

### Short Communication

## Soy and Isoflavone Consumption in Relation to Prostate Cancer Risk in China<sup>1</sup>

Marion M. Lee,<sup>2</sup> Scarlett Lin Gomez, Jeffrey S. Chang, Mercy Wey, Run-Tian Wang, and Ann W. Hsing

Department of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, California 94143-0560 [M. M. L., J. S. C., M. W.]; Northern California Cancer Center, Union City, California 94587 [S. L. G.]; Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California 94305 [S. L. G.]; Department of Epidemiology, Beijing Medical University, Beijing, China 10083 [R-T. W.]; and Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland 20892 [A. W. H.]

#### 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<sup>3</sup> 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

Received 11/25/02; revised 3/21/03; accepted 4/9/03.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

<sup>1</sup> Supported by the United States-China Urologic Research Group.

<sup>2</sup> To whom requests for reprints should be addressed, at Department of Epidemiology and Biostatistics, University of California, San Francisco, MU 420 West, Box 0560, San Francisco, CA 94143-0560. Phone: (415) 476-0743; Fax: (415) 476-6014; E-mail: mmlee@itsa.ucsf.edu.

<sup>3</sup> 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 <sup>2</sup> (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

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

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 <sup>a</sup>
	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

<sup>a</sup> Wilcoxon rank-sum test comparing the median consumption levels between cases and controls.

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 genistein, 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 (genistein 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 <sup>a</sup>	95% CI
Tofu (g/day) <sup>b</sup>				
<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) <sup>c</sup>				
<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) <sup>c</sup>				
<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) <sup>c</sup>				
<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)	

<sup>a</sup> Adjusted for total calories and age.

<sup>b</sup> ORs calculated by tertile.

<sup>c</sup> 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.

### Acknowledgments

We thank the United States-China Urological Research Group for support. Members include Dr. Leland W. K. Chung (Emory University), Dr. John D. McConnell (Southwestern Medical Center at Dallas), Dr. Gary Miller (University of Colorado), Dr. Andrew C. von Eschenbach (National Cancer Institute), Dr. Haiyen E. Zhou (Emory University), Dr. Hebert Lepor (New York University), Dr. Ellen Shapiro (New York University), Dr. Donald S. Coffey (Johns Hopkins University), Dr. Y. L. Kuo (Beijing Urology Institute), and Dr. Chieh-Ping Wu (Chinese Academy Medical School). We also thank Florence Lee and Christine Choy for assistance.

### References

1. Prehn, A., Lin, S., Clarke, C., Packel, L., Lum, R., Lui, S., Harper, C., Lee, M., Glaser, S., and West, D. Cancer Incidence in Chinese, Japanese, and Filipinos in the US and Asia, 1988–1992. Union City, CA: Northern California Cancer Center, 1999.
2. Hsing, A. W., Tsao, L., and Devesa, S. S. International trends and patterns in prostate cancer incidence and mortality. *Int. J. Cancer*, 85: 60–67, 2000.

3. Hsing, A. W., and Devesa, S. S. Trends and patterns of prostate cancer risk: what do they suggest? *Epidemiol. Rev.*, 23: 3–13, 2001.
4. Severson, R. K., Nomura, A. M., Grove, J. S., and Stemmermann, G. N. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res.*, 49: 1857–1860, 1989.
5. Jacobsen, B. K., Knutsen, S. F., and Fraser, G. E. Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study. *Cancer Causes Control*, 9: 553–557, 1998.
6. Kolonel, L. N., Hankin, J. H., Whitmore, A. S., Wu, A. H., Gallagher, R. P., Wilkens, L. R., John, E. M., Howe, G. R., Dreon, D. M., West, D. W., and Paffenbarger, R. S., Jr. Vegetables, fruits, legumes, and prostate cancer: a multiethnic case-control study. *Cancer Epidemiol. Biomark. Prev.*, 9: 795–804, 2000.
7. Strom, S. S., Yamaura, Y., Duphorne, C. M., Spitz, M. R., Babaian, R. J., Pillow, P. C., and Hursting, S. D. Phytoestrogen intake and prostate cancer: a case-control study using a new database. *Nutr. Cancer*, 33: 20–25, 1999.
8. Hsing, A. W., Wang, R. T., Gu, F. L., Lee, M., Wang, T., Leng, T. J., Spitz, M., and Blot, W. J. Vasectomy and prostate cancer risk in China. *Cancer Epidemiol. Biomark. Prev.*, 7: 285–288, 1994.
9. Lee, M. M., Wang, R., Hsing, A. W., Gu, F. L., Wang, T., and Spitz, M. Case control study of diet and prostate cancer in China. *Cancer Causes Control*, 9: 545–552, 1998.
10. Whittemore, A. S., Wu-Williams, A. H., Lee, M., Zheng, S., Gallagher, R. P., Jiao, D. A., Zhou, L., Wang, X., Chen, K., Jung, D., The, C. Z., Ling, C., Xu, J. Y., Paffenbarger, R. S., Jr., and Henderson, B. E. Diet, physical activity, and colorectal cancer among Chinese in North America and China. *J. Natl. Cancer Inst.* (Bethesda), 82: 915–926, 1990.
11. Wong, R. T. A study of gastric cancer in Beijing. *Chin. J. Epidemiol.*, 6: 23–28, 1992.
12. Horn-Ross, P. L., Barnes, S., Lee, M., Coward, L., Mandel, J. E., Koo, J., John, E. M., and Smith, M. Assessing phytoestrogen exposure in epidemiologic studies; development of a database (United States). *Cancer Causes Control*, 11: 289–298, 2000.
13. Hosmer D. W., and Lemeshow S. *Applied Logistic Regression*. New York: John Wiley & Sons, 1989.
14. Peterson, G., and Barnes, S. Genistein and biochanin A inhibit the growth of human prostate cancer cells but not epidermal growth factor receptor tyrosine autophosphorylation. *Prostate*, 22: 335–345, 1993.
15. Evans, B. A., Griffiths, K., and Morton, M. S. Inhibition of 5  $\alpha$ -reductase in genital skin fibroblasts and prostate tissue by dietary lignans and isoflavonoids. *J. Endocrinol.*, 147: 295–302, 1995.

16. Aronson, W. J., Tymchuk, C. N., Elashoff, R. M., McBride, W. H., Maclean, C., Wang, H., and Heber, D. Decreased growth of human prostate LNCap tumors in SCID mice fed a low-fat, soy protein diet with isoflavones. *Nutr. Cancer*, *35*: 130–136, 1999.
17. Bylund, A., Zhang, J. X., Bergh, A., Damber, J. E., Widmark, A., Johansson, A., Adlercreutz, H., Aman, P., Shepherd, M. J., and Hallmans, G. Rye bran and soy protein delay growth and increase apoptosis in human LNCap prostate adenocarcinoma in nude mice. *Prostate*, *42*: 304–314, 2000.
18. Zhou, J. R., Gugger, E. T., Tanaka, T., Guo, Y., Blackburn, G. L., and Clinton, S. K. Soybeans phytochemicals inhibit the growth of transplantable human prostate carcinoma and tumor angiogenesis in mice. *J. Nutr.*, *129*: 1628–1635, 1999.
19. Mentor-Marcel, R., Lamartiniere, C. A., Eltoun, I. E., Greenberg, N. M., and Elgavish, A. Genistein in the diet reduces the incidence of poorly differentiated prostatic adenocarcinoma in transgenic mice (TRAMP). *Cancer Res.*, *61*: 6777–6782, 2001.
20. Horn-Ross, P. L., John, E. M., Lee, M., Stewart, S. L., Koo, J., Sakoda, L. C., Shiau, A. C., Goldstein, J., Davis, P., and Perez-Stable, E. J. Phytoestrogen consumption and breast cancer risk in a multiethnic population. *Am. J. Epidemiol.*, *154*: 434–441, 2001.
21. Pillow, P. C., Duphorne, C. M., Chang, A., Contois, J. H., Strom, S. S., Spitz, M. R., and Hursting, S. D. Development of a database for assessing dietary phytoestrogen intake. *Nutr. Cancer*, *33*: 3–19, 1999.
22. Arai, Y., Watanabe, S., Kimira, M., Shimoi, K., Mochizuki, R., and Kinae, N. Dietary intakes of flavonols, flavones, and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. *J. Nutr.*, *130*: 2243–2250, 2000.
23. Davis, J. N., Singh, B., Bhuiyan, M., and Sarkar, F. H. Genistein-induced upregulation of p21WAF1, downregulation of cyclin B, and induction of apoptosis in prostate cancer cells. *Nutr. Cancer*, *32*: 123–131, 1998.
24. Dalu, A., Haskell, J. F., Coward, L., and Lamartiniere, C. A. Genistein, a component of soy, inhibits the expression of the EGF, and ErbB2/Neu receptors in the rat dorsolateral prostate. *Prostate*, *37*: 36–43, 1998.

## Soy and Isoflavone Consumption in Relation to Prostate Cancer Risk in China

Marion M. Lee, Scarlett Lin Gomez, Jeffrey S. Chang, et al.

*Cancer Epidemiol Biomarkers Prev* 2003;12:665-668.

**Updated version** Access the most recent version of this article at:  
<http://cebp.aacrjournals.org/content/12/7/665>

**Cited articles** This article cites 21 articles, 7 of which you can access for free at:  
<http://cebp.aacrjournals.org/content/12/7/665.full#ref-list-1>

**Citing articles** This article has been cited by 14 HighWire-hosted articles. Access the articles at:  
<http://cebp.aacrjournals.org/content/12/7/665.full#related-urls>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and  
Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications  
Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link  
<http://cebp.aacrjournals.org/content/12/7/665>.  
Click on "Request Permissions" which will take you to the Copyright Clearance Center's  
(CCC)  
Rightslink site.