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Soy product and isoflavone intake and breast cancer risk defined by hormone receptor status

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The association between soy food consumption and breast cancer risk has been inconsistent. A hospital-based case–control study was conducted to assess the relationship between soy food intake and breast cancer risk according to the estrogen receptor (ER) and/or progesterone receptor (PR) status of breast cancer in Chinese women residing in Guangdong province from June 2007 to August 2008. A total of 438 consecutively recruited cases with primary breast cancer were frequency matched to 438 controls by age (5-year interval) and residence (rural/urban). Dietary intake was assessed by face-to-face interviews using a validated food frequency questionnaire. Odds ratios (OR) and 95% confidence intervals (CI) were obtained by using multiple unconditional logistic regression adjusted for the potential confounders. We observed a statistically significant inverse association between soy isoflavone and soy protein intake with breast cancer risk. The multivariate ORs (95% CIs) of breast cancer risk for the highest quartile compared with the lowest quartile were 0.54 (0.34–0.84) for soy isoflavone and 0.62 (0.40–0.96) for soy protein, respectively. A preventive effect of soy food was found for all subtypes of ER and/or PR status of breast cancer. The inverse association was more evident among premenopausal women. This study suggests that consumption of soy food, soy isoflavone, is inversely associated with the risk of breast cancer. The protective effects of soy did not seem to differ by ER and PR breast cancer status. (*Cancer Sci* 2010; 101: 501–507)

The breast cancer incidence rate is much lower in Asian than in Western populations.[1] Although the incidence of breast cancer in China has been rapidly increasing over the past two decades,[2] on average, the incidence rate was 5.3 times lower in China than in North America (18.7 *vs* 99.4 per 100 000).[1] Migrant studies have found that breast cancer rates increase in persons who move from low to high incidence areas.[3,4] Therefore, it has been suggested that environmental factors, including diet, may play an important role in breast cancer etiology.

Soy-containing diets have long been known to be typical of some ethnic groups who experience low breast cancer risk, such as those in Asian countries. There has been tremendous interest in the possible role of soy in the prevention of breast cancer. So far, over 35 epidemiologic studies evaluating the association between soy or isoflavone intake and breast cancer risk have been published. Of these, 21 were conducted in Asia. Several studies, but not all, showed protective effects of soy in Asian populations.[5–14] Studies conducted in Western populations have also reported inconsistent results.[15–21]

It has been found that some of the breast cancer risk factors such as parity and body mass index (BMI) may vary with estrogen receptor (ER) and progesterone receptor (PR) status.[22] However, few studies have specifically evaluated the association between the intake of soy food and the risk of breast cancer by receptor status, and the results have been inconsistent.[5,12,13,23]

We examined the relationship between soy product and soy isoflavone intake and the risk of breast cancer, using hospital-based case–control data from Chinese women residing in Guangdong province. We also evaluated whether these relationships were modified by hormone receptor status.

Materials and Methods

Study subjects. Details of the selection of cases and controls into this study have been reported previously.[24] In brief, potential case subjects were recruited from June 2007 to August 2008 from among patients admitted to the surgical units of two affiliated hospitals of Sun Yat-sen University, Guangzhou, China. Inclusion criteria were female subjects aged 25 to 70 years and natives of the province of Guangdong or having lived in Guangdong for at least 5 years, with incident, primary, histologically confirmed breast cancer diagnosed no more than 3 months before the interview. Women were excluded if they could not understand or speak Mandarin/Cantonese or if they had a prior history of breast or other cancers. A total of 438 (96%) cases out of 455 eligible cases were successfully interviewed. Infiltrating ductal carcinoma was the most common histological type of breast carcinoma (388, 88.6%), followed by ductal carcinoma *in situ* (27, 6.2%), mucoid carcinoma (8, 1.8%), lobular carcinoma (5, 1.1%), neuroendocrine carcinoma (4, 0.9%), medullary carcinoma (3, 0.7%), tubular carcinoma (2, 0.5%), and micropapillary carcinoma (1, 0.2%).

Control subjects were patients without a history of cancer who were admitted to the same hospitals during the same time period as the case subjects. They were frequency matched by age (5-year interval) and residence (rural/urban) to the case patients. The controls were consecutively selected from the Departments of Ophthalmology, Plastic and Reconstructive Surgery, Vascular Surgery, Ear-Nose-Throat, and Orthopedics and Microsurgery. These patients presented with the following diseases, by category and in descending order: glaucoma/uveitis/keratitis/pterygium/dacryocystitis/optic neuritis (191, 43.6%), sudden deafness/acute bacterial/viral otitis media (94, 21.5%), sinusitis/deviation of nasal septum (68, 15.5%), varicose veins (29, 6.6%), traumatic skeletal disorders/osteoarthritis/degenerative joint disease (27, 6.2%), orthopedics (18, 4.1%), tonsillitis (5, 1.1%), trifacial neuralgia (4, 0.9%), and acute appendicitis (2, 0.5%). In total, 448 controls were identified and invited to participate in the study. Among them 10 (2%) potential control subjects refused.

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The authors' responsibilities were as follows: CX Zhang conceived the project design, data collection, and writing of this paper. Professor Suzanne C. Ho supervised and contributed to the manuscript writing. JH Fu, SZ Cheng, and FY Lin were responsible for connecting and coordinating the field work. YM Chen provided significant advice regarding the analyses and interpretation of the data.

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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 (age, residence, urban/rural status, marital status, occupation, education, household income), current body weight, height, menstrual and reproductive history, use of exogenous hormones, use of contraceptive drugs, history of benign breast disease, family history of breast cancer, physical activity, active and passive smoking, alcohol use, and prior disease history. BMI was calculated by dividing the body weight in kilograms by height in meters squared. Relevant medical information, medical diagnosis, histologic findings, and ER and PR status were abstracted from hospital medical records. Information on the ER and PR status of the tumor was available for 399 (91.1%) of the cases. Written informed consent was obtained from all the participants before each interview. The Ethical Committee of the Chinese University of Hong Kong approved the study.

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 81 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 (e.g. slice, glass or unit such as one apple, one banana). For soy, vegetable, and animal foods, the liang (1 liang = 50 g), a common weight measure familiar to the study subjects, was used to estimate their usual portion size. Food portion photographs were used to help participants estimate and record the amounts of the foods taken.

The FFQ was evaluated for its validity and reproducibility in 61 subjects recruited from the community in Guangzhou city.[25] Study participants completed two FFQs administered 1 year apart and six times 3-day diet records at intervals of 2 months during a 12-month period. The correlation coefficients between the second FFQ and 18-day dietary records were 0.25–0.65 for nutrients, 0.30–0.68 for food groups, and 0.45 for soy food. The correlations between the two FFQs were 0.46–0.71 for nutrients, 0.36–0.66 for food groups, and 0.61 for soy 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 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[26] was used to estimate intake of soy protein and soy isoflavone.

Statistical analysis. SPSS 13.0 was used to conduct the data analysis. The χ^2-test was used for the comparison of categorical variables between cases and controls, and the *t*-test was used for continuous variables. Quartiles of soy isoflavone and soy protein were defined based on the distribution among controls. Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of each quartile using the lowest quartile group as the reference. The relationships between soy food intake with the risk of breast cancer was further examined after adjusting for various potential confounding factors using logistic regression models. Age at menarche (continuous), BMI (continuous), family history of breast cancer in a first-degree relative (yes/no), history of benign breast disease (yes/no), physical activity (categorical, never, occasional, and ≥1 time per week), passive smoking from a husband (yes/no), total vegetable (continuous), and total fruit intake (continuous) were selected as potential confounders based on literature review and comparison of baseline characteristics between cases and controls. Total energy intake was adjusted based on the standard multivariate method by including total energy intake (continuous) in the risk model along with the soy food.[27] Tests for trend were performed by entering the categorical variables as continuous variables in the models.

Stratified analyses were conducted to investigate whether the observed association between consumption of soy product and isoflavone and the risk of breast cancer was modified by ER/PR status. As pre- and postmenopausal breast cancer probably have a separate disease etiology, analyses were also stratified by pre- and postmenopausal status. Obesity is a known risk factor for breast cancer, especially for postmenopausal women. Subgroup analysis was conducted to evaluate the potential modifying effect of BMI (<25 *vs* ≥25) on the association of soy intake and breast cancer risk. All *P*-values were two sided and statistical significance was determined at the $P < 0.05$ level.

Results

Table 1 shows the selected demographic, menstrual, and reproductive characteristics of the study subjects. Compared to the controls, cases had an earlier age at menarche and higher BMI, were more likely to have a family history of breast cancer, history of benign breast disease, and history of passive smoking from a husband, and were less likely to be physically active. No significant differences were found between the case and control subjects in socio-demographic factors, including educational level, occupational status, marital status, and household income, or in reproductive factors, including nulliparous, age at first live birth, number of live births, months of breast feeding, age at menopause, and use of an oral contraceptive.

The mean daily intake of soy isoflavone was 11.94 mg, soy protein 3.48 g in control group (Table 2). Compared with controls, consumption of soy isoflavone, soy protein, vegetables, and fruits was significantly lower in the case subjects. No significant differences between cases and controls were observed for total energy, fat, and carbohydrate intake.

Table 3 shows the associations between soy isoflavone and soy protein intake with breast cancer risk. The highest quartile of soy isoflavone intake was associated with a 46% decrease in the risk of breast cancer compared with the lowest quartile after adjustment for the potential dietary and non-dietary confounding factors in the multivariate models (OR = 0.54, 95% CI = 0.34–0.84). Higher consumption of soy protein was also associated with the reduced risk of breast cancer. The adjusted OR in the highest quartile was 0.62 (95% CI = 0.400.96, trend test $P = 0.003$).

Among case women with information on hormone receptor status, case positive for ER and PR accounted for 292 (73.2%) and 348 (87.2%) respectively. A total of 275 (68.9%) were diagnosed with an ER+/PR+ tumor, 17 (4.3%) had an ER+/PR− tumor, 73 (18.3%) had an ER−/PR+ tumor, and 34 (8.5%) had an ER−/PR− tumor.

Table 4 shows the impact of soy isoflavone consumption on breast cancer risk according to estrogen and progesterone receptor status. The inverse association between consumption of soy isoflavone and breast cancer risk was observed in all subtypes of ER and/or PR status, although there was no statistical significance among women with PR-negative, ER+/PR−, and ER−/PR− breast cancer tumors. A similar pattern was found between soy protein intake and breast cancer risk according to types of ER and/or PR status (data not shown).

We conducted additional stratification analyses by menopausal status and BMI level (Table 5). The inverse association between soy isoflavone intake with the risk of breast cancer was statistically significant in premenopausal women but not in postmenopausal women. Compared with women in the lowest quartile of isoflavone consumption, the highest quartile had an

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Table 1. Comparison of demographic and selected risk factors among breast cancer cases and controls

	Case (n = 438)	Controls (n = 438)	P-values
Age (mean ± SD, years)	47.04 ± 9.53	47.14 ± 9.58	0.875
Residence (n, %)			0.932
Rural	86 (19.6)	87 (19.9)	
Urban	352 (80.4)	351 (80.1)	
BMI (mean ± SD)	22.92 ± 3.33	22.46 ± 3.05	0.038
Regular smoker (n, %)	7 (1.6)	2 (0.4)	0.094
Passive smoker from husband (n, %)	202 (46.1)	170 (38.8)	0.029
Regular drinker (n, %)	12 (2.7)	10 (2.3)	0.666
Physical activity (exercise for health) (n, %)			0.016
Never	170 (38.8)	139 (31.7)	
Occasional	46 (10.5)	35 (8.0)	
≥1 times/ week	222 (50.7)	264 (60.3)	
Age at menarche (mean ± SD, years)	14.82 ± 1.88	15.11 ± 1.84	0.019
Nulliparous (n, %)	17 (3.9)	19 (4.3)	0.734
Number of live births† (mean ± SD, years)	1.98 ± 1.12	2.03 ± 1.20	0.532
Age at first live birth† (mean ± SD, years)	25.58 ± 3.42	25.15 ± 3.45	0.074
Months of breast feeding‡ (mean ± SD, months)	21.56 ± 17.66	22.13 ± 17.70	0.658
Age at menopause§ (mean ± SD, years)	49.33 ± 3.96	49.06 ± 3.93	0.579
Menopausal status (n, %)			0.423
Premenopausal	306 (69.9)	295 (67.4)	
Postmenopausal	132 (30.1)	143 (32.6)	
Mother/sister/daughter with breast cancer (n, %)	17 (3.9)	4 (0.9)	0.004
Ever had benign breast disease (n, %)	177 (40.4)	84 (19.2)	<0.001
Ever used oral contraceptive (n, %)	27 (6.2)	21 (4.8)	0.373

†Among women who had live birth(s). ‡Among women who had ever breast fed. §Among menopausal women. BMI, body mass index.

Table 2. Mean and median consumption of soy food and selected dietary variables among breast cancer cases and controls

	Cases		Controls		P-values*
	Mean	Median (25th, 75th)	Mean	Median (25th, 75th)	
Soy isoflavone (mg/day)	8.44	5.24 (2.52, 10.33)	11.94	8.07 (3.26, 16.89)	<0.001
Soy protein (g/day)	2.47	1.56 (0.72, 3.05)	3.48	2.33 (0.93, 4.66)	<0.001
Energy intake (kcal/day)	1464	1408 (1156, 1698)	1504	1446 (1191, 1734)	0.142
Total fat intake (g/day)	29.40	26.02 (18.88, 36.52)	30.63	26.66 (19.23, 37.90)	0.207
Total carbohydrate intake (g/day)	246.26	232.33 (191.26, 289.64)	252.16	238.50 (197.44, 295.53)	0.250
Total vegetable intake (g/day)	354.33	313.00 (215.20, 441.40)	458.49	406.22 (290.74, 577.38)	<0.001
Total fruit intake (g/day)	186.62	151.77 (88.36, 248.54)	225.78	193.54 (99.47, 301.91)	<0.001

*Wilcoxon rank-sum test comparing the median consumption levels between cases and controls.

Table 3. Odds ratios and 95% confidence intervals for breast cancer according to soy food intake

	Cases	Controls	Crude OR (95% CI)	Model I†	Model II‡
Soy isoflavone (mg/day)					
<3.26	140	109	1	1	1
3.26–8.07	158	110	1.12 (0.79–1.59)	1.07 (0.74–1.54)	1.13 (0.78–1.65)
8.07–16.89	81	110	0.57 (0.39–0.84)	0.60 (0.40–0.89)	0.68 (0.45–1.02)
>16.89	59	109	0.42 (0.28–0.63)	0.41 (0.27–0.63)	0.54 (0.34–0.84)
P-trend			<0.001	<0.001	0.001
Soy protein (g/day)					
<0.93	140	109	1	1	1
0.93–2.33	156	110	1.10 (0.78–1.57)	1.17 (0.81–1.70)	1.25 (0.86–1.82)
2.33–4.66	77	110	0.54 (0.37–0.80)	0.57 (0.38–0.85)	0.64 (0.42–0.97)
>4.66	65	109	0.46 (0.31–0.69)	0.48 (0.32–0.74)	0.62 (0.40–0.96)
P-trend			<0.001	<0.001	0.003

†Odds ratios were adjusted for age at menarche, body mass index (BMI), history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, and passive smoking. ‡Odds ratios were adjusted as in Model I, further controlling for total energy, total vegetable, and total fruit intake. CI, confidence interval; OR, odds ratio.

Table 4. Odds ratios and 95% confidence intervals for breast cancer according to soy isoflavone intake stratified by ER/PR status

	Q1	Q2	Q3	Q4	*P*-trend
ER+					
No. cases/controls	91/109	114/110	49/110	38/109	
Adjusted OR (95% CI)†	1	1.25 (0.83–1.90)	0.67 (0.42–1.08)	0.54 (0.32–0.91)	0.004
ER−					
No. cases/controls	37/109	32/110	22/110	16/109	
Adjusted OR (95% CI)†	1	0.84 (0.48–1.48)	0.60 (0.32–1.13)	0.46 (0.23–0.92)	0.016
PR+					
No. cases/controls	112/109	129/110	60/110	47/109	
Adjusted OR (95% CI)†	1	1.16 (0.78–1.72)	0.62 (0.40–0.97)	0.52 (0.32–0.85)	0.001
PR−					
No. cases/controls	16/109	17/110	11/110	7/109	
Adjusted OR (95% CI)†	1	0.96 (0.44–2.10)	0.83 (0.35–1.94)	0.47 (0.18–1.27)	0.147
ER+PR+					
No. cases/controls	87/109	107/110	44/110	37/109	
Adjusted OR (95% CI)†	1	1.25 (0.82–1.91)	0.62 (0.38–1.00)	0.55 (0.32–0.92)	0.003
ER+PR−					
No. cases/controls	4/109	7/110	5/110	1/109	
Adjusted OR (95% CI)†	1	1.44 (0.37–5.68)	1.63 (0.40–6.64)	0.27 (0.03–2.67)	0.439
ER−PR+					
No. cases/controls	25/109	22/110	16/110	10/109	
Adjusted OR (95% CI)†	1	0.84 (0.43–1.62)	0.62 (0.30–1.30)	0.42 (0.18–0.96)	0.030
ER−PR−					
No. cases/controls	12/109	10/110	6/110	6/109	
Adjusted OR (95% CI)†	1	0.82 (0.32–2.08)	0.55 (0.19–1.60)	0.50 (0.17–1.50)	0.155

†Odds ratios were adjusted for age at menarche, body mass index (BMI), history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking, total energy, total vegetable, and total fruit intake. CI, confidence interval; ER, estrogen receptor; OR, odds ratio; PR, progesterone receptor.

Table 5. Odds ratios and 95% confidence intervals for breast cancer according to soy isoflavone intake stratified by menopausal status and body size

	Q1	Q2	Q3	Q4	*P*-trend
Menopausal status					
Premenopausal					
No. cases/controls	88/64	123/78	56/76	39/77	
Adjusted OR (95% CI)†	1	1.25 (0.79–1.98)	0.64 (0.39–1.07)	0.46 (0.26–0.82)	<0.001
Postmenopausal					
No. cases/controls	52/45	35/32	25/34	20/32	
Adjusted OR (95% CI)†	1	0.82 (0.42–1.63)	0.77 (0.37–1.62)	0.66 (0.30–1.44)	0.281
Body size					
BMI < 25					
No. cases/controls	112/94	128/88	60/95	41/88	
Adjusted OR (95% CI)†	1	1.21 (0.80–1.83)	0.62 (0.39–0.98)	0.49 (0.29–0.82)	0.001
BMI ≥ 25					
No. cases/controls	28/15	30/22	21/15	18/21	
Adjusted OR (95% CI)†	1	0.89 (0.36–2.23)	1.03 (0.37–2.87)	0.68 (0.24–1.96)	0.568

†Odds ratios were adjusted for age at menarche, BMI, history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking, total energy, total vegetable, and total fruit intake. CI, confidence interval; BMI, body mass index; OR, odds ratio.

adjusted OR of 0.46 (95% CI = 0.26–0.82, trend test $P < 0.001$) for premenopausal women, and OR of 0.66 (95% CI = 0.30–1.44, trend test $P = 0.281$) for postmenopausal women. The inverse association between the intake of soy protein with the risk of breast cancer was also statistically significant in premenopausal women but not in postmenopausal women (data not shown). For the stratification of BMI level, we observed a significant inverse association of soy isoflavone and soy protein intake with breast cancer risk among women who had a BMI of 25 or lower (OR = 0.49, 95% CI = 0.29–0.82, trend test $P = 0.001$ for soy isoflavone; other data not shown).

Because all case patients and control subjects were recruited from the university hospitals, they may have a relatively higher socioeconomic status than those recruited from other hospitals or clinics. We also conducted a stratification analysis by socioeconomic status (income, occupation, and educational level). No interaction was observed between socioeconomic status and soy isoflavone intake (data not shown). The linear regression analysis was conducted to evaluate whether intake of soy foods increased with age. No significant association was found between age and soy food intake (data not shown).

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Discussion

Our hospital-based case–control study found a significant inverse association between soy product and isoflavone intake and breast cancer risk; however, this association did not differ by ER/PR subtypes of breast cancer status. The inverse association was more evident among premenopausal women and women who had normal BMI than those with a BMI ≥25.

Our results supported previous epidemiological studies, which reported that soy intake is protective for breast cancer. Among case–control studies, Lee *et al.*[10] first reported a reduced risk of breast cancer in premenopausal Singapore Chinese women who were high consumers of soy. Other case–control studies conducted in Asian countries, but not all, have found similar results.[5,7–9,12,23] Soy food and soy isoflavone consumption were also inversely related to breast cancer risk in three large prospective studies conducted in Asian populations.[13,14,28] However, seven prospective studies reported non-significant inverse association between soy food or isoflavone intake and the risk of breast cancer.[19–21,29–32] The low-level of soy intake in Western populations may partly explain a lack of a protective effect of soy foods on breast cancer risk. Various studies have shown that the median soy isoflavone intake was 0.37 mg/day among Dutch women,[21] 0.423 mg/day in UK women,[29] and 0.289 mg/day in German women.[16] A recent meta-analysis[33] separating studies conducted among Asian and Western populations reported that soy intake was unrelated to breast cancer risk (OR = 1.04, 95% CI = 0.97–1.11) in studies conducted in 11 Western populations whereas soy intake was significantly inversely associated with the risk of breast cancer among Asian populations (OR = 0.71, 95% CI = 0.60–0.85).

Soy is the major source of isoflavones in food, with the primary dietary isoflavones being genistein, daidzein, and glycetein. These soy isoflavones are structurally similar to estrogens and bind to the ER, so it is biologically plausible that they protect against the development of breast cancer. It has also been suggested that soy isoflavones may influence breast cancer risk via their anti-proliferative, anti-angiogenic, anti-oxidative and anti-inflammatory properties.[34] The mean intake of soy isoflavone (11.94 mg/day) in the current study among control women corresponds to the moderate level of isoflavone intake in Asian countries.[33] But this intake is lower than that previously reported in the Shanghai Breast Cancer Study (40.9 mg/day).[5] Difference in soy isoflavone intake between studies could be explained by differing food habits, but may also be due to differences in food items included in the FFQ employed for assessing soy food intake. Moreover, the estimation of isoflavone contents based on different food composition tables may also influence the results.

A few previous studies addressed the possible preventive effects of soy products on breast cancer by ER and PR status, but the results were inconsistent. The Shanghai Breast Cancer Study found that the protective effect of soy was stronger for breast cancer positive for both ER and PR (OR = 0.44, 95% CI = 0.25–0.78) than those with other ER/PR status.[5] One case–control study reported that total isoflavone intake was associated with a dose-response reduced risk for all receptor subtypes of breast cancer.[23] Another case–control study in Japan observed a significantly reduced risk in patients with ER-positive tumors.[12] Our study found a protective effect of soy products on all subtypes of ER/PR status of breast cancer, although the association was statistically non-significant for some subtypes due to their small number.

Lee *et al.*[10] reported a reduction in breast cancer risk with high soybean consumption among premenopausal women in Singapore, but no association was observed among postmenopausal women. Six other case–control studies[7–9,11,12,16] and one prospective study[28] also showed a statistically significant inverse association between soy food intake and breast cancer risk in premenopausal women. Consistent with these results, we found that the inverse association between soy isoflavone intake and breast cancer risk was apparent mainly in premenopausal women, and was not observed in postmenopausal women. The potential protective mechanisms of high soy intake and breast cancer risk in premenopausal women may be through the reduction of serum estradiol concentrations, suppression of midcycle surge of gonadotropins, and increasing the menstrual cycle length.[35–37] However, two prospective studies[13,14] reported a protective association between soy intake and breast cancer only in postmenopausal women. Two case–control studies[5,38] reported that the protective effect of high soy food intake was observed in both pre- and postmenopausal women.

Few studies have investigated whether body size modifies the soy–breast cancer association. A case–control study conducted in Shanghai, China, reported that the inverse soy–breast cancer association was more evident in women with a higher BMI (>25kg/m^2) than their lower BMI counterparts (adjusted OR = 0.30, 95% CI 0.10–0.94).[5] Wu *et al.* found that the inverse association between soy intake and breast cancer was statistically significant in postmenopausal women with a higher BMI (adjusted RR = 0.67, 95% CI 0.51–0.88) but not in those below the median BMI value (adjusted RR = 0.83, 95% CI 0.62–1.11).[13] However, we observed a significant inverse association of soy isoflavone and soy protein intake with breast cancer risk among women who had a BMI of 25 or lower. Perhaps the small sample size in the subgroup (BMI >25) in the subgroup analysis may lack sufficient power to detect significant differences, if one exists. Further work is needed to clarify the modifying effects of body size on the association of soy food intake and the risk of breast cancer.

Chinese populations generally have a diet rich in vegetables and fruits, but low in animal protein.[39] Subjects with a high consumption of soy foods may also be more likely to have high intake of vegetables and fruits. This dietary habit could contribute to a lower risk of breast cancer. Our study also found an inverse association between vegetable and fruit intake and risk of breast cancer among Chinese women.[24] Soy foods and isoflavones, however, were independently associated with lower breast cancer risk after adjustment for diet (including vegetable and fruit intake) and other lifestyle factors in the current study.

The length of exposure time is probably an important factor which may influence the relationship between soy food intake and breast cancer risk. Compared with the older women, the period of exposure to soy among younger women is relatively shorter. However, the FFQ used in the nutritional epidemiology can only determine past dietary habits but not lifetime cumulative intake. The frequency matching of cases and controls by age would eliminate the confounding effect of age on the relationship between soy food intake and breast cancer risk. Moreover, in our study, the linear regression analysis found no significant association between age and soy food intake based on the previous 1-year intake; therefore, consumption of soy food did not increase with the age. Further studies to develop an effective way to measure lifetime diet intake may help to clarify this point.

The present study has some methodological strength. A validated FFQ was used to inquire about frequency and portion size of food item intake. So it is possible to estimate the intake of soy protein and soy isoflavone. The wider range of soy foods consumed by our study participants facilitated the evaluation of the effect of usual soy food consumption in this population. In addition, we had information on a wide range of potential confounders including non-dietary and dietary factors and were able to adjust for them in the analyses.

Several potential limitations should be considered. Case and control subjects recruited from university hospitals usually have

a relatively higher socioeconomic status. However, stratified analyses showed no interaction between socioeconomic status and soy isoflavone intake. Therefore, socioeconomic status is unlikely to have a strong influence on the soy food on breast cancer association. And the method of recruiting case and control subjects from the same hospitals would also minimize the confounding effects of socioeconomic status. The use of hospital-based controls with conditions potentially related to diet is a major concern. To minimize this selection bias, an attempt was made to recruit controls from several conditions with no apparent association with a dietary cause. Another problem is that the dietary habits of hospital controls may differ from those of the general population. To evaluate the potential bias in this study, consumption of nutrients and food groups by the hospital-based controls was compared with that by participants in the validation of the FFQ. Comparison of the results showed that there was no significant difference in the consumption of most nutrients and food groups. In addition, the high participation rate (96% and 98% for cases and controls, respectively) and high comparability in socio-demographic factors between cases and controls indicated that selection bias should not be serious.[40,41]

Recall bias is another concern. To reduce this bias, we tried to interview patients as soon as diagnoses were made. The average interval between diagnosis and interview for cases was 7.15 days. Moreover, every effort was made to interview cases before operations. A comparison of consumption of soy foods for the case subjects interviewed pre- and post-operatively showed similar levels of intake. We also provided photographs with usual intake portions of foods to assist participants with quantification of intake. Moreover, the interviewing of all subjects in a hospital setting ensured the comparability of the recall between case and control subjects.[42]

Introducing the study to the interviewers as a general 'women's health' study, keeping the main hypothesis from the data gatherers, and training interviewers to elicit information from cases and controls in a standardized way minimized the possibility of interviewer bias. Misclassification of soy intake may have occurred due to measurement error. This misclassification, however, is likely to be non-differential among cases and controls and would attenuate the true association between diet intake and breast cancer risk.[43]

In summary, this study found that consumption of soy foods and soy isoflavone was inversely associated with the risk of breast cancer among Chinese women residing in Guangdong, especially among premenopausal women. The protective effects of soy did not seem to differ by ER and PR breast cancer status.

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