Null Results in Brief

Cohort Study of Tofu Intake and Prostate Cancer: No Apparent Association

Abraham M.Y. Nomura,[1] Jean H. Hankin,[2] James Lee,[1] and Grant N. Stemmermann[3]

[1]Kuakini Medical Center and [2]Cancer Research Center, University of Hawaii, Honolulu, Hawaii and
[3]Department of Pathology, University of Cincinnati Medical Center, Cincinnati, Ohio

Introduction

Three case-control studies and one cohort study have suggested that soy products reduce the risk of prostate cancer (1-4), but overall evidence from these epidemiologic studies is still limited. To investigate this issue further, we conducted a cohort study on the association of tofu (soybean curd) intake with prostate cancer among Japanese Americans in Hawaii. The annual mortality rate of prostate cancer among Japanese American men is 11.7 per 100,000, which is lower than the mortality rate of 24.1 per 100,000 among U.S. Whites (5). However, unlike clinical prostate cancer, occult prostate cancer, as determined by step sections of the prostate at autopsy, is as common among the Japanese Americans in Hawaii as among the U.S. Whites (6). This suggests the operation of factors that inhibits the progression of this tumor after induction among Japanese American men.

Materials and Methods

Japanese American men (n = 8,006) were examined on the Hawaiian island of Oahu from 1965 to 1968, as described previously (7), and 6,860 men returned for another examination from 1971 to 1975. Because of delays in designing the dietary questionnaire, 983 (14.3% of 6,860) subjects did not fill it out. The remaining 5,877 participants recorded their weekly frequency of intake of tofu and the average serving size. A small portion was 60 g, medium portion 120 g, and large portion 180 g. Twenty-two men with prevalent prostate cancer were excluded from the study.

Incident cases of prostate cancer were identified through surveillance of discharge records of all general hospitals on Oahu. To reduce the number of missing cases, a computer linkage file was established with the Hawaii Tumor Registry, a member of the Surveillance, Epidemiology and End Results Program of the National Cancer Institute. The surveillance should be nearly complete, because only 2.5% of the 6,860 reexamined men could not be located on Oahu during a survey completed in 1993.

There were 304 cases of prostate carcinoma diagnosed from 1972 to 1995 and confirmed by tissue examination. Of the 304 cases, 82 had occult tumors, which were found incidental to transurethral resections in no more than three of all totally embedded tissue chips. These small occult tumors are comparable with the occult tumors found when step sectioning the prostate at autopsy. Of the remaining 222 with clinically apparent disease, 61 had metastatic disease to regional nodes or distant sites. An additional 29 cases were diagnosed clinically but were not confirmed histologically and these were excluded from the study.

The risk of prostate cancer associated with tofu intake was assessed by the relative risk (RR) and 95% confidence interval (95% CI) estimated by the Cox proportional hazards regression model (8). Tofu intake was categorized into five groups (0, 1-60, 61-120, 121-240, and >240 g/wk). These groups were used to create a set of binary indicator variables with 0 g/wk as the reference group. The indicator variables and other confounding covariates (age, cigarette smoking, alcohol intake, total calories, arm muscle area, and body mass index) were used as explanatory variables in the model for the estimation of RRs. The test for trend was done using the class midpoints of tofu intakes as explanatory variables. All Ps and 95% CIs are based on a two-sided test. Statistical analysis was done with the SAS software.

Results

The 5,826 men in this study provided 113,159 person-years of follow-up. Table 1 shows the age-adjusted RRs of prostate cancer according to tofu intake. The RR in the highest group (>240 g/wk) was 0.80 for all prostate cancer cases. When the analysis was limited to the 222 clinical cases, the RRs were similar and the trend test was still not statistically significant (P = 0.37). Additional

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Note: Signed informed consent forms were obtained from all participants in the study. The institutional review board approval from Kuakini Medical Center's Research and Institutional Review Committee was received and last updated on March 7, 2003. The Committee follows the human experimentation guidelines of the U.S. Department of Health and Human Services.

Requests for reprints: Abraham Nomura, Japan-Hawaii Cancer Study, Kuakini Medical Center, 347 North Kuakini Street, Honolulu, HI 96817. Phone: 808-521-5071; Fax: 808-526-0046. E-mail: anomura@hawaii.rr.com

Table 1. RR and 95% CIs for prostate cancer by tofu intake

Prostate cancer	Tofu intake (g/wk)					*P* for trend
	0 (*n* = 1,835)	1-60 (*n* = 917)	61-120 (*n* = 1,262)	121-240 (*n* = 1,092)	>240 (*n* = 720)	
All cases						
Cases/person-years	93/36,500	52/17,551	64/24,869	64/20,610	31/13,629	
Age-adjusted RR (95% CI)	1.0	1.15 (0.83-1.61)	0.99 (0.72-1.36)	1.16 (0.84-1.60)	0.80 (0.53-1.21)	0.66
Multivariate RR* (95% CI)	1.0	1.17 (0.83-1.65)	1.01 (0.74-1.39)	1.18 (0.86 (1.63)	0.82 (0.54-1.23)	0.76
Clinical cases						
Cases/person-years	73/36,221	39/17,388	44/24,625	40/20,300	26/13,563	
Age-adjusted RR (95% CI)	1.0	1.10 (0.74-1.62)	0.87 (0.60-1.26)	0.93 (0.63-1.37)	0.85 (0.54-1.34)	0.37
Multivariate RR* (95% CI)	1.0	1.13 (0.76-1.66)	0.88 (0.61-1.29)	0.94 (0.64-1.38)	0.87 (0.56-1.37)	0.42

*Adjusted for age, cigarette smoking, alcohol intake, total calories, arm muscle area, and body mass index.

adjustment for cigarette smoking history, alcohol intake, total calories, arm muscle area, and body mass index did not substantially change the results (RR of 0.87 in the highest group).

Next, analysis was further restricted to the 61 cases with metastatic disease and the five categories of tofu intake were collapsed into three groups (0, 1-120, and >120 g/wk). After multiple adjustment for the same six variables, the RRs (95% CIs) were 1.11 (0.59-2.09) for the low consumers and 1.26 (0.67-2.39) for the high consumers of tofu (>120 g/wk).

Discussion

After following 5,855 Japanese American men for over 20 years, we found no discernible association between tofu intake and prostate cancer risk. The highest group of tofu consumers had a RR of 0.80 for prostate cancer compared with the lowest group, but the inverse relation was not statistically significant. When the analysis was limited to the clinical cases, the RR was 0.85 in the highest intake group. Further restriction of the analysis to the metastatic cases did not provide any evidence of a protective effect of tofu against prostate cancer progression.

There are several limitations in our prospective study. The tofu data were based on just two questions (i.e., frequency of tofu intake during the past week and the average serving size). The original dietary questionnaire in 1971 was limited to 32 other foods and was not designed to explore isoflavone intake in depth. Thus, the consumption of other sources of soy foods, such as soybean milk, cooked soybeans, fermented soybeans, and fried soybean curd, were not included in the diet questionnaire. This led to an underestimation of soy consumption in our study, although it has been suggested that >80% of soy intake among Japanese Americans has been from tofu (9). In addition, Japanese American men ate less tofu than that of men living in Japan. It is estimated that they consumed an average of 47 g of tofu daily,[4] whereas the median intake was 120 g/wk or ~17 g/d in our study. If the protective effect of tofu intake is more apparent at high levels of consumption, then our data are limited in this regard. However, other studies in populations that did not have a high intake of soy foods still showed an inverse association with prostate cancer risk (1, 3, 4).

Epidemiologic evidence of a protective effect of soy intake against prostate cancer comes mainly from three case-control studies. In a large multicenter study with 1,619 cases and 1,618 community controls, soy foods were inversely related to prostate cancer (*P* for trend = 0.06) for all cases, but less so for advanced cases (*P* for trend = 0.13; (1). The results were adjusted for age, education, geographic area, and calories. A smaller study in China with 133 cases and 265 community controls found an inverse association for tofu intake after adjustment for age and total calories (2). In the third study in Texas with 83 Caucasian cases and 107 controls, an inverse association was reported for the intake of the phytoestrogens coumestrol (*P* = 0.03) and daidzein (*P* = 0.07; ref. 3). However, there was a positive association with other phytoestrogens, such as campesterol (*P* = 0.08) and stigmasterol (*P* = 0.03). The authors in some of these studies cautioned against possible dietary recall bias in case-control studies and recommended that longitudinal follow-up studies would be helpful in clarifying the association (1, 2).

In a cohort study among 12,395 California Seventh Day Adventists, 5% drank soy milk at least once a day, whereas 88% reported no intake of soy milk (4). The intake of tofu was not included in this study. Of the 225 incident cases of prostate cancer in the study, 14 occurred among the soy milk consumers, which resulted in a statistically significant trend in risk (*P* = 0.02). However, when the analysis was limited to cases with invasive tumors, the association was weakened (*P* for trend = 0.09). Each of the above studies, including our investigation, has limitations that need to be overcome by a well-designed dietary questionnaire in a cohort study of a large population with a wide variation in soy intake.

Several biological mechanisms have been proposed by which soy isoflavones could reduce prostate cancer risk. They include inhibition of angiogenesis (2), antioxidant activity (4), and inhibition of tyrosine protein kinases, DNA topoisomerases, and other enzymes involved in signal transduction pathways of cellular growth factors (2). Isoflavones also inhibit 5-α-reductase, an enzyme that metabolizes testosterone to 5-α-dihydrotestosterone (4). Because of these potential beneficial

[4] H. Shimizu, personal communication.

properties of isoflavones, it is important to determine if the intake of tofu and other soy products prevents prostate cancer.

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