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ORIGINAL REPORT

Prediagnosis Soy Food Consumption and Lung Cancer Survival in Women

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ABSTRACT

Purpose
We recently reported an inverse association between soy food intake and lung cancer risk among nonsmoking women. The effect size for aggressive lung cancers was larger than that observed for other types of lung cancer. Therefore, we hypothesized that soy consumption may favorably affect the overall survival of patients with lung cancer.

Patients and Methods
This analysis included 444 women with incident lung cancer identified from the Shanghai Women's Health Study. Prediagnosis soy food intake was assessed at enrollment and reassessed 2 years later. Proportional hazards models were used to evaluate the association between soy food intake and overall survival.

Results
Of the 444 patients with lung cancer, 318 died during follow-up. Initial analyses including all patients showed that higher intake of soy food was associated with better overall survival after adjusting for demographic and lifestyle characteristics and other nonclinical factors. Larger effect sizes for the association were found after additional adjustment for tumor stage and treatment in analyses including 301 patients with data available on these clinical factors. Compared with the median intake of soy food, fully adjusted hazard ratios for total mortality associated with the 10th, 30th, 70th, and 90th percentiles of intake were 1.81 (95% CI, 1.26 to 2.59), 1.25 (95% CI, 1.09 to 1.42), 0.88 (95% CI, 0.80 to 0.97), and 0.89 (95% CI, 0.68 to 1.16), respectively. Similar inverse associations were observed for dietary isoflavone intake.

Conclusion
This study suggests, to the best of our knowledge for the first time, that, among women with lung cancer, prediagnosis intake of soy food is associated with better overall survival.

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INTRODUCTION

Lung cancer is the leading cause of cancer death among women worldwide.[1] With a 5-year survival rate of only 15%, it is estimated that lung cancer will cause almost twice as many deaths as breast cancer among US women in 2012.[2] Several clinicopathologic characteristics of patients with lung cancer, such as age at diagnosis, tumor stage, and histologic grade and type, have been associated with prognosis.[3-5] Emerging evidence suggests that female sex hormones may also affect lung cancer survival.[6,7]

Estrogen signaling has been shown to promote lung cancer progression, and this estrogen-induced tumor progression can be blocked by estrogen receptor (ER) antagonists or aromatase inhibitors.[8,9] The lung is among the nonreproductive tissues with the highest levels of ER transcripts, especially ER

beta.[10] Recently, the Women's Health Initiative,[6] a large, randomized clinical trial, found an increased risk of death as a result of lung cancer among users of hormone replacement therapy (HRT). Past use of HRT in women with lung cancer was also linked to increased mortality in several long-term follow-up studies.[7] In contrast, use of antiestrogens such as tamoxifen (a selective estrogen receptor modulator) was associated with reduced risk of lung cancer mortality in a large breast cancer follow-up study.[11]

Plant-derived estrogens, such as isoflavones found mainly in soy food, appear to act as natural selective estrogen receptor modulators. These phytoestrogens can bind competitively to ERs in estrogen-responsive cells and possess both estrogen-like and antiestrogenic properties.[12,13] Both in vitro and animal studies have shown that soy and soy isoflavones can inhibit cell transformation, induce apoptosis, and inhibit angiogenesis and metastasis.[14-18]

Administration of soy isoflavones to female mice has been found to significantly inhibit the growth of non–small-cell lung cancer.[19]

In a recent analysis of data from the Shanghai Women's Health Study (SWHS), we found a significant inverse association between soy food intake and lung cancer risk among nonsmoking women.[20] The effect size for the inverse association was even larger for aggressive lung cancer, a form of lung cancer that generally has a short survival time. This finding prompted us to hypothesize that soy food consumption may favorably affect the natural history of lung cancer. In this report, we examine whether prediagnosis intake of soy food is related to lung cancer survival in women.

PATIENTS AND METHODS

Study Participants

In this longitudinal follow-up study, incident cases of lung cancer were identified from the SWHS. The SWHS is a prospective cohort study of Chinese women; details of the study design and methods have been described elsewhere.[21] Briefly, from 1997 to 2000, the cohort recruited 74,941 adult Chinese women from seven urban communities in Shanghai (response rate, 93%). The cohort has been tracked for occurrence of cancer by in-person follow-up surveys conducted every 2 to 3 years and annual record linkages to the Shanghai Cancer Registry (all follow-up response rates, > 96%). All cancer cases were verified by home visits. Inpatient medical records were reviewed to verify the diagnosis. The study was approved by the relevant institutional review boards for human research in both China and the United States. Written informed consent was obtained from all study participants.

We identified 469 incident cases of lung cancer (International Classification of Diseases, 9th Revision; codes 162.0-162.9) from 1997 to 2010. We excluded patients with missing information on primary cancer treatment (n = 25), leaving a total of 444 incident patients with lung cancer for the analysis.

Data Collection

Assessment of prediagnosis dietary intake. In the SWHS, information on usual dietary intake was collected at cohort enrollment from all participants and updated 2 to 3 years later for approximately 91% of the cohort.[21] We used a comprehensive, quantitative food-frequency questionnaire (FFQ) to assess usual dietary intake that covered virtually all soy foods commonly consumed in Shanghai, including soy milk, tofu, fried tofu, dried or pressed tofu, fresh green soy beans, dry soy beans, soy sprouts, and other soy products. Our FFQ validation study showed that its validity and reproducibility were comparable with the FFQs used in most existing cohort studies.[22] Nutrient intakes were calculated on the basis of the Chinese Food Composition Tables.[23] Because the water content of soy foods varies widely,[23] we also calculated total soy food intake in dry weight.

To improve estimates for usual prediagnosis intake of soy food, we used the average of dietary intakes estimated from the two FFQ surveys for 321 (72.3%) of the 444 patients included in this project. For patients who provided no second FFQ data or reported having diabetes diagnosed between the two FFQs, only the intake estimates from the first FFQ were used (27.7%). The median time interval between the first FFQ and cancer diagnosis was 5.8 years (interquartile range, 3.4 to 8.5 years). We did not collect additional information on dietary intake after cohort participants were diagnosed with cancer, including the 444 patients with lung cancer included in this study.

Outcome ascertainment. The primary outcome for this analysis was overall survival. The vital status of the cohort members, including patients with cancer, was ascertained through a combination of in-person home visits conducted every 2 to 3 years and annual searches of death certificates at Shanghai Vital Statistics.

Covariates. In addition to dietary intake, the baseline survey also collected information from all cohort members on demographic characteristics, lifestyle habits, medical history, and other exposures. Anthropometric measurements were also taken. Ever cigarette smokers were defined as those who

reported ever smoking at least one cigarette per day for more than 6 consecutive months. Comprehensive information on passive smoking was collected for 91.3% of never smokers in the cohort (66,520 of 72,829) at the first follow-up 2 to 3 years after the baseline interview.[24]

For patients with cancer, clinical information, including tumor stage, pathologic type, and primary treatment (surgery, chemotherapy, or radiotherapy), was collected from inpatient medical records by health professionals (registered nurses or physicians) and was reviewed by a senior oncologist.

Statistical Analysis

Overall survival time was calculated from the date of cancer diagnosis to the date of death as a result of any cause. Patients alive at the date of last linkage to death certificates (December 31, 2010) were censored at this time or at the date of last in-person follow-up, whichever was the latest date. We divided patients into three groups according to tertiles of soy food intake and estimated covariate-adjusted survival curves for each group on the basis of a stratified proportional hazards model by using a direct adjustment method.[25,26] We also evaluated the difference in adjusted survival probabilities at 12 months across groups.[25] We used the proportional hazards model with age as the time scale to calculate hazard ratios (HRs) and 95% CIs for total mortality associated with intakes of soy food and isoflavones with adjustment for potential confounders. Intakes of soy food and isoflavones were modeled as restricted cubic spline functions (three knots) to account for possible nonlinear effects.[27] Likelihood ratio tests were used to evaluate nonlinearity by comparing the model with and without the nonlinear terms with 2 *df*. We used the 50th percentile of soy intake as the reference point and estimated multivariable-adjusted HRs for total mortality associated with the 10th, 30th, 70th, and 90th percentiles of intake.

Potential confounders that were adjusted for included age at diagnosis; TNM stage; primary treatment (surgery, chemotherapy, or radiotherapy); education; cigarette smoking; body mass index; menopausal status; family history of lung cancer; intakes of total calories, fruits, and nonsoy vegetables; and use of nonsteroidal anti-inflammatory drugs and vitamin supplements. We also adjusted for the time interval between the baseline dietary assessment and disease diagnosis. In this study, tumor histologic type was not associated with lung cancer survival; this variable was not included in the final model. Of 444 patients with incident lung cancer included in this study, 143 had missing data on certain clinical factors such as TNM stage. We first conducted analyses in all patients without adjusting for clinical factors. We then conducted analyses accounting for all potential confounders, including nonclinical and clinical variables, among patients with data available on all these covariates (n = 301). A two-sided $\alpha = .05$ was used for all tests.

RESULTS

Mean age at cancer diagnosis was 66.3 years (standard deviation, 8.8 years). Approximately 92% of patients with lung cancer were never smokers. Mean intakes, on a dry weight basis, were 18.0 g/d for soy food, 8.8 g/d for soy protein, and 30.3 mg/d for isoflavones. Soy food intake was not related to important patient characteristics such as age at diagnosis, smoking, obesity, family history of lung cancer, tumor stage, treatment regimens, and the time interval between the baseline dietary assessment and disease diagnosis (data not shown).

The median follow-up time since cancer diagnosis among the censored patients was 36 months (interquartile range, 17 to 77 months). During the follow-up, 318 deaths were documented, including 301 deaths (94.7%) for which lung cancer was the primary cause and 17 deaths (5.3%) from other causes. Table 1 summarizes selected patient characteristics in relation to overall survival after mutual adjustment for each other. Older age at cancer diagnosis was associated with poorer survival, although TNM stage at presentation had the greatest impact on prognosis.

Table 1. Demographic and Clinical Characteristics and Total Mortality Among Patients With Lung Cancer: Shanghai Women's Health Study, 1997 to 2010

Characteristic	No. of Patients	No. of Deaths	HR	95% CI*
Age (years)				
Per 5-year increment	301	231	2.65	2.64 to 4.27
Education (high school and above)				
No	201	162	1.0	
Yes	100	69	0.78	0.57 to 1.06
Cigarette smoking				
No	279	213	1.0	
Yes	22	18	1.39	0.81 to 2.40
Overweight/obese (BMI ≥ 25 kg/m²)				
No	183	140	1.0	
Yes	118	91	0.85	0.64 to 1.13
Tumor stage				
I and II	72	34	1.0	
III	86	70	2.65	1.75 to 4.03
IV	143	127	4.06	2.72 to 6.06
Chemotherapy				
No	100	79	1.0	
Yes	201	152	0.69	0.51 to 0.94
Surgery				
No	179	161	1.0	
Yes	122	70	0.71	0.48 to 1.06
Radiotherapy				
No	237	178	1.0	
Yes	64	53	0.87	0.62 to 1.21
Pathologic type†				
Nonadenocarcinoma	49	34	1.0	
Adenocarcinoma	143	97	1.14	0.75 to 1.72

NOTE. Analyses were restricted to patients with lung cancer who had data available on both nonclinical and clinical variables (n = 301).
Abbreviations: BMI, body mass index; HR, hazard ratio.
*HRs (95% CIs) for total mortality were estimated by using multivariable proportional hazards models, mutually adjusted for all other variables listed in the table except for pathologic type.
†Data on the histologic type of tumors were missing for 109 patients.

Initial analyses of soy food and overall survival that included all 444 patients showed that higher prediagnosis intake of soy food was significantly associated with better survival after adjusting for demographic and lifestyle characteristics and other nonclinical factors (Table 2). The effect size of the association was even larger after additional adjustment for tumor stage and treatment regimens in analyses that included 301 patients with data available on these clinical factors (Table 2). Figures 1 and 2 visually depict the relationship between soy food intake and overall survival after adjusting for all potential confounding variables. As shown in Figure 1, patients in the highest tertile of soy intake had better survival than those in the lowest tertile during the follow-up period. The adjusted survival rate at 12 months was 0.60 (95% CI, 0.51 to 0.69) for the highest tertile versus 0.50 (95% CI, 0.40 to 0.60) for the lowest tertile. As indicated in Figure 2, the risk of death decreased with increasing soy food intake until the intake level reached approximately the 70th percentile; further increases in soy intake did not appear to convey additional benefits. Compared with the median intake of soy food, adjusted HRs for total mortality associated with the 10th, 30th, 70th, and 90th percentiles of intake were 1.81 (95% CI, 1.26 to 2.59), 1.25 (95% CI, 1.09 to 1.42), 0.88 (95% CI, 0.80 to 0.97), and 0.89 (95% CI, 0.68 to 1.16), respectively (Table 2

and Fig 2), with *P* for overall significance = .004, *P* for linearity = .03, and *P* for nonlinearity = .01.

The association was more pronounced among never smokers. Compared with the median intake of soy food, multivariable adjusted HRs for total mortality associated with the 10th, 30th, 70th, and 90th percentiles of intake were 2.40 (95% CI, 1.47 to 3.91), 1.42 (95% CI, 1.17 to 1.72), 0.85 (95% CI, 0.76 to 0.96), and 0.92 (95% CI, 0.66 to 1.28), respectively, with *P* for overall significance = .002.

A similar inverse association was found for lung cancer-specific survival (data not shown) and when dietary isoflavone intake was evaluated (Table 2). Results were essentially unchanged when only the first FFQ data were analyzed (data not shown).

DISCUSSION

In this longitudinal follow-up study of predominantly lifetime non-smoking women, we found, for the first time, that usual intake of soy food before cancer diagnosis was associated with significantly improved survival of patients with lung cancer, although not in a linear manner. This finding, along with our previous observation of an approximately 40% reduction in risk of incident lung cancer associated with high intake of soy food,[20] provides further support for the role of soy food intake in lung cancer development and prognosis.

In direct contrast to the significant survival advantage among patients with lung cancer who consumed greater amounts of soy food in our study, a detrimental impact has been associated with HRT use among patients with lung cancer.[7] Use of estrogen plus progestin therapy was found to significantly increase the risk of developing aggressive lung cancer (poorly differentiated and metastatic tumors) and risk of death as a result of lung cancer in the Women's Health Initiative trial.[6] However, use of the antiestrogen tamoxifen was linked to a reduction in lung cancer deaths in a large breast cancer follow-up study.[11]

Potential mechanisms underlying the observed survival benefit among patients with lung cancer with high prediagnosis intake of soy food are likely to be multifarious. Soy isoflavones can compete with endogenous estrogens in binding to ERs[12,13] and can modulate estrogen levels by increasing clearance and lowering bioavailability.[28,29] Besides ER-mediated effects, it has been suggested that soy isoflavones modulate multiple signaling pathways involved in neoplastic transformation, for example by acting as a tyrosine kinase inhibitor, enhancing the antitumor effect of epidermal growth factor receptor tyrosine kinase inhibitors for non–small-cell lung cancer[13,30] and inhibiting oxidative stress and proinflammatory mediators.[31,32] Administration of soy isoflavones has been shown to significantly decrease tumor development and the number of tumors in vivo and increase the life span of tumor-bearing animals[19,33,34] by inducing cell cycle arrest in the G2-M phase, inducing apoptosis, and inhibiting tumor angiogenesis and invasion in a dose- and time-dependent manner.[15,16,35]

This study, to the best of our knowledge, is the largest follow-up study of lung cancer survival in female nonsmokers and the first study on the potential beneficial effect of soy food on lung cancer outcomes. The population is well suited for the study of soy and lung cancer in nonsmokers, given its high yet diverse soy food intake levels and extremely low prevalence of smoking. Dietary intake was assessed by using a validated FFQ that covered virtually all soy foods consumed in the study population and was administered by an in-person interview

Table 2. Multivariable-Adjusted HR for Total Mortality Among Patients With Lung Cancer According to Prediagnosis Intakes of Soy Food and Isoflavones: Shanghai Women's Health Study, 1997 to 2010

Intake	Percentile	HR for All Patients (N = 444)*	95% CI	P for Overall Significance	P for Linearity	P for Nonlinearity	HR for Patients With Data on Clinical Characteristics (n = 301)*†	95% CI	P for Overall Significance	P for Linearity	P for Nonlinearity
Soy food (g/d)‡											
6.3	10th	1.42	1.08 to 1.87	.04	.11	.05	1.81	1.26 to 2.59	.004	.03	.01
11.5	30th	1.15	1.03 to 1.28				1.25	1.09 to 1.42			
16.0	50th	1.00	Reference				1.00	Reference			
21.4	70th	0.92	0.85 to 0.99				0.88	0.80 to 0.97			
31.4	90th	0.93	0.75 to 1.14				0.89	0.68 to 1.16			
Isoflavones (mg/d)											
10.2	10th	1.39	1.06 to 1.84	.06	.19	.05	1.76	1.22 to 2.54	.007	.04	.02
18.8	30th	1.14	1.02 to 1.28				1.24	1.08 to 1.42			
26.5	50th	1.00	Reference				1.00	Reference			
37.9	70th	0.93	0.85 to 1.01				0.87	0.78 to 0.97			
53.5	90th	0.97	0.78 to 1.20				0.89	0.67 to 1.17			

NOTE. Multivariable-adjusted HRs were estimated by the proportional hazards model with restricted cubic spline functions.

Abbreviation: HR, hazard ratio.

*Models were stratified on birth year and adjusted for age at diagnosis; education; cigarette smoking; body mass index; menopausal status; history of lung cancer in first-degree relatives; intakes of total calories, fruits and non-soy vegetables; time interval between the first food frequency questionnaire survey and lung cancer diagnosis; and use of nonsteroidal anti-inflammatory drugs and vitamin supplements.

†Further adjusted for tumor stage, surgery, radiotherapy, and chemotherapy.
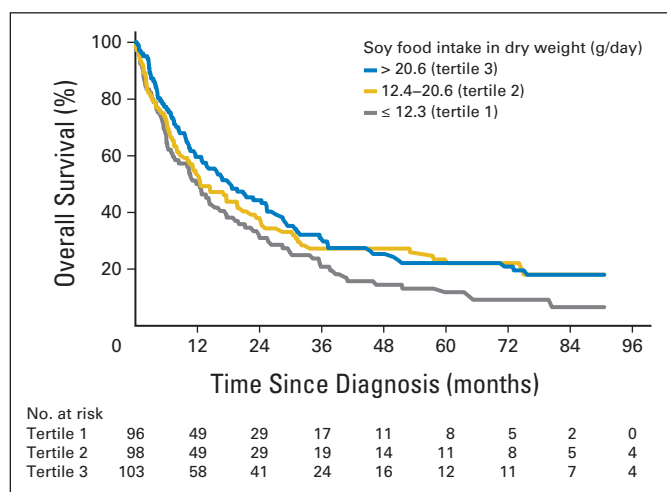
‡Assessed on a dry weight basis.

Fig 1. Adjusted survival curves of patients with lung cancer by prediagnosis intake of soy food, estimated from a stratified proportional hazards model by using a direct adjustment method.[25] Analyses were restricted to patients with data on clinical characteristics (n = 301). The gray line indicates the lowest tertile of intake, the gold line indicates the middle tertile, and the blue line indicates the highest tertile.

over two time periods to provide more stable estimates of usual intake.[22,36] Other strengths of our study include nearly complete identification of incident cases in the parent cohort and high follow-up rate by in-person biennial surveys and annual record linkage.[36] Another important strength is the ability to adjust for a wide range of potential confounding factors, including clinical prognostic indicators (age at diagnosis, disease stage, and treatment regimens) and other lifestyle
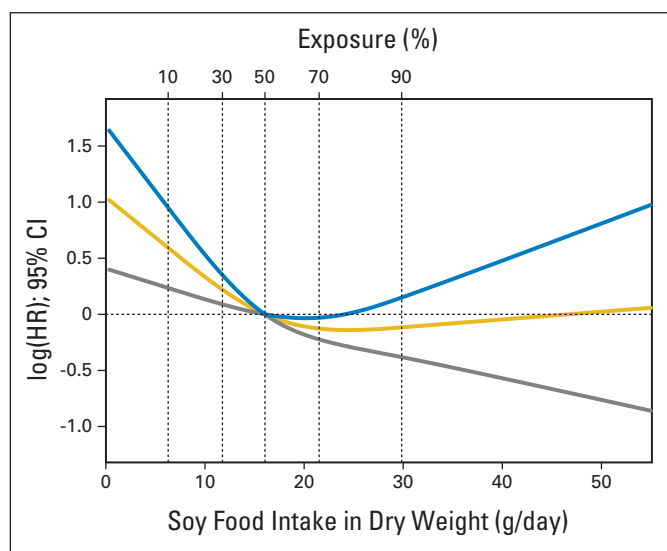

Fig 2. Smoothed plot for multivariable-adjusted hazard ratios (HRs) for total mortality of patients with lung cancer according to soy food intake. The log(HR) was estimated by using the restricted cubic-spline proportional hazards model with three knots placed at the 5th, 50th, and 95th percentiles of soy food intake. Analyses were restricted to patients with data available on clinical characteristics (n = 301). Patients with soy food intake above the 99th percentile were excluded. The median value of soy food intake was treated as the reference point. Exposure of 10%, 30%, 50%, 70%, and 90% indicate the 10th, 30th, 50th, 70th, and 90th percentiles of soy food intake distribution, respectively. The gold line indicates the point estimates of HR, and the blue and gray lines indicate the upper and lower bounds of the 95% CI of HR, respectively.

and dietary factors. Therefore, the observed favorable effect of prediagnosis intake of soy food on lung cancer survival is likely to be independent of these known prognosis predictors and cannot be explained by differences in other lifestyle and dietary factors.

Our study has several limitations. Despite having adjusted for a range of potential confounding variables, we could not completely rule out the possibility of residual confounding due to unmeasured or inadequately measured covariates. Another limitation is the presence of random measurement errors in dietary assessment, which may have attenuated the association between soy intake and lung cancer survival. Missing data on tumor stage in a sizable fraction of patients and lack of detailed information on lung cancer treatment may also be a concern. However, we found little evidence that patient's clinical characteristics, including tumor stage and treatment regimens, were associated with soy food intake, suggesting that these clinical parameters may not significantly confound the association of soy intake and lung cancer survival. In fact, similar associations were observed in the analyses with and without adjustment for clinical factors.

In this study, dietary assessment occurred before cancer diagnosis; thus, no inferences can be made on the role of postdiagnosis diet in lung cancer survival. Further investigation is needed to evaluate the association between postdiagnosis intake of soy food and lung cancer outcomes, particularly among patients with early-stage disease for whom any postdiagnostic intervention, including dietary changes, may have the most impact. Finally, our study was conducted among Chinese women with a low prevalence of cigarette smoking and postmenopausal hormone use; thus, it would be useful to study this association among smokers and HRT users.

In conclusion, this longitudinal follow-up study provides the first evidence that soy food consumption before cancer diagnosis may favorably affect clinical outcomes of lung cancer in women. More epidemiologic studies are needed to confirm this finding and provide support for launching randomized trials. Given that incidence of lung cancer among women is increasing steadily worldwide and that soy can be readily incorporated into most diets, our findings, if confirmed by future studies, could potentially contribute to the development of new strategies for control and management of this fatal malignancy.

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