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JAMA. 2009;302(22):2437-2443 (doi:10.1001/jama.2009.1783)

http://jama.ama-assn.org/cgi/content/full/302/22/2437

Soy Food Intake and Breast Cancer Survival

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Context Soy foods are rich in isoflavones, a major group of phytoestrogens that have been hypothesized to reduce the risk of breast cancer. However, the estrogen-like effect of isoflavones and the potential interaction between isoflavones and tamoxifen have led to concern about soy food consumption among breast cancer patients.

Objective To evaluate the association of soy food intake after diagnosis of breast cancer with total mortality and cancer recurrence.

Design, Setting, and Participants The Shanghai Breast Cancer Survival Study, a large, population-based cohort study of 5042 female breast cancer survivors in China. Women aged 20 to 75 years with diagnoses between March 2002 and April 2006 were recruited and followed up through June 2009. Information on cancer diagnosis and treatment, lifestyle exposures after cancer diagnosis, and disease progression was collected at approximately 6 months after cancer diagnosis and was reassessed at 3 follow-up interviews conducted at 18, 36, and 60 months after diagnosis. Annual record linkage with the Shanghai Vital Statistics Registry database was carried out to obtain survival information for participants who were lost to follow-up. Medical charts were reviewed to verify disease and treatment information.

Main Outcome Measures Total mortality and breast cancer recurrence or breast cancer–related deaths. Cox regression analysis was carried out with adjustment for known clinical predictors and other lifestyle factors. Soy food intake was treated as a time-dependent variable.

Results During the median follow-up of 3.9 years (range, 0.5-6.2 years), 444 deaths and 534 recurrences or breast cancer–related deaths were documented in 5033 surgically treated breast cancer patients. Soy food intake, as measured by either soy protein or soy isoflavone intake, was inversely associated with mortality and recurrence. The hazard ratio associated with the highest quartile of soy protein intake was 0.71 (95% confidence interval [CI], 0.54-0.92) for total mortality and 0.68 (95% CI, 0.54-0.87) for recurrence compared with the lowest quartile of intake. The multivariate-adjusted 4-year mortality rates were 10.3% and 7.4%, and the 4-year recurrence rates were 11.2% and 8.0%, respectively, for women in the lowest and highest quartiles of soy protein intake. The inverse association was evident among women with either estrogen receptor–positive or –negative breast cancer and was present in both users and nonusers of tamoxifen.

Conclusion Among women with breast cancer, soy food consumption was significantly associated with decreased risk of death and recurrence.

JAMA. 2009;302(22):2437-2443 www.jama.com

ESTROGEN IS BELIEVED TO PLAY a central role in breast cancer development and progression. Blocking the effect of estrogen, either by inhibiting estrogen action or by reducing estrogen production, has been widely used in breast cancer treatment as an adjuvant therapy.[1] Soy foods are rich in phytoestrogens, mainly in the form of isoflavones, which are natural estrogen receptor modulators that possess both estrogen-like and antiestrogenic properties. Soy constituents have also been shown to have other anticancer effects, including the inhibition of DNA topoisomerase I and II, proteases, tyrosine kinases, inositol phosphate, and angiogenesis and may also boost immune response and possess antioxidative effects.[2,3]

Consumption of soy food has been inversely related to the risk of breast cancer in many epidemiological studies.[4-6] However, genistein, a major form of isoflavone, has been shown to enhance the proliferation of breast cancer cells in vitro and to promote estrogen-dependent mammary tumor growth in ovariectomized rats.[3,7] In addition, breast cancer treatments often lead to a decrease in the endogenous estrogen supply of survivors, and a concern has been raised as to whether soy isoflavones may exert their estrogenic effects, promote cancer recurrence, and, thus, negatively influence overall survival.[7,8] Furthermore, both in vivo and in vitro studies have suggested that soy isoflavones may interact with tamoxifen, although both synergistic and antagonistic interactions have been reported.[3,9-13]

To our knowledge, only 1 epidemiological study, the Life After Cancer Epidemiology (LACE) study, has evaluated the association of postdiagnosis soy isoflavone intake with cancer recurrence. An inverse association was suggested for postmenopausal women who had used tamoxifen.[14]

Herein, we report a comprehensive evaluation of the association of soy food consumption after diagnosis of breast cancer with outcomes using data from a

For editorial comment see p 2483.

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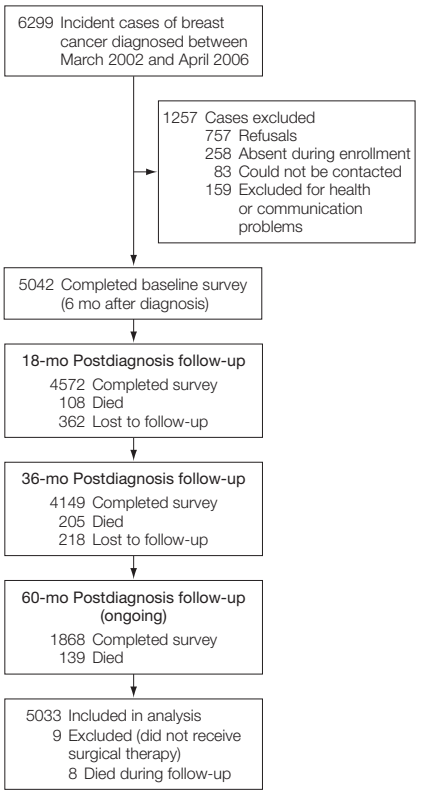
Figure. Patient Flow



longitudinal study of 5042 breast cancer patients, with a particular focus on differences in the association according to the estrogen receptor (ER) status of the cancer and tamoxifen use by patients.

METHODS

Study Population

The current report includes participants of the Shanghai Breast Cancer Survival Study, a longitudinal, population-based study of women aged 20 to 75 years who were diagnosed as having primary breast cancer between March 2002 and April 2006 and were permanent residents of Shanghai, China. Patients were identified from the population-based Shanghai Cancer Registry and recruited into the study approximately 6 months after cancer diagnosis.

Of the 6299 cases identified, 5042 provided written informed consent and participated in the study (participation rate, 80.0%). Among the remaining cases, 757 (12.0%) refused to participate, 258 (4.1%) were absent during study enrollment, 83 (1.3%) could not be contacted, and 159 (2.5%) were excluded for other miscellaneous reasons such as health or communication problems. Nonparticipants were similar in age at cancer diagnosis but were more likely to have an advanced stage of cancer than study participants. Nine patients did not receive surgical therapy and were excluded from the analysis, leaving a total of 5033 participants for the current study. Cancer diagnoses were confirmed by a combination of medical record review and central review of pathological slides.

Data Collection

In-person recruitment and interviews using a structured questionnaire were carried out approximately 6.5 months (SE, 0.7 months) after cancer diagnosis by trained interviewers who were retired health care professionals. The baseline survey questionnaire covered demographic characteristics, reproductive history, disease history, medication use, selected lifestyle factors, diet, use of complementary and alternative medicine, and quality of life.

Clinical information collected included cancer stage, tumor ER and progesterone receptor (PR) status, and primary treatments (surgery/mastectomy, radiation therapy, chemotherapy, immunotherapy, and hormone therapy such as tamoxifen). Inpatient medical charts were reviewed to verify clinical information. Anthropometric measurements, including height, weight, waist circumference, and hip circumference, were taken according to a standard protocol.

Habitual dietary intake was assessed for specific time windows: the preceding 6 months for the baseline survey, the preceding 12 months for the 18-month survey, and the preceding 18 months for the 36-month survey. We used a validated food frequency questionnaire[15] that was designed to measure consumption of soy foods commonly consumed in Shanghai, including tofu, soy milk, fresh soy beans, and other soy products, as well as meat, fish, and cruciferous vegetables. Nutrient consumption, including soy protein and isoflavone intake, was estimated by summing the product of food intake and the nutrient content of the food item based on the *Chinese Food Composition Tables 2002*.[16]

The cohort is being followed up by in-person interviews that take place at 18 months, 36 months, and 60 months after cancer diagnosis, supplemented by record linkage to the Shanghai Vital Statistics Registry (FIGURE). The follow-up interviews update soy food intake and complementary and alternative medicine use and collect information on disease progression and survival status.

As of June 30, 2009, the 36-month interview had been completed for 4354 of 4934 eligible patients (follow-up rate, 88.2%). The 60-month interview is still ongoing and has been completed for 1868 patients. Women who completed the 36-month follow-up and women who dropped out had similar intakes of soy food and other foods at the baseline survey. However, the 2 groups differed in age at diagnosis, body mass index (BMI), education level, and income, and these factors were adjusted for in the analyses.

Outcome information for dropouts was ascertained by annual linkage to the Vital Statistics Registry database. The most recent record linkage was conducted in October 2008. A Charlson comorbidity index was created for each woman based on a validated comorbidity scoring system[17] and the diagnostic codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification*.[18] The institutional review boards of all participating institutions approved the study protocol.

Statistical Analysis

The major end points for the study were any death (total mortality analysis) and cancer recurrence/metastasis or death related to breast cancer (recurrence analysis). Survival status was censored at the date of last in-person contact or May 31, 2008 (5 months before the most recent linkage to the Vital Statistics Registry), whichever was most recent. For 15 participants who died of breast cancer but had missing informa-

tion about disease recurrence, we used the disease stage (TNM)–specific median interval between disease recurrence and death to impute the date of disease recurrence. We excluded 20 patients who had a disease-free survival time of 0 from the recurrence analysis.

Cox proportional hazards models were used to evaluate the associations of soy intake with mortality and recurrence using age as the time scale.[19] Entry time was defined as age at diagnosis and exit time was defined as age at event or censoring. Soy protein and soy isoflavone intakes were categorized by quartile distribution and were treated as a time-dependent variable in multivariate analysis using a counting process approach to capture the changes in soy intake over the course of the follow-up period.[19] We applied the restricted cubic spline function in Cox regression analyses to evaluate the association pattern between soy food intake and mortality/recurrence. In these analyses, soy protein/isoflavone intake was treated as a continuous variable; knots were placed at the 5th, 10th, 50th, 90th, and 95th percentiles of intake; and the 10th percentile of intake was used as the reference.[20] Menopausal status at study enrollment was defined as cessation of menstruation for at least 12 months.

Differences in sociodemographic and clinical characteristics across baseline soy food intake categories were evaluated using the Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables. We adjusted in the multivariate analyses for known clinical prognosis predictors and lifestyle factors collected at baseline that were related to both soy food intake and survival. These included age at diagnosis, TNM stage, chemotherapy, radiotherapy, type of surgery, BMI, menopausal status, ER and PR status, tamoxifen use, education level, income, cruciferous vegetable intake, total meat intake, vitamin supplement use, tea consumption, and physical activity level.

Analyses stratified by the ER status of the cancer, disease stage, tamoxifen use, and menopausal status at study enrollment were conducted to evaluate whether these factors modified the associations of soy food intake with total mortality or recurrence. Multiplicative interaction was evaluated using the log likelihood ratio test, which compared the model including only the main effects with the model including both main effects and interaction terms.[19]

Table 1. Demographic and Clinical Predictors for Breast Cancer Survival in the Shanghai Breast Cancer Survival Study

Characteristics	No. of Participants	5-Year Overall Survival		
		Deaths, No.	Rate, %[a]	*P* Value
Age at diagnosis, y				
<40	242	23	89.3	<.001
40-49	2002	141	91.9	
50-59	1489	134	88.6	
≥60	1300	146	86.4	
Education				
None	190	30	78.8	<.001
Elementary	396	59	82.4	
Middle or high school	3642	313	90.0	
College or higher	804	42	93.3	
Income[b]				
<700	1403	165	87.0	<.001
700-999	1484	148	88.0	
1000-1999	1541	105	91.8	
≥2000	602	26	93.4	
Body mass index[c]				
<25	3273	267	90.3	.01
25-29	1476	138	88.7	
≥30	280	37	83.9	
Menopausal status				
Premenopausal	2461	186	91.3	<.001
Postmenopausal	2572	258	87.5	
Tamoxifen use				
No	2408	250	87.5	<.001
Yes	2622	193	91.1	
TNM stage				
0-II	4318	280	91.9	<.001
III-IV	492	147	65.6	
Unknown	223	17	92.1	
Estrogen receptor status				
Negative	1772	224	85.2	<.001
Positive	3181	202	92.0	
Missing	80	18	76.5	
Progesterone receptor status				
Negative	2043	238	86.0	<.001
Positive	2894	187	92.1	
Missing	96	19	79.4	
Chemotherapy				
No	444	39	88.5	.95
Yes	4589	405	89.5	
Radiotherapy				
No	3418	237	91.5	<.001
Yes	1615	207	84.9	
Radical mastectomy				
No	373	29	90.6	.77
Yes	4660	415	89.3	
Hormone therapy[d]				
No	2388	250	87.0	.01
Yes	175	8	94.6	

(continued)

Table 1. Demographic and Clinical Predictors for Breast Cancer Survival in the Shanghai Breast Cancer Survival Study (continued)

Characteristics	No. of Participants	5-Year Overall Survival		*P* Value
		Deaths, No.	Rate, %[a]	
No. of pregnancies				
0	202	21	88.7	.03
1	987	91	89.1	
2	1669	120	91.7	
3	1168	101	89.3	
≥4	1007	111	86.5	
Family history of cancer[e]				
No	4728	423	89.3	.29
Yes	305	21	91.1	
Comorbidity score				
0	4031	341	90.1	.06
≥1	1002	103	86.7	

[a] The survival rate was calculated by using the life table analysis method; ie, by dividing number of events by person-years of follow-up.
[b] Yuan renminbi/person/month. One US dollar = 6.83 yuan renminbi on November 17, 2009.
[c] Body mass index is calculated as weight in kilograms divided by height in meters squared.
[d] Among postmenopausal women. Refers to hormone use to alleviate symptoms of menopause.
[e] Family history of breast cancer or ovarian cancer.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina), and all statistical tests were based on 2-tailed probability and a significance level set at $\alpha < .05$.

RESULTS

After a median follow-up of 3.9 years (range, 0.5-6.2 years), 444 total deaths and 534 recurrences or breast cancer–related deaths were documented in the cohort. Older age at diagnosis, advanced disease stage, negative ER or PR status, high BMI, postmenopausal status, low education level, low income, presence of comorbidity, having more than 3 pregnancies, and receiving radiotherapy were inversely related to the survival rate, while tamoxifen use and ever use of hormone therapy to alleviate symptoms of menopause were positively associated with the survival rate (TABLE 1).

At the 6-month interview, women who had high levels of soy food intake tended to also have higher intakes of meats, including red meat, white meat, and fish, and cruciferous vegetables and were more likely to have received chemotherapy and/or radical mastectomy, to drink tea, to have high BMI, to engage in exercise, and to have more vitamin supplement use but were less likely to have received radiotherapy compared with women who had lower levels of soy food consumption (eTable 1 [available online at http://www.jama.com]). Soy food consumption did not vary by education level, number of pregnancies, tumor stage, hormone receptor status, ginseng use, income, or family history of breast or ovarian cancer. Alcohol consumption, cigarette smoking, and hormone therapy to alleviate symptoms of menopause are rare in this population and were not related to soy food consumption.

Soy food consumption after cancer diagnosis, measured as soy protein intake, was inversely associated with mortality and recurrence (TABLE 2). The hazard ratios (HRs) comparing the highest and the lowest quartiles of soy protein intake were 0.71 (95% confidence interval [CI], 0.54-0.92) for total mortality and 0.68 (95% CI, 0.54-0.87) for recurrence. The corresponding HRs were 0.79 (95% CI, 0.61-1.03) for mortality and 0.77 (95% CI, 0.60-0.98) for recurrence, when soy isoflavone intake was considered. The associations of soy protein/isoflavone intake with mortality and recurrence appear to follow a linear dose-response pattern until soy protein intake reaches 11 g/d (or soy isoflavone intake reaches 40 mg/d). After these points, the association appears to level off or even rebound (eFigure 1 and eFigure 2). The multivariate-adjusted 4-year mortality rates were 10.3% and 7.4% and the 4-year recurrence rates were 11.2% and 8.0%, respectively, for women in the lowest and highest quartiles of soy protein intake. The multivariate-adjusted mortality and recurrence curves by soy protein intake are shown in eFigure 3 and eFigure 4.

The associations of soy food intake with mortality and recurrence were observed for women with either ER-positive or ER-negative breast cancer (Table 2). The association between soy food intake and total mortality did not appear to vary by menopausal status (eTable 2) or by cancer stage (eTable 3). Excluding 156 women with stage 0 breast cancer did not change the results.

Tamoxifen was associated with reduced risk of relapse or breast cancer–specific mortality among women with ER-positive breast cancer (HR, 0.77; 95% CI, 0.59-1.02). Given that soy isoflavones and tamoxifen both bind to ER, we evaluated the combined effect of soy food intake and tamoxifen use on survival among women with ER-positive breast cancer (TABLE 3). We found that women in the highest soy food intake groups had the lowest mortality and recurrence rate compared with women in the lowest soy food intake group, regardless of tamoxifen use status. The inverse association of tamoxifen use and recurrence, however, was only seen among women with low to moderate levels of soy food intake.

Among women whose soy food intake was in the highest quartiles, tamoxifen use did not appear to confer any additional benefit. The HRs for recurrence associated with the highest quartile of soy protein intake were 0.65 (95% CI, 0.36-1.17) for nonusers of tamoxifen and 0.66 (95% CI, 0.40-1.09) for tamoxifen users, both of which were lower than the HRs among women who were in the lowest quartile of soy food intake and used tamoxifen (HR, 0.93; 95% CI, 0.58-1.51). These point estimates were not statistically significant because of the small sample size. Tests for multiplicative interaction between

soy intake and tamoxifen use were not statistically significant.

COMMENT

Although soy food consumption among US women is substantially lower than among women in China (the average isoflavone intake among US women is 1-6 mg/d[21] compared with 47 mg/d in our study population), soy food consumption in the United States has been increasing rapidly. The percentage of persons eating soy products at least once per week was 28% in 2003, up from 15% in 1997.[22]

Although soy constituents have been shown to have anticancer properties[1-7] and improve cardiovascular and bone health,[23-25] the estrogen-like effect of soy isoflavones[1,3,7,8] and conflicting data from in vivo and in vitro studies regarding the role of soy constituents in stimulating cell proliferation[3,7] have raised a concern about the safety of soy food consumption among breast cancer survivors.[7,8,26] Because concentrated soy isoflavones are increasingly being added to a wide variety of foods, including beverages, nutrition bars, yogurt, baked goods, meal replacements, and confections, exposure to isoflavones is becoming ubiquitous, which is heightening concern about soy food consumption among the rapidly increasing population of breast cancer survivors.

In our comprehensive evaluation of soy food consumption and breast cancer outcomes using data from a large, population-based cohort study, we found that soy food intake was inversely associated with mortality and recurrence. The inverse association did not appear to vary by menopausal status and was evident for women with ER-positive and ER-negative cancers and early and late-stage cancers.

Among the many constituents of soy food, soy isoflavones are the most intensively studied phytochemicals for their health-related effects. It has been shown that soy isoflavones compete with endogenous estrogens in the binding of estrogen receptors, increase the synthesis of sex hormone–binding globulin (thus lowering the biological

Table 2. Association of Soy Food Intake With Total Mortality and Recurrence in the Shanghai Breast Cancer Survival Study[a]

Quartile of Intake	No. of Participants	Total Mortality		Recurrence/Breast Cancer–Specific Mortality	
		No. of Events	HR (95% CI)	No. of Events	HR (95% CI)
All Participants					
Soy protein, g/d					
≤5.31	1254	117	1 [Reference]	137	1 [Reference]
5.32-9.45	1262	95	0.77 (0.59-1.00)	136	0.77 (0.61-0.98)
9.46-15.31	1256	112	0.72 (0.55-0.94)	128	0.69 (0.54-0.87)
>15.31	1260	120	0.71 (0.54-0.92)	133	0.68 (0.54-0.87)
Isoflavones, mg/d					
≤20.00	1256	119	1 [Reference]	144	1 [Reference]
20.01-36.50	1259	83	0.73 (0.56-0.95)	116	0.84 (0.67-1.06)
36.51-62.68	1258	123	0.77 (0.59-1.00)	141	0.65 (0.51-0.84)
>62.68	1259	119	0.79 (0.61-1.03)	133	0.77 (0.60-0.98)
Women With ER-Negative Breast Cancer					
Soy protein, g/d					
≤5.31	424	54	1 [Reference]	65	1 [Reference]
5.32-9.45	446	46	0.82 (0.57-1.18)	64	0.93 (0.67-1.29)
9.46-15.31	445	60	0.63 (0.42-0.94)	66	0.67 (0.47-0.97)
>15.31	457	64	0.78 (0.54-1.14)	72	0.77 (0.54-1.09)
Isoflavones, mg/d					
≤20.00	424	54	1 [Reference]	67	1 [Reference]
20.01-36.50	441	38	0.81 (0.56-1.18)	55	1.01 (0.72-1.40)
36.51-62.68	447	67	0.77 (0.52-1.13)	72	0.62 (0.43-0.89)
>62.68	460	65	0.85 (0.58-1.24)	73	0.88 (0.62-1.25)
Women With ER-Positive Breast Cancer					
Soy protein, g/d					
≤5.31	808	55	1 [Reference]	67	1 [Reference]
5.32-9.45	797	47	0.79 (0.53-1.18)	69	0.71 (0.50-1.01)
9.46-15.31	794	49	0.88 (0.61-1.30)	60	0.79 (0.56-1.10)
>15.31	781	51	0.67 (0.45-1.00)	59	0.69 (0.50-0.98)
Isoflavones, mg/d					
≤20.00	813	57	1 [Reference]	72	1 [Reference]
20.01-36.50	796	43	0.74 (0.50-1.11)	58	0.80 (0.56-1.14)
36.51-62.68	796	52	0.85 (0.58-1.24)	67	0.78 (0.55-1.10)
>62.68	775	50	0.78 (0.53-1.16)	58	0.77 (0.54-1.09)

Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio.

[a] Soy food intake was treated as a time-dependent variable. Hazard ratios were adjusted for age at diagnosis, TNM stage, chemotherapy, radiotherapy, type of surgery received, body mass index, menopausal status, ER and progesterone receptor status, tamoxifen use, education level, income, cruciferous vegetable intake, total meat intake, vitamin supplement use, tea consumption, and physical activity. *P* values for interaction between ER status and soy food intake were as follows: for soy protein intake, *P*=.36 for total mortality and *P*=.35 for recurrence or breast cancer–specific mortality; for isoflavone intake, *P*=.89 for total mortality and *P*=.31 for recurrence/breast cancer–specific mortality.

Table 3. Soy Food Intake and Tamoxifen Use in Association With Total Mortality and Recurrence Among Women With Estrogen Receptor–Positive Breast Cancer in the Shanghai Breast Cancer Survival Study[a]

	Total Mortality						Recurrence/Breast Cancer–Specific Mortality			
	No Tamoxifen Use			Tamoxifen Use			No Tamoxifen Use		Tamoxifen Use	
Quartile of Intake	No. of Participants	No. of Events	HR (95% CI)	No. of Participants	No. of Events	HR (95% CI)	No. of Events	HR (95% CI)	No. of Events	HR (95% CI)
Soy protein, g/d										
≤5.31	249	20	1 [Reference]	559	35	0.90 (0.52-1.57)	25	1 [Reference]	42	0.93 (0.58-1.51)
5.32-9.45	248	14	0.65 (0.33-1.29)	548	32	0.79 (0.45-1.39)	24	0.73 (0.41-1.32)	44	0.65 (0.39-1.09)
9.46-15.31	240	24	1.24 (0.69-2.22)	554	25	0.62 (0.35-1.12)	25	1.10 (0.65-1.88)	35	0.58 (0.34-0.98)
>15.31	275	18	0.65 (0.33-1.29)	506	33	0.61 (0.34-1.08)	22	0.65 (0.36-1.17)	37	0.66 (0.40-1.09)
Isoflavones, mg/d										
≤20.00	253	20	1 [Reference]	560	37	0.92 (0.53-1.60)	25	1 [Reference]	47	0.91 (0.56-1.48)
20.01-36.50	253	13	0.72 (0.37-1.42)	542	29	0.69 (0.39-1.23)	22	0.84 (0.47-1.50)	35	0.71 (0.43-1.18)
36.51-62.68	237	26	1.15 (0.63-2.09)	559	26	0.62 (0.34-1.12)	28	1.04 (0.61-1.77)	39	0.58 (0.34-0.98)
>62.68	269	17	0.74 (0.38-1.43)	506	33	0.74 (0.42-1.29)	21	0.71 (0.39-1.28)	37	0.73 (0.44-1.19)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Soy food intake was treated as a time-dependent variable. Hazard ratios were adjusted for age at diagnosis, TNM stage, chemotherapy, radiotherapy, type of surgery received, body mass index, progesterone receptor status, education level, income, cruciferous vegetable intake, total meat intake, vitamin supplement use, tea consumption, and physical activity. *P* values for interaction between tamoxifen use and soy food intake were as follows: for soy protein intake, *P*=.18 for total mortality and *P*=.26 for recurrence or breast cancer–specific mortality; for isoflavone intake, *P*=.40 for total mortality and *P*=.39 for recurrence/breast cancer–specific mortality.

availability of sex hormones), inhibit 17β-hydroxysteroid dehydrogenases (thus reducing estrogen synthesis), and increase clearance of steroids from the circulation.[2,3] These antiestrogenic effects may be one of the underlying mechanisms through which soy food consumption is associated with better breast cancer outcomes.

We did not find that risk estimates associated with soy isoflavone intake were stronger than risk estimates associated with soy protein intake. This may be because measurement errors related to the assessment of isoflavone intake are larger than measurements errors related to soy protein intake. On the other hand, these results may also suggest that other known and unknown constituents of soy foods, such as folate, protein, protease inhibitors, calcium, or fiber, individually or in combination, are responsible for the survival benefits of soy food consumption. It has been reported in some studies that the health effects of soy supplements and soy isoflavone supplements may differ. For example, soy milk supplements have been found to reduce circulating levels of estrogen,[27-29] while soy isoflavone supplements failed to do so.[30] Similarly, soy milk or soy protein supplements were found to relieve menopausal symptoms,[31-33] but soy isoflavone supplements showed no effect.[34] More studies are needed to replicate our findings and to disentangle whether the benefit of soy food consumption on breast cancer prognosis is the result of soy isoflavones or other soy constituents or is the result of a combination of the effects of multiple soy constituents.

In our study population, soy food intake was associated with other characteristics of a healthy lifestyle, including more exercise and high vegetable and fish intake. Earlier studies have shown that high vegetable intake may be related to an improved survival rate, although evidence is not entirely consistent.[35-37] We carefully adjusted for other dietary intake and lifestyle factors in our analyses. However, residual confounding resulting from measurement errors or unmeasured lifestyle factors could not be entirely ruled out, which would likely lead to an underestimation of the true association. Another concern is reverse causation; ie, poor health and appetite among breast cancer patients who had subclinical recurrence may have led to a reduction of soy food consumption. If this were true, we would expect to see that other dietary intakes were also inversely related to survival. However, in our study, meat consumption was not associated with breast cancer survival, which argues against reverse causation.

Because isoflavones and tamoxifen both bind to estrogen receptors and because of the conflicting results from in vivo and in vitro studies, which have reported both synergetic and antagonistic effects between isoflavones and tamoxifen use, there is concern that soy isoflavones may affect the efficacy of this widely used adjuvant treatment for breast cancer. In our study, we found that soy food intake was associated with improved survival regardless of tamoxifen use, while tamoxifen use was related to improved survival only among women who had low or moderate levels of soy food intake. Tamoxifen was not related to further improvement of survival rates among women who had the highest level of soy food intake. More importantly, women who had the highest level of soy food intake and who did not take tamoxifen had a lower risk of mortality and a lower recurrence rate than women who had the lowest level of soy food intake and used tamoxifen, suggesting that high soy food intake and tamoxifen use may have a comparable effect on breast cancer outcomes.

Our study is the largest population-based study of breast cancer survival to date and was specifically designed to evaluate the influence of soy food intake on breast cancer outcomes. Soy

food intake was assessed using a validated dietary questionnaire and was updated during the course of follow-up. The high response rate and ability to adjust for other lifestyle factors also improved the quality of our study. However, the follow-up period of our study is still relatively short, which prevented an evaluation of the long-term effects of soy intake on breast cancer outcomes. Continued follow-up of the cohort would overcome this limitation. Our study also has limited statistical power for subanalyses (eg, ER status, tamoxifen use status).

In summary, in this population-based prospective study, we found that soy food intake is safe and was associated with lower mortality and recurrence among breast cancer patients. The association of soy food intake with mortality and recurrence appears to follow a linear dose-response pattern until soy food intake reached 11 g/d of soy protein; no additional benefits on mortality and recurrence were observed with higher intakes of soy food. This study suggests that moderate soy food intake is safe and potentially beneficial for women with breast cancer.

Author Contributions: Dr Shu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Shu, W. Zheng, Lu.
Acquisition of data: Y. Zheng, Gu, Lu.
Analysis and interpretation of data: Shu, Cai, Chen.
Drafting of the manuscript: Shu.
Critical revision of the manuscript for important intellectual content: Shu, Y. Zheng, Cai, Gu, Chen, W. Zheng, Lu.
Statistical analysis: Cai.
Obtained funding: Shu, W. Zheng.
Administrative, technical, or material support: Y. Zheng, Gu, Chen, Lu.
Study supervision: Shu.
Financial Disclosures: Dr Shu reports having received a research development fund from the United Soybean Board in 2005. No other disclosures were reported.
Funding/Support: This study was supported by grants from the US Department of Defense Breast Cancer Research Program (grant DAMD 17-02-1-0607) and the National Cancer Institute (grant R01 CA118229).
Role of the Sponsors: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation and approval of the manuscript.
Disclaimer: The content of the report does not necessarily reflect the position or the policy of the US government, and no official endorsement should be inferred.
Additional Information: eTables 1-3 and eFigures 1-4 are available online at http://www.jama.com.
Additional Contributions: We thank Fan Jin, MD, a paid consultant for the Shanghai Institute of Preventive Medicine, for her support of the study's implementation. She received compensation for her assistance. We thank Bethanie Hull, BA, Vanderbilt University, for her assistance in manuscript preparation. She received salary support from the grants. We thank the participants and staff members of the Shanghai Breast Cancer Survival Study for making this study possible.

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