Mammographic Parenchymal Patterns and Self-reported Soy Intake in Singapore Chinese Women[1]

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Abstract

The study aimed to investigate whether self-reported dietary variables were associated with mammographic parenchymal patterns, which have been shown to predict risk of breast cancer. Among the 3,421 women, ages 45–74 years, common to two independent population-based cohorts, mammographic parenchymal patterns and current dietary habits were assessed for 406 randomly chosen participants. Logistic regression methods were used to compare dietary and other lifestyle profiles between subjects classified as displaying high (cases) and low risk (controls) parenchymal patterns. After adjustment for energy intake and other potential confounders, dietary soy protein intake was inversely related to risk of high-risk parenchymal pattern (odds ratio, 0.41; 95% confidence interval, 0.18–0.94, highest *versus* lowest quartile of intake). Similarly, the highest *versus* lowest quartile of dietary soy isoflavone intake was significantly related to low-risk parenchymal patterns (odds ratio, 0.44; 95% confidence interval, 0.20–0.98). The association between high soy intake and a reduced risk of mammographic parenchymal patterns that are associated with high breast cancer risk may have important implications in breast cancer prevention.

Introduction

For much of the twentieth century, the etiology of breast cancer has been documented in terms of reproductive risk factors for the disease, such as low parity or late age at first childbirth (1). A largely hormonal epidemiological profile of the disease has been built up. In its simplest terms, large lifetime numbers of ovulatory cycles are associated with increased risk of breast cancer, possibly because of their relationship with increased mitotic activity in the breast (2).

It has long been observed that breast cancer rates are lower in most Asian countries than in Western Europe and the United States (3). This has led to hypotheses of dietary effects on breast cancer risk. Analytic epidemiological studies suggest that diets high in animal products and low in fresh fruit and vegetables are associated with increased risk (4), although these have largely relied on retrospective evidence, which has not yet been confirmed by prospective cohort studies. One result that has been observed prospectively is the positive association between high meat intake and risk (5). This raises the question of protein sources and hormonal dietary components as potential risk factors or protective agents. In particular, the issue of soy intake as a potential protective factor has been suggested, because dietary intakes of soy products are high in many low-risk countries, and soy is a rich source of phytoestrogens (6).

The potential of isoflavonic phytoestrogens to protect from breast cancer in animal models is long established (7). This has been confirmed in numerous animal studies, as have other biochemical effects (8–11). Until recently, epidemiological studies in humans have yielded conflicting results with respect to soy intakes and breast cancer risk (12–16), despite clear effects on hormone levels and menstrual cycle length (17, 18). A recent study by Shu *et al.* (19) broke new ground by finding a strong inverse association between soy intakes during adolescence and risk of breast cancer. Focusing on intakes at later periods in life may be partly responsible for the varying results in different studies.

This has considerable potential implications in terms of explaining the difference between incidence of breast cancer in East Asian populations and those in the West, and in terms of linking the established hormonal etiology with the suspected dietary etiology models. A possible mechanism of the phytoestrogen effect is that the exogenous plant estrogens, which are essentially weak estrogens, supplant endogenous (strong) estrogens, thus reducing exposure of breast tissue to active ovarian estrogens.

One risk factor that has received little attention, possibly because of an uncertainty about its practical implications, is the mammographic parenchymal pattern. High ductal and nodular densities observed on a mammogram are associated with increased risk of breast cancer (20). Thus, it is possible to visualize changes in the breast tissue, which may be precursors or markers of the malignant process. The mammographic pattern has potential application in designing screening regimes for breast cancer and may assist in understanding the natural history of the disease. Refinements to the Wolfe pattern classification have been developed, including that of Tabar (21).

This study was designed to investigate whether high intake of soy protein, and more particularly of soy isoflavones, re-

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duces the likelihood of high-risk mammographic patterns. This has potential implications for control of the disease. If high intake of soy reduces the rate of high-risk patterns, this would provide strong concomitant evidence that the relationship between dietary soy and breast cancer is indeed part of a causal process. This, in turn, would help facilitate and inform future research on prevention.

The Singapore Chinese population, which includes a proportion of individuals with relatively high soy intake, is an ideal setting in which to carry out such research (12). We propose a cross-sectional study correlating mammographic parenchymal patterns from the SBSP (22) with dietary intake of soy from a baseline survey for the SCHS (23).

Patients and Methods

Study Population. Subjects reported in this study were selected at random from a group of women who were common to two independent population-based cohorts. First, the SCHS,[3] with a focus on the role of diet and nutrition in cancer etiology, recruited a cohort of 63,257 Chinese men and women, ages 45–74 years, between April 1993 and December 1998 (23). During 1994 and 1997, Singaporean women aged between 50 and 64 years were randomly assigned to single screen (two view) mammography followed by observation or observation alone (controls) as part of the SBSP (22). In addition, a small sample ($n = 1{,}000$) of women ages 45–49 and 65–69 were also recruited to the study to assess compliance. Of the 67,656 eligible women randomized and invited to the mammography arm of the SBSP, 28,231 were screened.

In May 1998, 3421 women were identified as being common to both cohorts, and from this subgroup 406 were randomly selected for this study. Median time between dietary assessment (SCHS) and mammogram (SBSP) was 1.8 years (interquartile range, 0.8, 2.6), with 90% of study subjects having their dietary assessment before the mammogram.

Dietary Data. The SCHS performed a comprehensive dietary assessment using a Quantitative FFQ, which was developed before initiation of recruitment of the cohort in April 1993 and asks about usual diet during the last 12 months. On the basis of the actual food intakes obtained in a pilot 24-hour recall study, Singapore Chinese food and beverage items were grouped into 165 categories to form the FFQ. The FFQ consisted of eight frequency levels for food items ranging from "never or hardly ever" to "two or more times a day," and nine levels of frequency for beverage items. For most items, colored photographs were shown to subjects during the interview to assist in determining portion sizes.

As part of the SCHS, a food composition table based on edible portions of foods commonly consumed by Singapore Chinese was developed (23). Gram weights of foods derived from questionnaire data were linked to the food composition database to obtain individual levels of energy/nutrient intakes among study subjects. The validity of the FFQ in assessing Singapore Chinese diet has been established in a study involving 1022 cohort subjects (23). In addition, a statistically significant association between urinary levels of isoflavones and estimates of dietary soy intake using the FFQ has been observed (24).

[3] The abbreviations used are: SCHS, Singapore Chinese Health Study; SBSP, Singapore Breast Screening Project; FFQ, Food Frequency Questionnaire; OR, odds ratio; CI, confidence interval; BMI, body mass index; HRT, hormone replacement therapy.

Classification of Mammograms. Parenchymal patterns, according to Tabar's classification system (21), were determined by one radiologist (F-C. N.), who was blinded to the identity of the subjects, in the Department of Radiology, Singapore General Hospital. Both cranio-caudal and medio-lateral-oblique views were used in the classification.

Tabar's classification consists of five categories, as follows: (*a*) I Mammogram, composed of scalloped contours with some lucent areas of fatty replacement and 1-mm evenly distributed nodular densities; (*b*) II Mammogram, composed almost entirely of lucent areas of fatty replacement and 1-mm evenly distributed nodular densities; (*c*) III Prominent, ducts in the retroareolar area; (*d*) IV Extensive, nodular and linear densities, with nodular size larger than normal lobules; and (*e*) V Homogeneous, ground glass-like appearance with no perceptible features.

Pattern I represents the classic appearance of the premenopausal breast. Pattern II represents the normal postmenopausal breast with glandular tissue replaced by fatty tissue. Pattern III indicates more periductal elastosis. Pattern IV probably represents proliferation. Pattern V represents extensive fibrosis, which may be but is not necessarily associated with any malignant or proliferative process. It has been demonstrated that Patterns IV and V show a relationship with breast cancer risk factors, and it has been suggested that these patterns may be associated with increased risk of disease (21).

Demographic data, including known risk factors for breast cancer, were gathered in both the SCHS and the SBSP. For these factors we found almost perfect agreement between the two studies. However, factors such as menopausal status and use of hormone therapy were likely to be strongly associated with parenchymal pattern and so we used the demographic data collected at the same time the mammogram was performed, as part of the SBSP, for these analyses.

Statistical Considerations. Assuming a roughly equal number of high-risk and low-risk patterns, it was calculated that 400 subjects would give 90% power to detect a 60% reduction in high-risk patterns between the highest and lowest quartiles of dietary intake.

Geometric means and their corresponding CIs were calculated for nutrient intakes, as these tend to have a skewed distribution that could be readily log transformed. Statistical analyses were performed by logistic regression (25), giving OR estimates of relative risk and 95% CI, for outcome Tabar Pattern IV or V in association with dietary intakes adjusted for potential confounding variables. The latter were identified as factors that were significantly associated with the outcome in a multiple logistic regression. For the dietary variables, trends across quartiles of intake were presented as ORs pertaining to an increase in intake of one quartile adjusting for energy intake, age, BMI (weight/height squared) and parity (all continuous). All of the *P*s quoted are 2-sided.

Results

Table 1 describes the study population characteristics including demographic features, potential confounding variables, and the distribution of Tabar's parenchymal patterns. One quarter of the population demonstrated the properties of patterns IV and V. Table 2 lists geometric means and corresponding 95% CI of the dietary nutrients and food groups.

ORs for nondietary variables are listed in Table 3. The OR for being Tabar IV or V reduced significantly with increasing age, high BMI, increasing number of child deliveries, and if the subject was postmenopausal. ORs for being Tabar IV or V

Table 1 Characteristics of the study group

	n	Mean	SD
Age (years)	406	56.36	4.33
Height (cm)	406	153.06	5.41
Weight (kg)	406	56.95	9.84
BMI (kg/m^2)	406	24.29	3.90

	n	Percent
Highest education		
No formal	168	42
Primary School	176	43
Secondary/vocational	54	13
A level/university	8	2
Age at menarche		
<13	50	12
13	78	19
14	69	17
15	72	18
16+	137	34
Age at first delivery		
<20	50	13
20–24	161	43
25–29	122	32
30+	46	12
Number of deliveries		
0	27	7
1/2	83	20
3/4	164	40
5+	132	33
Breast feed any children?		
No	133	35
Yes	246	65
Menopausal status		
Pre-	53	13
Post	353	87
OC[a] use		
No	246	61
Yes	160	39
HRT use		
Never	357	88
Ex	25	6
Current	24	6
Tabar classification		
I	233	57
II	62	15
III	12	3
IV	44	11
V	55	14
Total	406	100

[a] OC, oral contraceptive.

Table 2 Description of dietary intake of the study group (n = 406)

	Geometric mean	95% CI
Nutrients (daily intake)		
Total energy (kcal)	1348	1306–1391
Total soybean protein (g)	4.5	4.1–4.9
Total fat (g)	36.9	35.4–38.4
Saturated fat (g)	12.6	12.0–13.2
Omega-3 fatty acid (g)	0.8	0.7–0.9
Omega-6 fatty acid (g)	6.7	6.3–7.1
Carbohydrate (g)	199.2	193.1–205.6
Fiber (g)	11.2	10.7–11.8
Total nonstarch polysaccharides (g)	7.3	6.9–7.7
Beta carotene (mcg)	1839	1732–1953
Vitamin C (mg)	66	61–71
Vitamin E (mg)	5.3	5.0–5.5
Total soy isoflavone (mg)	13.7	12.6–14.8
Food groups (daily intake)		
Fish (g)	43	39–47
Cruciferous vegetables (g)	37	34–40
Ethanol (g)	0.005	0.003–0.007

increased at the highest levels of education, and for current users of HRT. In the multivariate model, which included all of the variables (fitted as the raw values) that were statistically significant in univariate analyses, the variables that remained significant were age, BMI, and parity.

ORs and 95% CI for dietary variables, adjusted for age, BMI, and parity, are shown in Table 4. Increasing intake of soy protein was associated with a statistically significant reduced risk (P for linear trend = 0.01). Relative to the lowest quartile of intake, the highest quartile was associated with an OR of 0.41 (95% CI, 0.18–0.94). Similarly, the highest *versus* lowest quartile of soy isoflavone intake was significantly related to a reduction in risk (OR, 0.44; 95% CI, 0.20–0.98). Total fat exhibited an inverse association with risk that approached statistical significance (P for linear trend = 0.07), although none of the ORs associated with the higher quartiles was statistically significant (Table 4). No other dietary variable was statistically significantly related to mammographic parenchymal pattern.

The association of dietary soy protein became stronger after adjustment for total fat (Table 4). The OR for 4th *versus* 1st quartile of intake was 0.33 (95% CI, 0.13–0.83). Similarly, the association of dietary soy isoflavone remained statistically significant after adjustment for total fat (OR, 0.41; 95% CI, 0.18–0.96, 4th *versus* 1st quartile of intake). On the other hand, the association of total fat on the risk of being Tabar IV or V was attenuated after adjustment for intake of total soy protein (P for linear trend = 0.3; Table 4).

We repeated all of the above dietary analyses using as exposure variables: (*a*) nutrients as continuous; (*b*) nutrient densities as continuous and quartile variables; and (*c*) calorie-adjusted nutrients (26) as continuous and quartile variables. The associations between soy protein and soy isoflavone with Tabar patterns IV and V remained in all of the cases with similar effect size and significance level.

Discussion

This is a cross-sectional study of a random sample of participants in two independent population-based studies. The dietary assessment and classification of the mammographic parenchymal pattern were each performed blind to the other. Therefore, it is unlikely that the findings are because of bias through either selection of the participants or because of the radiologist who classified the mammograms having knowledge of the dietary assessment.

Maskarinec and Meng (27) have demonstrated that women with higher soy intake had lower percentage mammographic densities when compared with women with lower soy intake. Arguably our most interesting finding is the statistically significant association of dietary soy on risk of Tabar patterns IV and V. These are mammographically dense patterns that are known to be associated with increased risk of breast cancer (20). The results show a reduction in risk of these patterns with higher intake of soy protein or soy isoflavone. To date, the epidemiological evidence linking soy intake to breast cancer risk is derived primarily from case-control studies with inherent inability to dispel the possibility of spurious findings because of recall and/or other biases. The present study circumvents those

Table 3 Risk for being Tabar IV or V (high-risk for breast cancer) in relation to nondietary factors

	Tabar I/II/III (*n*)	Tabar IV/V (*n*)	OR	95% CI	Two-Sided P^a
Age (years)					
<55	110	57	1.00		0.001
55–59	113	30	0.51	(0.31, 0.86)	
60+	84	12	0.28	(0.14, 0.55)	
BMI (kg/m^2)					
<22	75	43	1.00		0.001
22–24	98	29	0.52	(0.30, 0.90)	
25–27	76	21	0.48	(0.26, 0.90)	
28+	58	6	0.18	(0.07, 0.45)	
Highest education					
No formal	133	35	1.00		0.01
Primary	135	41	1.15	(0.69, 1.92)	
Secondary	36	18	1.90	(0.97, 3.74)	
Tertiary	3	5	6.33	(1.44, 27.79)	
Age at menarche (years)					
<13	34	16	1.00		0.6
13	62	16	0.55	(0.24, 1.23)	
14	51	18	0.75	(0.34, 1.67)	
15	56	16	0.61	(0.27, 1.37)	
16+	104	33	0.67	(0.33, 1.37)	
Age at first delivery					
<20	39	11	1.00		0.2
20–24	131	30	0.81	(0.37, 1.77)	
25–29	92	30	1.16	(0.53, 2.54)	
30+	33	13	1.40	(0.55, 3.53)	
Number of deliveries					
0	12	15	1.00		0.001
1/2	53	30	0.45	(0.19, 1.09)	
3/4	131	33	0.20	(0.09, 0.47)	
5+	111	21	0.15	(0.06, 0.37)	
Ever breast feed?					
No	102	31	1.00		0.7
Yes	193	53	0.90	(0.55, 1.50)	
Menopausal status					
Pre-	26	27	1.00		0.001
Post-	281	72	0.25	(0.14, 0.45)	
OC[b] use					
−ve	180	66	1.00		0.2
+ve	127	33	0.71	(0.44, 1.14)	
HRT use					
Never	277	80	1.00		0.001
Ex	20	5	0.87	(0.31, 2.38)	
Current	10	14	4.85	(2.07, 11.32)	

[a] Test for trend.
[b] OC, oral contraceptive.

methodological flaws. Our findings considerably strengthen the hypothesis that soy consumption protects against breast cancer development.

The reduction in risk of Tabar IV/V patterns associated with high fat intakes is to be expected. A higher fat diet or higher body adiposity are likely to lead to an increase in fatty replaced tissue in the breast and, therefore, reduced mammographic density (28). Our results and those of others suggest that the association of high BMI and other measures of obesity with increased risk of breast cancer are not because of associations of these factors with dense mammographic patterns. Breast cancer risk in postmenopausal women increases with increasing weight (29, 30). However, high BMI in this study was associated with a reduced risk of high risk (dense) mammographic pattern. Several other researchers have found the same result (31–36). Thus, there is negative confounding between the two risk factors for breast cancer, high risk patterns, and high BMI. Brisson *et al.* (32) suggest that adjusting for weight and height is important when evaluating the relationship between mammographic pattern and breast cancer risk, because of this confounding. It is possible that the effects of both factors have been underestimated in the past because of failure to adjust each for the other. Similarly, the reduced risk with increasing age and postmenopausal status are consistent with the fact that fibroglandular tissue (mammographically dense) is replaced by fatty tissue (nondense) with the menopause.

The increased risk with early menarche, higher socioeconomic status as measured by education, low parity, and late age at first birth are all consistent with the effect of these factors on breast cancer risk. The increased risk with HRT use has been observed in other studies (37) and is consistent with the mechanism of such therapy in supplementing the endogenous estrogens that are reduced with menopause. The analysis of dietary intake and mammographic density was repeated on a subset (n = 337) of postmenopausal women who were not currently using HRT, and the associations between total soy protein, total

Table 4 Risk of being Tabar IV or V (high-risk for breast cancer) per increase in quartile of dietary component

	Tabar I/II/III (*n*)	Tabar IV/V (*n*)	OR[a]	95% CI	Two-Sided P^b
Nutrients					
Total energy			0.93	(0.75, 1.16)	0.5
Total soy protein[c]			0.71	(0.55, 0.93)	0.01
1st quartile	75	27	1.00		
2nd quartile	69	32	0.93	(0.47, 1.84)	
3rd quartile	82	20	0.51	(0.24, 1.06)	
4th quartile	81	20	0.41	(0.18, 0.94)	
Total soy isoflavone[d]			0.79	(0.62, 1.02)	0.07
1st quartile	74	28	1.00		
2nd quartile	75	26	0.66	(0.33, 1.32)	
3rd quartile	77	25	0.78	(0.38, 1.59)	
4th quartile	81	20	0.44	(0.20, 0.98)	
Total fat[e]			0.74	(0.53, 1.03)	0.07
1st quartile	75	27	1.00		
2nd quartile	73	28	1.00	(0.49, 2.05)	
3rd quartile	81	21	0.54	(0.24, 1.22)	
4th quartile	78	23	0.45	(0.15, 1.30)	
Saturated fat			0.88	(0.65, 1.20)	0.4
Omega-3 fatty acid			0.94	(0.70, 1.27)	0.7
Omega-6 fatty acid			0.88	(0.67, 1.16)	0.4
Carbohydrate			0.79	(0.52, 1.20)	0.3
Fiber			1.23	(0.93, 1.64)	0.1
Total nonstarch polysaccharides			1.06	(0.82, 1.39)	0.6
Beta carotene			1.08	(0.85, 1.37)	0.6
Vitamin C			1.12	(0.88, 1.44)	0.3
Vitamin E			0.88	(0.66, 1.17)	0.4
Food groups					
Fish			1.12	(0.87, 1.43)	0.4
Cruciferous vegetables			1.11	(0.87, 1.40)	0.4
Ethanol			1.03	(0.90, 1.19)	0.7

[a] Adjusted for energy intake, age, parity, and BMI.
[b] Test for trend across quartiles.
[c] After additional adjustment for total fat, OR, 0.88 (95% CI, 0.44–1.76) for 2nd quartile; 0.45 (0.21–0.98) for 3rd quartile; and 0.33 (0.13–0.83) for 4th quartile.
[d] After additional adjustment for total fat, OR, 0.73 (95% CI, 0.36–1.46) for 2nd quartile; 0.71 (0.34–1.49) for 3rd quartile; and 0.41 (0.18–0.96) for 4th quartile.
[e] After additional adjustment for total soy protein, OR, 1.07 (95% CI, 0.52–2.20) for 2nd quartile; 0.63 (0.27–1.49) for 3rd quartile; and 0.61 (0.19–1.94) for 4th quartile.

soy isoflavone, and total fat remained with similar effect sizes (data not shown). In addition, the dietary associations remained unchanged when interaction terms for BMI and soy protein ($P = 0.8$), and for age and soy protein ($P = 0.3$) were fitted in the regression model.

In this study, the dietary questionnaire is targeted on consumption in the last 12 months, *i.e.*, adult consumption. However, in this Chinese population it is likely that those with high intakes of soy protein in adulthood also had high intakes in childhood and adolescence. Thus, our results are consistent with the work of Shu *et al.* (19), who found a reduction in risk of breast cancer in women who had high intakes of soy products in adolescence. It should also be noted that particularly strong chemopreventive effects have been found in animals fed phytoestrogens in the prepubertal period (9).

Our results are consistent with a strong dependency of mammographic patterns on hormonal profile. Those factors that reduce estrogen levels were observed in this study to reduce the probability of high-risk parenchymal patterns, as they have been shown in other studies to reduce risk of breast cancer. The results suggest that high-risk parenchymal patterns may be useful as markers of progression to estrogen-induced breast cancer. The association of high soy intake with a reduced risk of high-risk pattern is consistent with observations that it reduces estrogen levels in animals and humans (6, 17, 38).

The reduced risk of dense mammographic patterns adds to the evidence that a diet rich in soy products may protect against breast cancer. This should be qualified by the observation that most epidemiological observations of such a protective effect have been in populations where the exposure is likely to date from childhood and it may be that this is necessary to obtain the preventive benefit. To determine whether changing in adulthood to a diet rich in soy products confers protection is a target for current and future prospective research.

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