RESEARCH COMMUNICATION

Positive Effects of Soy Isoflavone Food on Survival of Breast Cancer Patients in China

Ya-Feng Zhang, Hong-Bin Kang*, Bi-Li Li, Rui-Ming Zhang

Abstract

Aim: Soy foods are the major source of isoflavones, which are believed to play important roles in genesis of breast cancer and its progression. We here conducted a prospective study to evaluate the association of soy isoflavone food consumption with breast cancer prognosis. Methods: A prospective study was performed from January 2004 and January 2006 in China. Trained interviewers conducted face-to-face interviews using a structured questionnaire to collect information on dietary habits and potential confounding factors. The relative risk [hazard ratio (HR)] and 95% CI were calculated from the Cox regression model for all significant predictors from cancer diagnosis to the endpoint of the study (event). Results: After a median follow up of 52.1 months (range, 9-60 months), a total of 79 breast cancer related deaths were recorded in our study, risk being inversely associated with a high intake of soy isoflavone. With an average intake of soy isoflavone above 17.3 mg/day, the mortality of breast cancer can be reduced by about 38-36%. We also found the decreased breast cancer death with high soy protein intake, with a HR (95% CI) of 0.71 (0.52-0.98). Stratified analysis with reference to the ER status, further demonstrated a better prognosis of ER positive breast cancer with a high intake of soy isoflavone (HR 0.59, 0.40-0.93). Conclusion: Our study shows the soy food intake is associated with longer survival and low recurrence among breast cancer patients. A cohort study with a larger sample size and long term follow-up is now needed.

Keywords: Soy isoflavone - soy protein - breast cancer - prognosis - Chinese patients

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Introduction

About 1.38 million new cases of breast cancer among women were estimated to have occurred in 2008, making it currently the second most common malignant among women worldwide (10.9% of all cancers). Most of cases occur both in developed and developing regions with around 690,000 new cases estimated in each region, and the incidence rates vary from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe (IARC, 2008). The wide geographic variation at an international levels of breast cancer in terms of incidence and mortality suggested the role of environmental factors in the pathogenesis of this cancer.

Soy foods are the major source of isoflavones, a group of phytoestrogens shows both antiestrogenic and estrogen-like properties. These phytochemicals have been shown to complete with endogenous oestrogens for oestrogen receptors in many in vitro and in vivo systems (Adlercreutz and Mazur, 1997). Thus the potential cancer-inhibitory effect of soyfood may be found in breast cancers expressing oestrogen receptor. Many epidemiologic studies showed that soy consumption may protect against breast cancer, while some experimental studies showed that isoflavones could enhance the proliferation of breast cancer cells in vitro and promote mammary tumor growth in rats (Helferich et al., 2008; Taylor et al., 2009). However, 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 (Helferich et al., 2008; Velentzis et al., 2008).

Previous, only one epidemiologic study in Chinese population showed the soy isoflavone containing foods do not adversely affect breast cancer prognosis, do not counteract the benefits of tamoxifen (Shu et al., 2009). However, another epidemiologic study conducted in the United States suggested an inverse association for postmenopausal women who had ER breast cancer (Guha et al., 2009). Therefore, we conducted the present prospective study focusing on 616 Chinese breast cancer patients to evaluate possible associations of soy isoflavone food consumption with breast cancer prognosis, with especial attention to an exploration of the ER status of the cancers.

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Materials and Methods

Study population

The breast cancer patients were recruited between January 2004 and January 2006 admitted to the Affiliated Hospital of Inner Mongolia Medical College of China. All study subjects were permanent residents of Hohhot with no prior history of cancer. A total of 649 eligible breast cancer cases were identified during the study period, and in-person interviews were completed for 616 (94.9%). The major reasons for non-participation were physical, mental health situation, or death prior to interview. Trained interviewers conducted face-to-face interviews by using a structured questionnaire to collect information on potential confounding factors, including socio-demographic characteristics, current body weight, height, menstrual and reproductive history, oestrogen (ER), age at menopause, use of exogenous hormones, previous cancer history, physical activity, tobacco smoking and alcohol use. Soy food intake were assessed by a comprehensive quantitative food-frequency questionnaire (FFQ) in our previous study (Liu et al., 2011). These food items were shown to account for over 90% of soyfoods consumed.

Soy food intake was estimated based on the intake of six foods or food groups: (1) hard tofu, fried tofu pop; (2) soft tofu; (3) processed soy products: tofu curd, vegetarian chicken; (4) soy milk; (5) bean curd pudding; and (6) soybean: fresh soybean, dried soybean. Total soy food consumption was measured by summing up the soy protein intake for all soy food items. Soy isoflavone intake was defined as the sum of the three individual isoflavones, daidzein, genistein and glycitein. The Chinese Food Composition Table was used to estimate intake of soy protein and soy isoflavone.

Survival was determined from the time of biopsy proven diagnosis, and the end point for survival analysis was cancer-specific death. The person-months of follow-up were counted for each subject from the date of study enrollment until the date of death, or the end of the study period (January 2011). The follow-up period consisted of a total of 34588 person-months (median=44.2 Months). A total of 9 subjects were lost to follow up during the study period. 79 deaths from all causes were identified.

Statistical analysis

We used the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA) for the data analysis. Difference in sociodemographic and clinical characteristics were evaluated using X^2 test for categorical variables. We adjusted in the multivariate analysis for known clinical prognosis predictors and lifestyle factors collected at baseline that were related to both soy food intake and survival/recurrence. These factors included age at diagnosis, TNM stage, type of surgery, BMI, menopausal stage, ER and PR status, age at menopause, use of exogenous hormones, previous cancer history, physical activity, tobacco smoking and alcohol use. A univariant Cox's regression analysis was used to assess the association between soy food intake and survival. In these analysis, soy food intake was treated as a continuous variable. Below 25th percentile of intake was used as the reference for above 20th, 50th and 75th percentiles of intake. Menopausal status at study enrollment was defined as cessation of menstruation for at least 12 months. The relative risk [hazard ratio (HR)] and 95% CI were calculated from the Cox regression model for all significant predictors from cancer diagnosis to the endpoint of the study (event). All statistical tests were based on 2-tailed probability and a significance level set

Table 1. Demographic and Selected Risk Factors of Breast Cancer Prognosis Among Cases and Controls

	No. of participants n=616(%)	No. of Death n=79	5-year % survival rate,%	pvalue
Age (years)	45.7±6.2			
<40	32(5.2)	2(2.5)	93.8	0.31
40-49	316(51.3)	35(44.3)	88.9	
50-59	149(24.2)	21(24.2)	85.9	
≥60	131(21.3)	21(21.3)	84	
Annual income				
<5000	289(46.9)	43(54.4)	85.1	0.27
5000-9999	192(31.2)	19(24.1)	90.1	
≥10000	136(21.9)	17(21.5)	87.4	
Education				
None	125(20.3)	20(25.3)	84	0.04
Elementary	152(24.7)	27(34.2)	83.6	
Middle or high school	209(33.9)	20(26.6)	90	
College or higher	130(21.1)	12(15.2)	90.8	
BMI (mean±SD)	23.10±2.45			
<23	342(55.5)	36(45.6)	89.5	0.11
23-25	150(24.4)	21(26.6)	86	
>25	124(20.1)	22(27.8)	82.3	
Smoking (%)				
Ever	78(12.7)	13(16.5)	83.3	<0.05
No	537(87.2)	66(83.5)	87.7	
Passive smoking	352(57.1)	22(37.8)	93.8	
Drinking				
Ever	118(19.2)	17(21.5)	85.6	0.57
No	498(80.8)	62(78.5)	87.6	
Family history of cancer				
Yes	57(9.3)	11(13.9)	80.7	0.13
No	559(90.7)	68(86.1)	87.8	
Menopausal status				
Post- or perimenopausal	290(47.1)	31(39.2)	89.3	0.14
Premenopausal	326(52.9)	48(60.8)	85.3	
Tamoxifen use				
Yes	350(56.8)	33(41.8)	90.6	<0.05
No	266(43.2)	46(58.2)	82.7	
TNM stage				
0-II	501(81.3)	42(53.2)	91.6	<0.05
III-IV	115(18.7)	37(46.8)	67.8	
Estrogen receptor status				
Negative	238(38.6)	44(55.7)	81.5	<0.05
Positive	378(61.4)	35(44.3)	90.7	
Chemotherapy				
Yes	534(86.7)	63(79.7)	88.2	<0.05
No	82(13.3)	9(20.3)	80.5	
Radiotherapy				
Yes	400(64.9)	54(59.5)	88.3	0.28
No	216(35.1)	25(40.5)	85.2	
Hormone therapy				
Yes	47(7.6)	3(3.8)	93.6	0.17
No	569(92.4)	76(96.2)	86.6	

Table 2. Association Between Soy Food Intake and Breast Cancer Prognosis

Soy food	Participants N=616(%)	Number of death N=79(%)	5-year survival rate(%)	HR(95% CI)[1]
Soy isoflavone (mg/day)				
Mean±SD				
<7.56	189(30.7)	37(46.8)	80.4	1.0(Reference)
7.56-	208(32.8)	23(29.1)	88.9	0.79(0.54-1.07)
17.32-	101(16.4)	9(11.4)	91.1	0.64(0.45-0.93)
>28.83	118(19.2)	10(12.7)	91.5	0.62(0.42-0.90)
Soy protein (g/day)				
<2.12	116(18.7)	32(40.5)	72.4	1.0(Reference)
2.12-	253(41.3)	30(38.0)	88.1	0.72(0.55-0.99)
7.03-	87(14.1)	10(12.7)	88.5	0.73(0.43-1.13)
>13.03	110(17.9)	7(8.9)	93.6	0.71(0.52-0.98)

[1]Adjusted for age, education level, smoking, drinking, family history of cancer, menopause status, Tamoxifen use, TNM stage, ER status, chemotherapy and radiotherapy.

Table 3. Association Between Soy Food Intake and Breast Cancer Prognosis Stratified by Estrogen Receptor Status

Soy food	Participants N=616(%)	Number of death N=79(%)	5-year survival rate(%)	HR(95% CI)[1]
Women with ER-negative breast cancer				
Soy isoflavone (mg/day)				
Mean±SD				
<7.56	74(31.1)	18(40.9)	83.5	1.0(Reference)
7.56-	79(33.2)	13(29.5)	92.2	0.83(0.57-1.13)
17.32-	40(16.8)	7(15.9)	96.7	0.76(0.52-1.04)
>28.83	45(18.9)	6(13.6)	94.5	0.78(0.47-0.98)
Soy protein (g/day)				
<2.12	76(31.9)	17(38.6)	62.5	1.0(Reference)
2.12-	86(36.1)	15(34.1)	91	0.88(0.55-1.17)
7.03-	40(16.8)	6(13.6)	91.5	0.80(0.54-1.13)
>13.03	36(15.1)	6(13.6)	98.6	0.77(0.53-1.00)
Women with ER positive breast cancer				
Soy isoflavone (mg/day)				
Mean±SD	Mean±SD	Mean±SD		
<7.56	115(30.4)	19(54.3)	83.5	1.0(Reference)
7.56-	129(34.1)	10(28.6)	92.2	0.77(0.56-1.04)
17.32-	61(16.2)	2(5.7)	96.7	0.66(0.43-0.94)
>28.83	73(19.3)	4(11.4)	94.5	0.59(0.40-0.93)
Soy protein (g/day)				
<2.12	40(10.6)	15(42.9)	62.5	1.0(Reference)
2.12-	167(44.2)	15(42.9)	91	0.80(0.61-1.02)
7.03-	47(12.4)	4(11.4)	91.5	0.76(0.48-0.98)
>13.03	74(19.6)	1(2.9)	98.6	0.66(0.44-0.93)

[1]Adjusted for age, education level, smoking, drinking, family history of cancer, menopause status, Tamoxifen use, TNM stage, chemotherapy and radiotherapy

set at $p<0.05$.

Results

After a median follow up of 52.1 months (range, 9-60 months), a total of 79 breast cancer related deaths were recorded in our study. Higher education, tamoxifen use, positive estrogen receptor status and receiving chemotherapy were positively associated with the longer survival rate, while smoking and higher TNM stage were inversely related to the poor prognosis (Table 1). No significantly association was found between annual income, BMI, drinking, menopausal status, family history of cancer, radiotherapy and hormone therapy and breast cancer survival.

In our study, we found the high intake of soy isoflavone was inversely associated with deaths of breast cancer (Table 2). With an average intake of soy isolfavone above 17.32 mg/day, the mortality of breast cancer can be reduced by about 38-36%. But we did not find a linear dose-response between soy food intake and breast cancer survival. We found an increased trend of survival rate with the increase dosage of soy isoflavone. We also found the decreased breast cancer death in high soy protein intake, with the HR (95% CI) of 0.71 (0.52-0.98).

We further conducted stratified analysis between soy isoflavone food intake and breast cancer survival by ER status. We found the association between the high soy food intake and better breast cancer survival did not significantly changed by the ER status. However, we found more better prognosis of breast cancer when had high intake of soy isoflavone among women with ER positive breast cancer, with HR (95% CI) of 0.59 (0.40-0.93).

Discussion

The soy food intake among Chinese women is substantially higher than that in other countries, with about 48 grams/day in Chinese population (Horn-Ros, 2003). The soy constituents have been observed to have anti-cancer properties (Adlercreutz et al., 1997; Mouridsen et al., 2003; Lee et al., 2009; Taylor, 2009) and could improve cardiovascular and bone health (Clarkson, 2002; Ishimi, 2009). Previous in vivo and in vitro studies regarding the role of soy constituents could stimulate cell proliferation. Due to soy isoflavones are increasing added to variety of food, including beverages, yogurt, baked goods and confection, etc., the isflavones intake has been become common in daily life, which raises our concern about the safety of soy intake among the rapid increased number of breast cancer survivors. Our results of this prospective study suggested that regular intake of soy food intake, particularly very high intake of soy isoflavone and soy protein, may be associated with a reduced risk of death or recurrence of breast cancer. This inverse association appeared variable by women with different ER cancer.

Soy isoflavones in the soy food are the most important constituents, which showed it played a competitive role with endogenous estrogens in the binding of estrogen receptors. This would increase synthesis of sexhormone binding globulin (thus lowering the biological availability of sex hormones), inhibit 17β-hydroxysteroid dehydrogenases (thus reducing estrogen synthesis), and increase clearance of steroids from the circulation (Trock et al., 2006; Taylor et al., 2009). These anti-estrogenic effect by soy food intake may play a positive role in the better breast cancer outcomes. In our study, we found the high intake of soy food was positively associated with with better prognosis and longer survival, which was in line with the previous hypothesis.

The high soy food intake is usually associated with a healthy lifestyle of high intake of vegetable,

fish meat, tofu and low intake of red meat. However, previous epidemiologic studies showed the high intake of vegetables, fish meat and low consumption of meat might decrease the incidence of breast cancer and increase the survival of breast cancer patients (Pierce et al., 2007; Pierce, 2009). In our study, we found the HR of high soy food intake for breast cancer death or recurrence were higher than that adjusted for vegetable, fruit and meat intake (data not shown). Therefore, it is hypothesis that high soy food intake may be related with a characteristics of healthy dietary habits.

Our study suggests that effect of soy on breast cancer prognosis may differ according to ER status. Several epidemiological studies have examined the effect of soy intake with stratification by receptor status but reported mixed findings. A case control study in China found that a greater risk reduction was associated with ER+ tumors but not with ER- women (Zhang et al., 2010). Our previous study also showed a possibly stronger protective effect of isoflavone intake on breast cancer risk among postmenopausal and ER+ women(Liu et al., 2011). In this study, our findings may indicate the possible anticarcinogenic effect of isoflavones comes from their antiestrogenic or estrogenic activity mediated by their affinity for ERs. However, isoflavones can exert hormonal and antiestrogenic effects in many ways without direct interaction with the ER (Kao et al., 1998), and thus further studies are needed to elucidate the underlying mechanism.

In a words, our study showed the soy food intake is associated with longer survival and low recurrence among breast cancer patients. However, the limited number of patients and relative short follow-up period could limited the outcome of our study, therefore, further large sample size and long term follow-up cohort study is warranted.

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