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Food Sources of Phytoestrogens and Breast Cancer Risk in Mexican Women

Luisa Torres-Sánchez, Lizbeth López-Carrillo, Malaquías López-Cervantes, Celina Rueda-Neria, and Mary S. Wolff

Abstract: *We analyzed the intake of selected foods that contain phytoestrogens in relation to breast cancer (BC) risk using data from a hospital-based case-control study performed in Mexico City from 1994 to 1995. A total of 198 women with BC, aged 21–79 years, were individually age matched to an identical number of women with no breast disease. By a direct interview, information on socioeconomic characteristics and diet was obtained. A semiquantitative questionnaire was used to estimate the frequency of consumption of 95 foods. The effect of selected foods that contain phytoestrogens on BC risk was estimated using logistic regression models. The adjusted odds ratio for the consumption of more than one slice of onion per day and BC was 0.27 (95% confidence interval = 0.16–0.47), with a statistically significant trend (*$p < 0.001$*). This protective effect remained after adjustment for known risk factors of BC. Among premenopausal women, there was also a protective and significant effect due to the intake of lettuce and spinach and nonsignificant protective effects for the consumption of apples and herbal tea. Additional studies aimed at evaluating the potential protective effect of particular phytoestrogens on BC risk are needed.*

Introduction

It has been suggested that phytoestrogens, which are hormonelike compounds found in plant foods, might play a protective role in the etiology of breast cancer (BC) (1–3). Evidence from epidemiological studies suggests that the intake of some fruits and vegetables (4), such as soy (5–9), might reduce the risk for BC. Isoflavones are found in soy products (10), whereas other vegetables and fruits contain lignans and flavonoids, respectively (11,12).

Flavonoids and lignans are phytoestrogens that inhibit some types of tumor growth *in vitro* (13) and weakly bind to estrogen receptors (14,15), hence, becoming potentially anticarcinogenic compounds. The consumption of soy milk decreased serum estrogen levels in a Japanese study (16). Urinary levels of the lignans equol and enterolactone were associated with a substantial reduction of BC risk in an epidemiological study performed in Australia (17), and a similar reduction in BC risk was also the case with the urinary levels of total isoflavonoids in a recent study performed in Shanghai (18).

BC mortality is higher in the United States than in Japan (32.7 vs. 11.3 per 100,000) and also much higher than in Mexico (7.1 per 100,000) (19). The consumption of foods rich in phytoestrogens, which are common in the Mexican diet (20) (e.g., onion, lettuce), might play a protective role in the BC incidence.

We evaluated the intake of foods that contain phytoestrogens in relation to BC risk in women from Mexico City.

Material and Methods

From March 1994 to August 1995 a hospital-based case-control study was carried out in Mexico City. The study population was assembled from women seeking care at three large public hospitals of Mexico City (Instituto Nacional de Cancerología, Hospital General, and Hospital Gea González).

A total of 198 recruited cases were women between 21 and 79 years of age. Participants had a histologically confirmed diagnosis of BC, were being seen for the first time at the participating hospitals with no previous treatment for BC, were free from any other type of cancer, and had lived in the Mexico City Metropolitan Area for ≥20 years. Tumor stage was classified using the tumor, nodes, metastasis (TNM) system.

For each case we selected one age-matched control (±3 yr) from other clinical services of the participating hospitals, except gynecology and oncology. These controls had no history of cancer or any other breast disease, and they had lived in the Mexico City Metropolitan Area for ≥20 years.

Dietary, reproductive, and socioeconomic information of the study population was obtained by means of a personal

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structured interview. Every woman was measured and weighed to estimate the body mass index (Quetelet index, kg/m^2).

A modified version of a previously validated semiquantitative food frequency questionnaire that showed good reproducibility, including 95 food items, was used for the study (21). Cases were queried about their dietary habits during the 12 months before onset of symptoms. Controls were queried about their dietary habits during the 12 months before the interview. The daily frequency of consumption according to a predetermined portion size was obtained for each food item. Response options ranged from never to six times per day. The consumption of vegetables and fruits was corrected for seasonal availability.

For the present analysis, we selected individual food items that are frequently consumed in Mexico and have been reported to be sources of phytoestrogens, namely, onion, tea, apple, lettuce, and spinach (12,22,23).

Odds ratios (OR) for the total study population and by menopausal status were estimated by means of logistic regression models and adjusted for age, total energy intake (kcal), number of children, and age at first birth (≥3 children and <20 yr at 1st birth, <3 children and <20 yr at 1st birth, ≥3 children and ≥20 yr at 1st birth, <3 children and ≥20 yr at 1st birth, or nulliparous), lifetime lactation history (accumulated months of breast-feeding), family history of BC (yes/no), and Quetelet index (kg/m^2).

Trends across levels of food consumption were tested by using daily frequency of consumption for foods with two categories of consumption or by fitting the categorical variables as continuous for foods with more than two categories of consumption. All these analyses were performed using Stata software (24).

Results

On average, participating women were 49 years old (range 21–79 yr). Their reproductive characteristics in relation to BC risk are shown in Table 1. The risks for BC were higher among nulliparous women, those with fewer than four births, those with older age at first birth, and those with positive familial BC history. In contrast, breast-feeding after the first delivery and all deliveries was protective. Age at menarche, menopausal status, and obesity (measured by Quetelet index) did not show significant associations with BC risk in this study population.

Table 1. Age-Adjusted ORs for Known Breast Cancer Determinant Factors in the Study Population[a]

Variables	OR	95% CI	*P* Value for Trend
Age at menarche			
≥12 yr	1.0		
<12 yr	0.89	0.51–1.54	
Parity			
≥4	1.0		
1–3	2.31	1.46–3.67	
Nulliparous	2.85	1.52–5.37	0.000
Age at 1st birth			
<20 yr	1.0		
20–24 yr	2.12	1.16–3.84	
≥25 yr	3.00	1.47–6.15	0.002
Breast-feeding at 1st birth[b]			
0 mo	1.0		
1–6 mo	0.89	0.45–1.75	
7–12 mo	0.76	0.39–1.52	
>12 mo	0.60	0.27–1.35	0.20
Breast-feeding all births[b]			
0 mo	1.0		
1–6 mo	1.17	0.44–3.06	
7–12 mo	0.58	0.22–1.58	
>12 mo	0.50	0.22–1.15	0.020
Menopausal status			
No	1.0		
Yes	1.18	0.62–2.24	
Familial breast cancer			
No	1.0		
Yes	2.88	1.29–6.43	
Quetelet index			
≤24 kg/m^2	1.0		
25–29 kg/m^2	0.84	0.52–1.35	0.89
≥30 kg/m^2	1.05	0.60–1.84	

a: Abbreviations are as follows: OR, odds ratio; CI, confidence interval.
b: Nulliparous women were excluded.

Table 2. Effect of Intake of Some Selected Foods on Breast Cancer Risk

Foods	Cases	Controls	Adjusted OR[a] (95% CI)
Vegetables			
Leafy green-yellow,[b] portions/wk			
<2.5	82	63	1.00
2.5–4.0	48	62	0.76 (0.43–1.36)
>4.0	51	65	0.56 (0.30–1.07)
Nonleafy yellow-orange,[c] portions/wk			
<1.5	74	61	1.00
1.5–4.0	52	68	0.58 (0.31–1.08)
>4.0	61	65	0.79 (0.41–1.52)
Fruits			
Citrus,[d,f] portions/wk			
<5.0	83	65	1.00
5.0–11	45	65	0.43 (0.23–0.81)
>11	62	65	0.44 (0.20–0.98)
Noncitrus,[e] portions/wk			
<3.5	69	61	1.00
3.5–8.0	58	69	0.55 (0.28–1.07)
>8.0	61	64	0.80 (0.36–1.83)
Fish, portions/wk			
Never	27	20	1.00
<1	53	55	0.72 (0.29–1.79)
1–1.5	65	62	0.89 (0.34–2.30)
>1.5	53	61	0.67 (0.26–1.72)
Meat (beef), portions/wk			
<1	64	70	1.00
≥1	127	126	1.34 (0.77–2.31)

a: Adjusted by total energy intake (kcal), age at menarche (yr), number of children and age at 1st birth (≥3 children and <20 yr at 1st birth, <3 children and <20 yr at 1st birth, ≥3 children and ≥20 yr at 1st birth, <3 children and ≥20 yr at 1st birth, nulliparous), lifetime lactation (mo of breast-feeding), family history of breast cancer (yes/no), menopausal status (pre/post), and Quetelet index (kg/m^2). Values in parentheses are 95% CIs.
b: Includes lettuce, spinach, cauliflower, and squash flower.
c: Includes beets, carrots, and zucchini.
d: Includes orange, tangerine, pineapple, and strawberries.
e: Includes banana, plums, peach, apple, grapes, pear, papaya, mango, watermelon, cantaloupe, and local fruits (marney, tuna, and zapote).
f: *t*-Test for trend, $p < 0.05$.

The effects of selected food items on BC risk are presented in Table 2; nonsignificant protective effects were observed for the consumption of particular groups of vegetables (leafy green-yellow and nonleafy yellow-orange) and citrus fruits and for all categories of fish intake. In contrast, meat (beef) intake showed a nonsignificant increased risk.

The adjusted OR for the consumption of foods that are sources of phytoestrogens are shown in Table 3. Onion consumption above the median was strongly protective among premenopausal and postmenopausal women (OR = 0.27, 95% confidence interval = 0.16–0.47). In addition, among premenopausal women, there was a significant protective effect for higher intake of lettuce and spinach. Apple and herbal tea showed a nonsignificant protective effect on BC among premenopausal women. Milk intake was not associated with BC risk.

Discussion

Our results show that premenopausal BC risk is inversely related to the intake of onion, lettuce, and spinach. The role of onion intake alone as a protective agent in the etiology of this disease is a recent finding. One other recent case-control study from France investigated the role of diet in BC and reported a reduction of 60–75% in BC with high consumption of onion and garlic (25). Also, our results suggest that the consumption of lettuce, spinach, herbal tea, and apples may protect against premenopausal BC.

These foods are also rich in the flavonoid quercetin. Onions are one of the richest sources of the flavonoid quercetin (26) in the diet (10–44 mg/100 g) (22,23). Daily human intake of quercetin is ~16 mg/day, and it is the highest food antioxidant source in the Western diet (22). Quercetin inhibits the proliferation of human BC cells *in vitro* and delays mammary tumorigenesis (27) *in vivo*. Potential mechanisms for the anticarcinogenic effects of quercetin might include its capacity to bind with type II estrogen receptors (28) and its potent antioxidant activity (22).

To the best of our knowledge, this is the first epidemiological study that has specifically assessed the intake of quercetin-containing foods with respect to BC risk. The epidemiological evidence for the protective effect on BC due to the consumption of vegetables, and particularly green vegetables, is ample and consistent, but only a few studies fo-

Table 3. Effect of Food Phytoestrogen Sources on Breast Cancer Risk According to Menopausal Status

	Premenopausal				Postmenopausal				All
Foods	Cases	Controls	Crude OR[a,b] (95% CI)	Adjusted OR[a,c] (95% CI)	Cases	Controls	Crude OR[a,b] (95% CI)	Adjusted OR[a,c] (95% CI)	Adjusted OR[a,c] (95% CI)
Onion, slice/day									
<1	33	10	1.0	1.0	39	20	1.0	1.0	1.0
≥1	53	81	0.20 (0.09–0.43)	0.18 (0.07–0.42)	66	84	0.38 (0.20–0.72)	0.37 (0.18–0.76)	0.27 (0.16–0.47)
t-Test for trend				0.004				0.01	0.000
Lettuce									
<1 leaf/wk	62	56	1.0	1.0	74	69	1.0	1.0	1.0
≥1 leaf/wk	24	35	0.59 (0.31–1.12)	0.66 (0.31–1.38)	31	35	0.81 (0.45–1.46)	0.73 (0.37–1.45)	0.70 (0.42–1.15)
t-Test for trend				0.04				0.30	0.03
Spinach									
<0.5 cup/wk	68	62	1.0	1.0	73	77	1.0	1.0	1.0
≥0.5 cup/wk	18	28	0.53 (0.26–1.08)	0.44 (0.20–0.98)	32	26	1.30 (0.70–2.38)	1.39 (0.69–2.78)	0.85 (0.51–1.40)
t-Test for trend				0.04				0.91	0.19
Apple									
<1 piece/wk	58	50	1.0	1.0	61	63	1.0	1.0	1.0
≥1 piece/wk	26	40	0.54 (0.28–1.00)	0.57 (0.28–1.15)	44	41	1.10 (0.63–1.91)	0.97 (0.51–1.84)	0.83 (0.54–1.28)
t-Test for trend				0.25				0.64	0.84
Herbal tea									
Never	28	17	1.0	1.0	26	24	1.0	1.0	1.0
<3 cups/wk	31	47	0.41 (0.20–0.87)	0.41 (0.18–0.92)	49	51	1.14 (0.58–2.27)	1.32 (0.62–2.82)	0.75 (0.44–1.30)
≥3 cups/wk	26	27	0.59 (0.26–1.32)	0.68 (0.28–1.62)	28	29	1.12 (0.52–2.40)	1.54 (0.67–3.54)	1.04 (0.57–1.88)
t-Test for trend				0.45				0.31	0.83

a: Values in parentheses are 95% CIs.

b: Adjusted by age.

c: Adjusted by total energy intake (kcal), age at menarche (yr), number of children and age at 1st birth (≥3 children and <20 yr at 1st birth, <3 children and <20 yr at 1st birth, ≥3 children and ≥20 yr at 1st birth, <3 children and ≥20 yr at 1st birth, nulliparous), lifetime lactation (mo of breast-feeding), family history of breast cancer (yes/no), Quetelet index (kg/m^2).

cused on evaluating the intake of individual vegetables. The consumption of lettuce and spinach has been associated with a decreased risk for BC (29,30) compared with other vegetables. Along with other compounds, these leafy-green vegetables contain precursors of lignans and might play a protective role for BC.

Flavonoids are also present in herbal teas, such as chamomile, lime blossom, and mint. To our knowledge, there are no published epidemiological studies in relation to herbal tea consumption and BC, although there is related evidence of a protective effect with green tea consumption in regard to cancer of the stomach, esophagus, and lung (31). One Japanese study reported a better prognosis for premenopausal BC patients in stages I and II (32) who reported a positive history of green tea consumption before the clinical onset of the disease. In Mexico, herbal tea is relatively common (i.e., 78% of control patients in our study), whereas green and black tea consumption is rare.

Green and herbal teas also contain quercetin and kaempferol (26), and green tea reduces the levels of a hormone-binding globulin that is a major determinant of bioavailable estradiol (33). Along with flavonoids, green tea also contains catechins, which are potential anticarcinogenic compounds in animal models (34). Recently, it has been reported that epigallocatechin-3 gallate, which is present in green tea, but not in black tea, binds to the enzyme urokinase, which is usually overexpressed in human cancer. This enzyme is involved in the metastasis and angiogenesis processes (35).

Our findings point to the need for additional studies aimed at evaluating the potential of specific phytoestrogen consumption to protect against the development of BC and also call for the development of composition tables and biological monitoring methods specific to these compounds.

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