 54% of cooked foojook; and 92% of soybean drink. Thus, we determined that 1 g of taukwa is equivalent to 2.8 g (31/11) of plain tofu. Similarly, 1 g of foopei and foojook are equivalent to 3.8 g (42/11) and 4.2 g (46/11) of plain tofu, respectively. Finally, 1 g of soybean drink is equivalent to 0.73 g (8/11) of plain tofu. The total soy intake for a given subject was the summation of all soyfoods expressed in units of plain tofu equivalent. Previously, we had measured concentrations of genistein, daidzein, and glycitein in market samples of common soyfoods in Singapore (6). Total soy isoflavone intake for a given subject was estimated from the summation of genistein, daidzein, and glycitein contents of all seven soyfoods. Likewise, total soy protein intake for each study subject was calculated from the protein contents of soyfoods listed in the Singapore Food Composition Table (6).

Identification of incident cancer cases and deaths among cohort members was accomplished through regular record linkage of the cohort database with databases for the nationwide Singapore Cancer Registry and the Singapore Registry of Births and Deaths. The Singapore Cancer Registry was estab-

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[2] To whom requests for reprints should be addressed, at USC/Norris Comprehensive Cancer Center, MC 9175, University of Southern California Keck School of Medicine, 1441 Eastlake Avenue, Los Angeles, CA 90089-9176. Phone: (323) 865-0827; Fax: (323) 865-0136; E-mail: canlan@hsc.usc.edu.

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Table 1 Distribution of selected demographic and lifestyle variables at baseline stratified by levels of total soy intake, Singapore Chinese Health Study[a]

	Quartiles of total soy intake[b]			
	<36.85	36.86–60.35	60.36–92.48	92.49+
No. of subjects	15,594	15,605	15,616	15,578
Men (%)	51.4	46.3	42.5	37.2
Body mass index (kg/m^2)	23.0	23.1	23.2	23.3
Level of education				
Secondary and higher (%)	24.7	27.7	29.8	30.8
Cigarette smoking				
Ever (%)	38.2	31.0	28.0	24.9
Cigarettes/day among ever smokers	17.8	17.3	17.0	16.7
Years of smoking among ever smokers	33.6	33.3	32.7	32.3
Mean food/nutrient density				
Soy foods/nutrients				
Total soy (g/1000 Kcal)[b]	22.2	48.4	74.9	137.8
Soy protein (% Kcal)	0.5	1.0	1.6	2.8
Soy isoflavones (mg/1000 Kcal)	3.5	7.9	12.4	23.5
Other foods				
All red meats (g/1000 Kcal)	18.8	19.5	19.5	17.8
All fish/shellfish (g/1000 Kcal)	33.6	35.6	37.3	38.1
Nonsoy legume (g/1000 Kcal)	1.4	1.8	2.1	2.4
All vegetables (g/1000 Kcal)	61.9	68.5	74.9	85.3
All fruit/fruit juice (g/1000 Kcal)	111.5	126.0	135.9	147.9
All grain products (g/1000 Kcal)	390.9	362.6	338.4	305.4
Other nutrients				
Total energy (Kcal)	1,490.4	1,545.7	1,585.3	1,596.8
Fat (% Kcal)	22.1	24.3	25.9	28.0
Protein (% Kcal)	14.2	14.9	15.5	16.2
Carbohydrate (% Kcal)	62.5	60.1	58.2	55.7
Vitamin A (IU/1000 Kcal)	2,828.8	3,113.7	3,375.7	3,800.6
Vitamin C (mg/1000 Kcal)	48.0	53.5	58.1	63.6
Total carotenoids (mcg/1000 Kcal)	3,132.8	3,467.4	3,804.9	4,317.5
Vitamin E (mg/1000 Kcal)	3.1	3.6	4.0	4.6

[a] All associations were statistically significant (two-sided $P < 0.05$).
[b] Expressed in units of tofu-equivalents (see "Subjects and Methods" section for details).

lished in 1968 and since then has been continuously included in the "Cancer Incidence in Five Continents" serial publications by the International Agency for Research on Cancer in Lyon, France. As of December 31, 2000, 61 incident cases of bladder cancer were identified among cohort members. The observed number of incident bladder cancer was comparable with the corresponding expected number (64 bladder cancer cases) based on age- and sex-specific bladder cancer incidence rates for all Chinese in Singapore during 1992–1997 (7). We reconfirmed the disease status of these 61 cases through manual review of their pathology reports.

For each study subject, person-years were counted from the date of baseline interview to the date of cancer diagnosis, date of death, or December 31, 2000, whichever occurred first. Eight hundred sixty-four cohort members with a personal history of cancer at baseline were excluded from the analysis. ANOVA was used to examine the associations between total soy intake and selected demographic/lifestyle characteristics and other dietary factors (8). Cox proportional hazard regression method was used to estimate RRs[3] and their corresponding 95% CIs and two-sided *P*s, with adjustment for age at baseline (years), year of recruitment, sex, dialect group (Cantonese or Hokkien), and other potential confounders (9). To adjust for energy intake, all foods and nutrients were expressed either as percentage of total energy or as weight/1000 Kcal. Intake levels of total soy, soy protein, and soy isoflavones were grouped in quartiles according to their distributions among all cohort subjects. All linear trend tests were based on the actual, continuous values of the dietary variables. Results in men and women were combined because the majority of the cases were men (77%) and no discernable difference in the soyfood-bladder cancer association was noted between the two sexes. Statistical computing was conducted using the SAS version 8.2 (SAS Institute, Inc.) and Epilog Windows version 1.0 (Epicenter Software).

Results

By December 31, 2000, 329,848 person-years of follow-up were accrued, and 61 incident bladder cancers (47 men, 14 women) were identified. The median age at cancer diagnosis was 68 years (range, 49–81 years). The median time interval between baseline interview and cancer diagnosis was 2.9 years (range, 1 month to 6.7 years). Fifty-five cases (90%) were transitional cell carcinomas.

Baseline characteristics of cohort subjects by quartiles of total soy intake are shown in Table 1. Women reported significantly higher consumption of total soyfood compared with men. Statistically significant higher intakes of soyfoods also were observed among lifelong nonsmokers (*versus* smokers) and subjects with higher (*versus* lower) levels of education. There were statistically significant positive associations between intake of total soy and consumption of fish, nonsoy legumes, vegetables, fruits, total energy, total fat, total protein, total carotenoids, and vitamins A, C, and E. Conversely, statistically significant inverse associations were observed between total soy intake and consumption of grain products and

[3] The abbreviations used are: RR, relative risk; CI, confidence interval.

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Table 2 Soyfood intake at baseline and risk of bladder cancer, Singapore Chinese Health Study

	No. of cases	Person-years	RR[a] (95% CI)	RR[b] (95% CI)
Total	61	329,848		
Total soy (g/1000 Kcal)[c]				
≤36.85	10	79,597	1.00	1.00
36.86–60.35	15	83,439	1.64 (0.74–3.66)	1.65 (0.74–3.68)
60.36–92.48	18	83,710	2.12 (0.98–4.61)	2.13 (0.98–4.62)
92.49+	18	83,102	2.32 (1.07–5.05)	2.34 (1.07–5.09)
Per 50 g/1000 Kcal			1.25 (1.03–1.53)	1.26 (1.03–1.54)
Soy protein (% Kcal)				
≤0.79	8	79,795	1.00	1.00
0.80–1.28	18	83,640	2.45 (1.06–5.64)	2.48 (1.08–5.71)
1.29–1.94	18	83,710	2.62 (1.14–6.04)	2.63 (1.14–6.07)
1.95+	17	82,703	2.73 (1.17–6.33)	2.74 (1.18–6.38)
Per 1% Kcal			1.25 (1.01–1.53)	1.25 (1.01–1.54)
Soy isoflavones (mg/1000 Kcal)				
≤5.77	10	79,521	1.00	1.00
5.78–9.83	14	83,070	1.51 (0.67–3.40)	1.52 (0.67–3.42)
9.84–15.42	21	83,944	2.48 (1.17–5.28)	2.47 (1.16–5.26)
15.43+	16	83,313	2.07 (0.94–4.57)	2.08 (0.94–4.60)
Per 10 mg/1000 Kcal			1.27 (1.03–1.56)	1.27 (1.03–1.57)

[a] RRs were adjusted for age at baseline interview (yr), year of recruitment, sex, and dialect group (Cantonese or Hokkien).
[b] Additional adjust for cigarette smoking status (never, ex, and current) and level of education (no formal education, primary school, and secondary school or higher).
[c] Expressed in units of tofu-equivalents (see "Subjects and Methods" section for details).

carbohydrate. Table 1 also shows the means of total soy, soy protein, and soy isoflavones across the four quartiles of total soy in all cohort subjects.

The risk of bladder cancer was positively associated with level of education. Compared with subjects without any formal education, those with a primary school education had a 30% increased risk of bladder cancer (RR = 1.32, 95% CI = 0.64–2.75), whereas those with a secondary school or higher education had a 2-fold increased risk of bladder cancer (RR = 2.13, 95% CI = 0.97–4.67; *P* for trend = 0.04). Therefore, all subsequent analyses were adjusted for level of education.

Compared with never smokers, ever smokers had a statistically significant 2-fold increased risk of bladder cancer after adjustment for level of education (RR = 2.12, 95% CI = 1.17–3.87). Among ever smokers, both duration and intensity of smoking were significantly related to risk (both sets of *P* for linear trend = 0.01). Smoking status (never, former, current) at baseline was the strongest predictor of bladder cancer risk in this study population; no other smoking variables contributed additionally toward risk once smoking status at baseline was included in the Cox regression model (all *P*s > 0.50). Therefore, smoking status at baseline was used to adjust for cigarette smoking in subsequent dietary analyses.

Table 2 presents intake of total soy, soy protein, and soy isoflavones at baseline in relation to risk of bladder cancer. There was a statistically significant increase in risk with higher intakes of total soy, soy protein, or soy isoflavones. The relationship did not change after adjustment for cigarette smoking and level of education.

Because soyfoods may be markers of other dietary factors that exert adverse effects on bladder cancer development, we explored whether the presence of other potential dietary confounders could explain the observed soyfood-bladder cancer risk association. We examined the relation between intake of soyfood and bladder cancer risk while simultaneously accounting for the following dietary nutrients: total fat; total carbohydrate; cholesterol; total carotenoids; and vitamins A, C, and E. Compared with the lowest quartile of intake, the adjusted RRs (95% CI) for the 2nd, 3rd, and 4th quartiles of total dietary soy were 1.73 (0.77–3.89), 2.37 (1.05–5.30), and 2.86 (1.21–6.80), respectively (*P* for linear trend = 0.01).

There is a possibility that because of disease symptoms, soy intake patterns in bladder cancer patients were already modified before the time of cancer diagnosis. An increase in intake among these patients would result in an artifactual positive association between dietary soy and bladder cancer. If this were the case, the soy-bladder cancer association would be stronger in subjects with a shorter duration of follow-up. In fact, a stronger soy-bladder cancer risk association was observed for those with a longer (≥3 years) duration of follow-up; the adjusted RRs (95% CI) for the 2nd, 3rd, and 4th quartile of total soy intake were 3.04 (0.82–11.25), 2.87 (0.76–10.86), and 4.02 (1.10–14.69), respectively, relative to the lowest quartile.

We repeated all analyses on cases of transitional cell carcinoma only (*n* = 55 cases). Results remained unchanged. The adjusted RR (95% CI) for the highest *versus* lowest quartile of total soy intake was 2.25 (1.02–4.94).

Discussion

Cigarette smoking is an established risk factor for bladder cancer, believed to be related to 50% of bladder cancer cases in the United States where a positive association between incidence rate and socioeconomic status also is observed (10). The present study confirmed both well-known risk factors for bladder cancer, and the magnitude of the associations were comparable with those in the published literature.

The relationship between soyfood intake and risk of cancer in humans is unclear, even for breast cancer, the most studied site. Four epidemiological studies reported a statistically significant inverse relationship between dietary soy and risk of breast cancer (11), whereas five others reported results compatible with a null association (12). Results based on *in vitro* (breast cancer cells) or *in vivo* models are similarly mixed. The

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major constituent of soy isoflavones, genistein, was shown to have anticarcinogenic properties at high concentrations (13) but procarcinogenic activities at low concentrations (14). In nude mice, genistein was found to both inhibit (15) and stimulate breast tumor growth (16).

To our knowledge, this study is the first epidemiological investigation on dietary soy and bladder cancer risk. The data from *in vitro* and whole animal studies have yielded conflicting results on the role of dietary soy in bladder carcinogenesis. Mokhtar *et al.* (4) reported that dietary soy reduced nitrosamine-induced bladder tumors in mice. Soy isoflavones or soy concentrate inhibited both growth of human bladder cancer cells *in vitro* and growth of implanted murine or human bladder cancer in nude mice (5). On the other hand, laboratory studies involving human bladder cancer cells (17) and whole animals (18) have supported a role of insulin-like growth factor-1 in bladder carcinogenesis, and a recent randomized, double-blind, placebo-controlled feeding experiment observed that men given soy protein supplements exhibited significant increase in serum insulin-like growth factor-1 level (19).

Results regarding the association between dietary soy and other cancers are equally conflicting. Soy was shown to inhibit growth of colon cancer cells (20) and the development of chemically induced colon cancer in rats (21). However, administration of genistein to male rats treated with a colon carcinogen led to enhanced colon cancer development (22). Available epidemiological data indicate that dietary soy has no effect on colon cancer risk (23). Additionally, genistein was shown to promote growth of human pancreatic tumor cells (24) and induce chromosomal aberrations in human peripheral blood lymphocytes (25).

It is possible that some unidentified substances in soyfoods are responsible for the observed adverse effect on the development of bladder cancer. In fact, our data showed a stronger positive association with total soy than with soy protein or soy isoflavones. It is also conceivable that soyfood is a surrogate of some other as-yet-unidentified constituents in the diet that relate to an increased risk of bladder cancer.

Since 1999, when the Food and Drug Administration concluded that soy protein included in a diet low in saturated fat and cholesterol may reduce the risk of coronary heart disease, there has been a noticeable increase in the consumption and production of soyfoods in the United States. According to national surveys conducted by the United Soybean Board, 27% of Americans reported using soy products at least once a week in the year 2000, up from 15% in the year 1998 (26). Therefore, the risk *versus* benefit of dietary soy in disease causation carries important public health implications.

Urine is an important route for the excretion of soy constituents such as genistein, daidzein, and their metabolites. In fact, the concentration of genistein in the urine is considerably higher than that in blood (27). Thus, a possible effect of dietary soy on bladder cancer risk warrants further study. We caution that our novel finding of a positive association between soy and bladder cancer risk is based on a relatively short period of follow-up and a modest number of cancer cases. If this provocative observation is confirmed by others, laboratory studies to delineate possible mechanisms will be needed.

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