RESEARCH COMMUNICATION

Relationship Between Soy Food Intake and Breast Cancer in China

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Abstract

Aims: Soy food intake may be associated with reduced risk of breast cancer, by far the most frequent cancer among women, but the results are inconsistent. We aimed to investigate the relationship further in Chinese population and to assess the importance of hormone receptor status. Methods: A case-control study was conducted with totals of 183 cases and 192 controls recruited from January 2008 to January 2011 among patients admitted to the General Hospital of PLA and the Second Affiliated Hospital of Guangzhou Medical University, China. Trained interviewers conducted face-to-face interviews using a structured questionnaire to collect information on dietary habits and potential confounding factors. Results: The highest relative to lowest soy isoflavone intake was associated with a 58% decrease risk of breast cancer (OR=0.42, 95% CI=0.22-0.80). Higher consumption of soy protein also decreased breast cancer risk, and the highest consumption reduced 54% cancer risk compared with the lowest (OR=0.46, 95%CI=0.24-0.88). The inverse association between highest intake of soy isoflavone and soy protein with the risk of breast cancer was statistically in postmenpausal women (OR=0.57, 95%CI=0.29-0.83; OR=0.50, 95%CI=0.38-0.95). In the ER/PR status stratified analysis, a significantly reduced risk was observed for ER+/PR+ breast cancer among highest intake of soy isoflavone and soy protein, with ORs of 0.47 and 0.63, respectively. Conclusion: Our study suggested that a high intake of soy food is inversely associated with breast cancer risk, the effect depending to some extent on the hormone receptor status.

Keywords: Soy isoflavone - soy protein - hormone receptor status - breast cancer risk

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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 a role for environmental risk factors in breast cancer (IARC, 2008).

Soy foods, a major source of phytoestrogens show both antiestrogenic and estrogen-like properties. Since Lee firstly reported a reduced risk of breast cancer in premenopausal women in relation to high soy intake in Singapore, there has been tremendous interest to further investigate the possible role of soy in reducing breast cancer risk (Lee et al., 1991; 1992). So far, lots of epidemiologic studies evaluating the association between soy or isoflavone intake and breast cancer risk has been conducted in the world. More than 10 studies were conducted in Asian countries, but the results are conflicting (Do et al., 2007; Kim et al., 2008; Wu et al., 2008). Also, studies conducted in Western populations have also reported inconsistent results (Peterson et al., Keinan-Boker et al., 2004; Travis et al., 2008).

Thus, our objective is to examine the association of soy isoflavones intake with risk of breast cancer, by conducting a population-based case-control study. We also evaluated whether the association were modified by hormone receptor status.

Materials and Methods

Study subjects

A total of 183 cases and 192 controls were recruited from January 2008 to January 2011 among patients admitted to the General Hospital of PLA and the Second Affiliated Hospital of Guangzhou Medical University, China. Inclusion criteria were female subjects who lived in Guangzhou and Beijing at least for 5 years, with newly

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diagnosed primary breast cancer between January 2008 to January 2011 in the hospital were invited for face-to-face interviews within three months after diagnosis.

Among a total of 183 eligible cases, 167 were successfully interviewed with a participant rate of 91.3%. Controls were randomly selected from people who requested general health examinations in the same hospital during the same period. Controls were required to be without any history of any type of cancer and frequency matched by a five-year age groups. Among a total of 192 eligible controls, 183 were successfully interviewed with a participation rate of 95.3%.

Data collection

Trained interviewers conducted face-to-face interviews using a structured questionnaire to collect information on dietary habits and potential confounding factors, including socio-demographic characteristics, current body weight, height, menstrual and reproductive history, age at menopause, use of exogenous hormones, history of breast disease, family history of breast cancer, physical activity, tobacco smoking and alcohol use. Dietary intake information was assessed by using an interviewer-administered food frequency questionnaire (FFQ) covering the habitual diet of participants during the previous year. The FFQ consisted of 84 food items, plus additional items related to recent dietary changes and use of nutritional supplements. A commonly used portion size was specified for each food.

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 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.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the social Sciences (SPSS) software 13.0 for windows. Chi square or t tests were used to test differences of sociodemographic factors and potential confounders between the 8 cases and controls. Unconditional logistic regression was used to estimate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for each exposure variable.

The relationships between soy food intake with the risk of breast cancer was further examined after adjusting for various potential confounding factors, including estrogen(ER), progesterone (PR), BMI, family history of cancer in a first-degree relative, history of breast disease, smoking and passive smoking, vegetable and fruit intake. A stratified approach was used to investigate the modification of ER/PR status on the association between soy food intake and breast cancer. In addition, because pre- and postmenopausal breast cancer probably have separate disease etiologies, analyses were also stratified by pre- and postmenopausal status.

Results

Subject characteristics

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 45.7±6.2 years among cases and 45.9±7.1 years among controls. There were no significant differences between cases and controls in education, smoking status, alcohol intake, body mass index, number of live births, months of breast feeding, age at menopause and menopausal status. The mean daily intake of isoflavone and soy protein was 18.02 mg/day and 7.79 g/day in cases, which was significantly lower than that in controls with 39.7 mg/day and 16.41 g/day, respectively (Table 2). We could see the highest soy isoflavone was associated with a decrease risk of breast cancer compared with soy isoflavone >28.83 g/day (OR=0.42, 95% CI=0.22-0.80). Also, we found a trend association between the increase of soy isoflavone and the decrease of breast cancer risk (trend test P=0.031). 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=0.46, 95% CI=0.24-0.88). Additionally, vegetable and fruit intake in cases was

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

	Cases n=183	Controls n=192	p value
Age (mean±SD, years)	45.7±6.2	45.9±7.1	0.6
Education			
Illiteracy (%)	42(23.0)	34(17.7)	0.2
BMI (mean±SD)	23.10±2.45	22.13±2.11	<0.001
Smoking (%)	12	9	0.43
Passive smoking	79	52	0.004
Drinking	21	17	0.4
Family history of cancer	9	2	0.03
History of breast disease	87	43	<0.001
Menopause age	48.50±4.20	48.70±3.95	0.68
Number of live births	1.81±1.02	1.92±1.12	0.16
Months of breast feeding	14.75±8.30	15.32±7.95	0.25
Menopausal status			
Post- or perimenopausal	105	95	
Premenopausal	78	97	0.13

Table 2. Mean and Median Consumption of Soy Food, Soy Protein and Other Dietary Food Among Cases and Controls

Soy food	Cases N=183	Controls N=192	P value
Soy isoflavone (mg/day)			
Mean±SD	18.0±11.6	39.7±17.3	<0.001
<7.56	62	46	<0.001
7.56-	61	48	
17.32-	31	47	
>28.83	29	51	
Soy protein (g/day)	7.79±6.43	16.4±8.54	<0.001
<2.12	57	48	<0.001
2.12-	70	44	
7.03-	28	49	
>13.03	28	51	
Vegetable intake (g/day)	297.9±57.9	496.5±47.1	<0.001
Total fruit intake (g/day)	187.7±52.3	247.9±51.0	<0.001

Table 3. OR and 95% CI of Soy Isoflavone for Breast Cancer by Menopausal Status and Body Size

Stratifying variables	Cases/Controls	Soy isoflavone			
		<7.56	7.56-	17.32-	>28.83
Menopausal status					
Post- or perimenopausal	105/95	1.0(reference)	0.85(0.37-1.33)	0.69(0.34-0.98)	0.57(0.29-0.83)
Premenopausal	78/97	1.0(reference)	1.32(0.89-2.11)	0.93(0.65-1.54)	0.66(0.31-1.07)
ER/PR status					
ER+/PR+	46/192	1.0(reference)	0.65(0.37-0.98)	0.55(0.25-0.93)	0.47(0.19-0.85)
ER-/PR-	42/192	1.0(reference)	1.04(0.67-1.93)	0.98(0.58-1.45)	0.80(0.49-1.41)
ER+/PR- or ER-/PR+	95/192	1.0(reference)	1.52(0.93-2.30)	1.49(0.87-2.09)	1.25(0.76-1.74)

Adjusted for age, smoking, passive smoking, drinking, family history of cancer, history of breast disease, vegetables and fruit

Table 4. OR and 95% CI of Soy Protein For Breast Cancer by Menopausal Status and ER/PR Status

Stratifying variables	Cases/Controls	Soy protein			
		<2.12	2.12-	7.03-	>13.03
Menopausal status					
Post- or perimenopausal	105/95	1.0(reference)	0.96(0.67-1.86)	0.85(0.47-1.07)	0.50(0.38-0.95)
Premenopausal	78/97	1.0(reference)	1.37(0.80-1.79)	1.14(0.78-1.65)	0.86(0.55-1.16)
ER/PR status					
ER+ or PR+	46/192	1.0(reference)	0.77(0.41-1.04)	0.62(0.43-0.94)	0.63(0.45-0.97)
ER- or PR-	42/192	1.0(reference)	1.13(0.67-2.10)	0.76(0.67-1.37)	0.79(0.79-1.59)
ER+/PR- or ER-/PR+	95/192	1.0(reference)	1.39(0.93-2.30)	1.32(0.89-2.23)	1.45(0.61-1.98)

Adjusted for age, smoking, passive smoking, drinking, family history of cancer, history of breast disease, vegetables and fruit

significantly lower than that in controls.

Tables 3 and 4 showed the association of soy intake with breast cancer risk by different menopausal and ER/PR status. The inverse association between high intake of soy isoflavone with the risk of breast cancer was statistically significant in postmonpausal women (OR=0.57, 95%CI=0.29-0.83), while a non-significant inverse association was found for perimenopausal women. For ER/PR status stratified analysis, a significantly reduced risk was observed for ER+/PR+ breast cancer among highest intake of soy isoflavone, with an OR of 0.47(0.19-0.85). In contrast, no significant reduced cancer risk was observed in ER-/PR-, ER+/PR- or ER-/PR+ women.

The inverse association between the highest intake of soy protein with the risk of breast cancer was also found in postmenopausal women (OR=0.50, 95%CI=0.38-0.95), but not in postmenopausal women. A reduced risk was observed for ER+/PR+ women with highest soy protein intake (OR=0.63, 95%CI=0.45-0.97), but no significantly decreased risk in ER-/PR-, ER+/PR- or ER-/PR+ women.

Discussion

The results of this population-based case-control study suggested that regular intake of soyfood intake, particularly very high intake of soy isoflavone and soy protein, may be associated with a reduced risk of breast cancer, particularly for premenopausal and ER+ or PR+ women. These findings are consistent with observations from in vitro and animal studies implicating the potential inhibitory effect of soy on breast carcinogenesis (Adlercreutz and Mazur, 1997).

Our study showed an inverse association between soyfood intake and breast cancer risk, which is supported by other epidemiologic studies (Lee et al., 1992; Hirose et al., 2003; Hirose et al., 2005; Kim et al., 2008) and animal experiments (Adlercreutz and Mazur, 1997). Zhang et al found a reduced risk of breast cancer in Guangdong Chinese women who had high consumption of soyfood (Greenstein et al., 1996; Key et al., 1999; Zhang et al., 2010), and other cohort studies showed a weak negative association, but not all reported the similar results (Hirayama, 1990). However, only one study has reported a statistically significant inverse association with soyfood intake and evaluated the potential modifying effects by menopausal and ER/PR status (Zhang et al., 2010), and our study findings are consistent with it. But our study found the soyfood intake could reduce about 56% cancer risk for women in Sichuan, which was significantly higher than that of Zhang et al. study, implying that soyfood intake in the previous Guangdong study was underestimated.

As endogenous estrogen has been recognized as a cause of breast cancer, the decline of hormones after menopausal may modify the effect of soy in breast cancer carcinogenesis. The in vivo studies suggest that the isoflavones have antiestrogenic effects in high-estrogen environments and estrogenic effects in low-estrogen environments (Messina et al., 2006). Our study only found a significant inverse association between the soy food intake and breast cancer among postmenopausal women. However, results from other studies are inconsistence, one study conducted in Japan showed an inverse association in premenopausal women (Hirose et al., 1995), another study showed significant association in post postmenopausal women (Yamamoto et al., 2003; Wu et al., 2008), and two meta-analysis showed protective effects of soy both on pre- and postmenopausal women (Trock et al., 2006; Wu et al., 2008). The possible antiestrogenic effects and antiproliferative effects of soy in postmenopausal women (Imhof and Molzer, 2008).

Our study suggested that effect of soy on breast cancer etiology may differ according to ER/PR 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+/PR+ tumors but not with ER-/PR- women (Zhang et al., 2010). Our study found a possibly stronger protective effect of isoflavone intake on breast cancer risk among postmenopausal and ER+/PR+ women. Our findings may indicate the possible anticarcinogenic effect of isoflavones comes from their antiestrogenic or estrogenic activity mediated by their affinity for ERs (Messina et al., 2006). 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.

There are two limitation in our study. There may be possible different recall bias between cases and controls. Cases may exaggerate their bad lifestyle or dietary habits in their recall. The small number of stratified analysis on menopausal status and ER/PR status may limit the power to find the difference between cases and controls, therefore, further large sample study is warranted.

In conclusion, our study suggested that a high intake of soy food was inversely associated with breast cancer risk, and the effect depends on the hormone receptor status and quantity of soy food. Our study provide more information on prevention of breast cancer, and further large-scale with stratification by factors are needed to understand the relationship between soy food and breast cancer risk.

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