RESEARCH COMMUNICATION

Study on Soy Isoflavone Consumption and Risk of Breast Cancer and Survival

Hong-Bin Kang[1]*, Ya-Feng Zhang[1], Jin-Dun Yang[2], Kuan-Liang Lu[2]

Abstract

Aim: Isoflavones in soy foods are part of a larger class of flayonoid compounds that have have been demonstrated to be potent dietary anti-cancer agents, and the effect of soy intake on the survival of ovarian cancer is conflicting. Therefore, we aimed to explore the whether soy intake is related to the risk of death of breast cancer. Methods: A prospective study was conducted. A total of 256 patients included in this study had breast cancer and were recruited between January 2004 and January 2006. All of them were followed up from since January 2011. A univariate Cox's regression analysis was used to assess the association between soy intake and survival. Results: The education level, menopausal status, ER/PR status and TNM stage were significant difference in the survival of breast cancer. The highest soy isoflavone was associated with a decreased death risk of breast cancer (OR=0.25, 95% CI=0.09-0.54). Moreover, the higher consumption of soy protein also presented a trend decreased breast cancer risk, and the highest consumption significantly reduced the cancer risk compared with the lowest consumption (OR=0.38, 95% CI=0.17-0.86). Conclusion: The present study suggests soy intake is associated with a significant reduced death risk of breast cancer in Chinese population. Further large sample studies are warranted to confirm the inverse association of soy consumption and breast cancer survival by menopausal status.

Keywords: Soy isoflavones consumption - breast cancer - survival

Asian Pacific J Cancer Prev, **13**, 995-998

Introduction

Breast cancer is by far the most frequent cancer among women with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and ranks second overall (10.9% of all cancers). It is now the most common cancer both in developed and developing regions with around 690,000 new cases estimated in each region (population ratio 1:4). Incidence rates vary from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe, and are high (greater than 80 per 100,000) in developed regions of the world (except Japan) and low (less than 40 per 100,000) in most of the developing regions. The high incidence of the cancer in certain geographic regions suggests the role of environmental risk factors in pathogenesis of breast cancer (IARC, 2008).

As we known, isoflavones in soy foods are part of a larger class of flayonoid compounds that have have been demonstrated to be potent dietary anti-cancer agents (Reinli and Block, 1996). The primary isoflavones daidzein, genistein, and glycetin comprise 40, 50, and 10% of the soybean isoflavones, respectively (Murphy et al., 1999). Soy intake is high in many Asian countries where breast cancer incidence is lower compared to Western countries (Rose et al., 1986; Parkin, 1989; Curado et al., 2007). Migrant studies have shown that after successive generations, breast cancer incidence in Asian women becomes similar to that of Western countries (Trichopoulos et al., 1984; Ziegler et al., 1984; Stanford et al., 1995; Kaur, 2000). Furthermore, an increasing incidence of breast cancer among Chinese women parallels the Westernization of the Chinese diet, which suggesting that the difference in breast cancer incidence rates between Western and Eastern women are mainly influenced by the lifestyle and diet habits rather than genetics (Parkin et al., 1996).

Litter is known about the effects of soy consumption on the breast cancer survival. Menopause is often prematurely induced during the course of breast cancer treatment with tamoxifen, an anti-estrogen widely prescribed to women with ER positive tumors as a long-term adjuvant therapy to prevent recurrences (Constantinou et al., 2005). Postmenopausal women would take soy isoflavones supplements as a therapy due to the nature source of exogenous estrogen (Morris et al., 2000; Harris et al., 2002). Also, there is no awareness of the effect of soy on the tumor growth when combined with tamoxifen, and previous study showed the high soy consumption may induce the risk of recurrence or stimulate the growth of existing positive ER tumors (Messina et al., 2006).

We therefore conducted a prospective study in Chinese

*[1]Department of General Surgery, The First Affiliated Hospital of Inner Mongolia Medical College, Hohhot, [2]The Hospital of Damao county, Damao, China *For Correspondence: liuyixia1993@126.com, khbpeter@163.com*

population to explore whether soy intake is related to the risk of death of breast cancer.

Materials and Methods

A prospective study was conducted. Patients included in this study had breast cancer and were recruited between January 2004 and January 2006 in the First Affiliated Hospital of Inner Mongolia Medical College in China. A total of 303 eligible breast cancer cases were identified during the study period, and in-person interviews were completed for 288 (94.9%). The major reasons for non-participation were physical, mental health situation, or death prior to interview.

The endpoint of interest for survival analysis was cancer-specific death. Survival time was calculated from the date of diagnosis to the date of last follow-up from any causes. A total of 288 patients were followed up until January 2011.

Trained interviewers conducted face-to-face interviews by using a structured questionnaire to collect information on potential confounding factors. The potential confounding factors were demographic characteristics, alcohol use, smoking status, menopausal status, ER/PR status, tamoxifen use, oral contraceptive use and TNM stage.

The diet was assessed for the 12 months prior to entering the study using a self-administered 95 items of Food Frequency Questionnaire (FFQ) developed by NIH. The soy food intake was estimated by FFQ with16 soy food items, including tofu, soy milk, soy yogurt, soy frozen yogurt, soy ice cream, soy cheese, soy hot dogs and cold cuts, other meat substitutes made from soy, tempeh, miso, soybeans, roasted soy nuts, soy sauce, soybean sprouts, alfalfa sprouts, and protein power supplements made from soy. The folate intake was computed by multiplying the food intake (in grams) and the folate content (per gram) of food in our questionnaire, and then the sum of all folate intake from various foods/food groups was calculated as the total folate intake. The continuous variables of folate intake were transferred to three categories as low, moderate and high by using tertile as the cut point.

All analysis was performed by using the STATA statistical package (version 10.0, STATA, College Station, TX). A univariate Cox's regression analysis was used to assess the association between soy intake and survival. The primary death of patients was defined as the failure event and the time of survival was the time between diagnosis and death. The cause of death was defined by specialists based on the clinical documents and reports by patient's family members. If patient died or other causes rather than breast cancer, she was censored at the date of death. All survived patients were censored at the date of last follow-up. 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). Statistical significance was defined as a 2-sided P-value of less than 0.05.

Results

The distribution of demographic characteristics and major risk factors for breast cancer among cases and controls are showed in Table 1. The mean age was 46.7±9.4 years among cases. The education level, menopausal status, ER/PR status and TNM stage were significant difference in the survival of breast cancer.

Table 2 showed the mean daily intake of isoflavone and soy protein was 18.3±9.5 mg/day and 8.4±5.6 g/day in breast cancer cases, respectively. The highest soy isoflavone was associated with a decreased death risk of breast cancer (OR=0.25, 95% CI=0.09-0.54). Moreover, we found a trend association between the increase of soy

Table 1. Demographic and Clinic Characteristics of Patients with Breast Cancer

Variables	Cases, N(%)	Death, N(%)	HR (95% CI)
Mean age (years)	46.7±9.4		
Education level			
Primary school	90(31.4)	58(46.7)	1.0(Reference)
Middle school	103(35.6)	45(36.3)	0.77(0.54-1.39)
University or above	95(33)	21(17)	0.65(0.43-0.94)
Alcohol use			
Never	206(71.5)	82(66.1)	1.0(Reference)
Ever	82(28.5)	42(33.9)	1.28(0.77-2.16)
Smoking			
Never	263(91.3)	110(88.7)	1.0(Reference)
Ever	25(8.7)	14(11.3)	1.34(0.62-2.78)
Passive smoking	185(64.3)	86(69.4)	1.22(0.67-2.23)
Menopausal status			
Post- or perimenopausal	181(62.7)	93(75.3)	1.0(Reference)
Premenopausal	107(37.3)	31(24.7)	0.57(0.34-0.94)
ER/PR status			
ER+/PR+	61(21.3)	14(11.3)	1.0(Reference)
ER-/PR-	69(23.8)	27(21.4)	1.71(0.78-3.85)
ER+/PR- or ER-/PR+	158(54.9)	83(67.3)	2.28(1.19-4.70)
Tamoxifen use			
Never	82(28.6)	46(36.7)	1.0(Reference)
Ever	206(71.4)	78(63.3)	0.64(0.41-1.08)
Oral contraceptive use			
Never	215(74.7)	85(68.6)	1.0(Reference)
Ever	73(25.3)	39(31.4)	1.36(0.82-2.27)
TNM stage			
I	69(23.9)	14(11.5)	1.0(Reference)
II	88(30.6)	33(26.3)	1.74(0.81-3.67)
III	96(33.2)	50(40.6)	2.57(1.27-5.42)
IV	35(12.3)	27(21.6)	3.80(1.65-7.21)

Table 2. Soy Isoflavone Intake and Survival of Breast Cancer

Variables	Cases, N(%)	Death, N(%)	HR (95% CI)[1]
Soy isoflavone (mg/day)			
Mean±SD	18.3±9.5		
<8.45	99(34.3)	57(45.8)	1.0(Reference)
8.45-	88(30.5)	46(36.7)	0.91(0.50-1.50)
20.24-	52(18.1)	17(13.6)	0.56(0.21-1.03)
>35.30	49(17.0)	5(3.9)	0.25(0.09-0.54)
Soy protein (g/day)			
Mean±SD	8.4±5.6		
<4.55	96(33.5)	52(42.3)	1.0(Reference)
4.55-	101(35.2)	50(40.5)	0.91(0.55-1.48)
9.54-	44(15.4)	13(10.3)	0.47(0.22-0.98)
>15.78	47(15.9)	9(6.9)	0.38(0.17-0.86)

[1]Adjusted for age, education level, alcohol use, smoking status, menopausal status, ER/PR status, tamoxifen use, oral contraceptive use and TNM stage

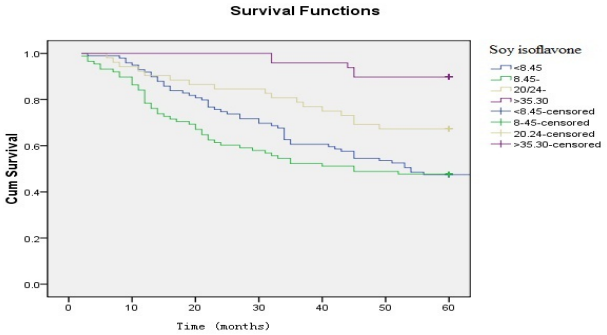

Figure 1. Survival of Breast Cancer and Soy Isoflavone

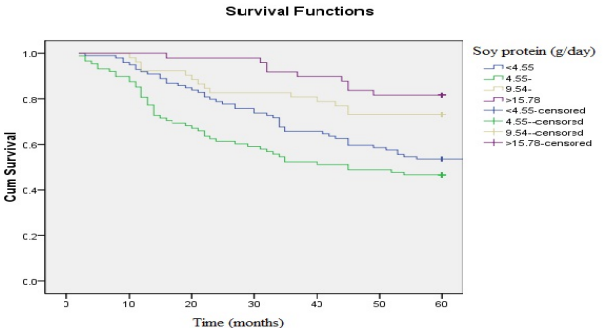

Figure 2. Survival of Breast Cancer and Soy Protein

isoflavone and the decrease of breast cancer risk (trend test P<0.05) (Figure 1). The higher consumption of soy protein also presented a trend decreased breast cancer risk, and the highest consumption significantly reduced the cancer risk compared with the lowest consumption (OR=0.38, 95% CI=0.17-0.86) (Figure 2).

Discussion

Our study explore the association between soy food intake and breast cancer prognosis. We found an inverse association between soy exposure and risk of breast cancer death. Menopausal status and ER/PR status showed an effect modifier in the association between soy intake and breast cancer.

Our finding showed the soy intake was inversely associated with breast cancer death in Chinese population, which is consistent with a previous study (Dong and Qin, 2011). However, previous study showed the soy intake did not associated with breast cancer death, the main reason might be the different amount of soy consumption between Asian and Western populations. The soy intake in Western population is significant lower than that in Chinese population, and another reason might be the protective effect in Asian population with early exposure to soy. Previous studies showed the effect of early soy intake on adult breast cancer risk provide consistent evidence that early isoflavone exposure is protective against breast cancer and early life influences play an important role in the cause of breast cancer (Shu et al., 2001; Wu et al., 2002; Thanos et al., 2006; Korde et al., 2009). Moreover, equol, a metabolite of daidzein, may also affect the soy and breast cancer association because the equol is superior to all other isoflavones in its antioxidant activity (Mitchell et al., 1998). Therefore, we could hypothesis that the soy intake also may have influence on the survival of breast cancer.

The current study suggests that menopausal status may be an important modifier of the effect of isoflavones on the death risk of breast cancer, and the reason might be the menopausal status might mediate the ovarian synthesis of hormones or the alteration of other menstrual cycle characteristics (Cassidy et al., 1994; Lu et al., 1996). This study showed pre-menopausal women had significantly decreased death risk of breast cancer, which suggested the menopausal status may be effective at low sex hormone concentrations as seemed in post-menopausal women. Further studies on the association between soy and breast cancer risk by pre- and post-menopausal are strongly warranted.

There were several limitations in this study. First is the measurement of soy intake, we measured the soy intake by 16 items in Chinese food, however, the apparent protective effect of isoflavones on risk of breast cancer may be due to other healthy lifestyles related to soy intake, such as high vegetable and fruit intake, more physical activity, and reduced alcohol use. However, as the results in our study, we have adjusted lots of confounding factors in our study to reduce the likelihood that residual confounding can explain the findings. Secondly, we did not find the dose-response relationship of soy intake, and the main reasons may be due to limited number of studies eligible for this analysis. Thirdly, further studies need to measure the soy intake by every year, because the patients may change in soy consumption and may weakened or strengthened the observed associations during the long follow-up period.

In conclusion, the present study suggests soy intake is associated with a significant reduced death risk of breast cancer in Chinese population. Further large sample studies are warranted to confirm the inverse association of soy consumption and breast cancer survival by menopausal status.

Acknowledgements

This work was financially supported by Natural Science Foundation of Inner Mongolia (2011MS1112).

References

Cassidy A, Bingham S, Setchell KD (1994). Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women. *Am J Clin Nutr,* **60**, 333-40.

Constantinou AI, White BE, Tonetti D, et al (2005). The soy isoflavone daidzein improves the capacity of tamoxifen to prevent mammary tumours. *Eur J Cancer*, **41**, 647-54.

Curado MP, Edwards B, Shin HR, et al (eds) (2007). Cancer incidence in five continents No. 160. IARC Scientific Publications, Lyon.

Dong JY, Qin LQ (2011). Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. *Breast Cancer Res Treat*, **125**, 315-23.

Harris PF, Remington PL, Trentham-Dietz A, Allen CI, Newcomb PA (2002). Prevalence and treatment of menopausal symptoms among breast cancer survivors. *J Pain Symptom Manage,* **23**, 501-9.

Kaur JS (2000). Migration patterns and breast carcinoma. *Cancer*, **88**, 1203-6.

Korde LA, Wu AH, Fears T, et al (2009). Childhood soy intake and breast cancer risk in Asian American women. *Cancer Epidemiol Biomarkers Prev*, **18**, 1050-9.

Lu LJ, Anderson KE, Grady JJ, Nagamani M (1996). Effects of soya consumption for one month on steroid hormones in premenopausal women: implications for breast cancer risk reduction. *Cancer Epidemiol Biomarkers Prev*, **5**, 63-70.

Messina M, McCaskill-Stevens W, Lampe JW (2006). Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. *J Natl Cancer Inst*, **98**, 1275-84.

Mitchell JH, Gardner PT, McPhail DB, et al (1998). Antioxidant efficacy of phytoestrogens in chemical and biological model systems. *Arch Biochem Biophys*, **360**, 142-8.

Morris KT, Johnson N, Homer L, Walts D (2000). A comparison of complementary therapy use between breast cancer patients and patients with other primary tumor sites. *Am J Surg*, **179**, 407-11.

Murphy PA, Song T, Buseman G, et al (1999). Isoflavones in retail and institutional soy foods. *J Agric Food Chem*, **47**, 2697-704.

Parkin DM (1989). Cancers of the breast, endometrium and ovary: geographic correlations. *Eur J Cancer Clin Oncol*, **25**, 1917-25.

Parkin DM, Khlat M (1996). Studies of cancer in migrants: rationale and methodology. *Eur J Cancer*, **32A**,761-71.

Reinli K, Block G (1996). Phytoestrogen content of foods–a compendium of literature values. *Nutr Cancer*, **26**, 123-48.

Rose DP, Boyar AP, Wynder EL (1986). International comparisons of mortality rates for cancer of the breast, ovary, prostate and colon, and per capita food consumption. *Cancer*, **58**, 2363-71.

Shu XO, Jin F, Dai Q, et al (2001). Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. *Cancer Epidemiol Biomarkers Prev*, **10**, 483-8.

Stanford JL, Herrinton LJ, Schwartz SM, Weiss NS (1995). Breast cancer incidence in Asian migrants to the United States and their descendants. *Epidemiology*, **6**, 181-3.

Thanos J, Cotterchio M, Boucher BA, et al (2006). Adolescent dietary phytoestrogen intake and breast cancer risk (Canada). *Cancer Causes Control*, **17**, 1253-61.

Trichopoulos D, Yen S, Brown J, Cole P, MacMahon B (1984). The effect of westernization on urine estrogens, frequency of ovulation, and breast cancer risk. A study of ethnic Chinese women in the Orient and the USA. *Cancer*, **53**, 187-92.

Wu AH, Wan P, Hankin J, et al (2002). Adolescent and adult soy intake and risk of breast cancer in Asian-Americans. *Carcinogenesis*, **23**, 1491-6.

Ziegler RG, Hoover RN, Pike MC, et al (1993). Migration patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst*, **85**, 1819-27.