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Greater vegetable and fruit intake is associated with a lower risk of breast cancer among Chinese women

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The effect of vegetable and fruit consumption on breast cancer risk is controversial. We examined the association between vegetable and fruit intake and breast cancer risk in a hospital-based case–control study conducted in Guangdong, China. Four hundred and thirty-eight cases 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. Multivariate logistic regression was used to estimate the odds ratios (ORs) and 95% confidence interval (CI) after adjusting for various potential confounders. Total vegetable and fruit intake was found to be inversely associated with breast cancer risk. The ORs of the highest quartile relative to the lowest quartile of total vegetable and fruit intake were 0.28 (95% CI 0.18–0.43) and 0.53 (95% CI 0.34–0.82), respectively. Consumption of individual vegetable and fruit groups such as dark green leafy vegetables, cruciferous vegetables, carrots and tomatoes, banana, watermelon/papaya/cantaloupe were all inversely and significantly related with breast cancer risk. An inverse association was also observed for vitamin A, carotene, vitamin C, vitamin E, and fiber intake. These data indicate that greater intake of vegetables and fruits is associated with a decreased risk of breast cancer among Chinese women residing in Guangdong.

Key words: vegetable; fruit; case–control study; breast cancer risk; China

Vegetables and fruits may play a protective role against the development of cancer, including breast cancer. There are many biologically plausible reasons for this, including the presence in vegetables and fruits the potentially anticarcinogenic substances such as carotenoids, vitamin C, vitamin E, dithiolthiones, isoflavones, and isothiocyanates.

The findings of epidemiological studies of the association between vegetable and fruit intake and breast cancer risk are inconclusive. Some studies have found the protective effects of total vegetable[1–5] or total fruit intake[1,3–6] against breast cancer, whereas others have not found evidence of their protective role.[7–14] A few studies have reported that specific types of vegetables[3,10,11,14–18] or fruits[11,14] are associated with a reduction in breast cancer risk. However, most of these studies have been performed in Western countries.

Chinese populations generally have a diet rich in vegetables and fruits, but low in animal protein.[19] Elucidation of the association between vegetable and fruit consumption and breast cancer would therefore be valuable. To date, only two studies have examined the relationship between vegetable and fruit intake and breast cancer risk in China.[5,11] Both were conducted in Shanghai, which is located in the Eastern part of China. Being a vast country, lifestyle, food availability and dietary habits vary substantially across the different geographic regions of China. For example, the consumption of dark green leafy vegetables is much higher in the South than in other regions.[20] Thus, further studies in different localities will help elicit the role of vegetable and fruit intake in breast cancer risk.

This study was specifically designed to evaluate the relationship between diet and breast cancer risk in Chinese women residing in Guangdong, in particular the role of total and specific vegetable and fruit intake.

Material and methods

Study subjects

Potential case subjects were recruited during June 2007 to August 2008 from 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 with prior history of breast cancer or other cancers. A total of 455 eligible cases were identified and 438 were interviewed, yielding a participation rate of 96%. Twelve patients did not finish the interview because of lengthy questionnaire or fatigue and the remaining five refused to participate.

Control subjects were patients with no history of cancer and 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. 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/degenerate joint disease (27, 6.2%), orthopedics (18, 4.1%), tonsillitis (5, 1.1%), trifacial neuralgia (4, 0.9%) and acute appendicitis (2, 0.5%). They were selected from the departments of Ophthalmology, Plastic and Reconstructive Surgery, Vascular Surgery, Ear-Nose-Throat, and Orthopedics and Microsurgery. In total, 448 controls were identified and 10 (2%) controls invited to take part in the study during their hospital stay refused to be interviewed.

Data collection

Trained interviewers conducted face-to-face interviews using a structured questionnaire to collect information on dietary habits and potential confounding factors. The subjects took, on average,

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1 hr to complete the questionnaire. Relevant medical information, medical diagnosis, histological findings, and so forth were abstracted from the hospital medical records. Written informed consent was obtained from all of the participants before each interview. The Ethical Committee of the Chinese University of Hong Kong approved the study.

Vegetable and fruit intake

Dietary data were collected using an interviewer-administered food frequency questionnaire (FFQ) covering the habitual diet of participants during the preceding 12 months. 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 or banana). For vegetables and animal foods, a Liang (1 Liang = 50 g), a common weight measure familiar to the study subjects, was used to estimate the usual portion size. Food photographs with usual intake portions were used to help participants estimate and record the amounts of food consumed.

The validity and reproducibility of the FFQ had been evaluated in 61 subjects recruited from the community in Guangzhou city. Study participants completed the six 3-day diet records at intervals of 2 months during a 12-month period and two FFQs that were administered 1 year apart. The correlation coefficients comparing the second FFQ and the six 3-day dietary records ranged 0.25–0.65 for nutrients and 0.30–0.68 for food groups. The mean proportion of subjects classified into the same quartile of nutrient and food intake was 36 and 43%, respectively. The correlations between the two FFQs were 0.46–0.71 for nutrients and 0.36–0.66 for food group items (unpublished data).

The Chinese Food Composition Table was used to estimate energy and nutrient intakes.[21] Among the 81 food items, 18 were fresh vegetable and 12 were fruit items. The average daily intakes of all vegetable and fruit items reported by each participant were summed to assess the consumption of total vegetables and fruits. We also created specific vegetable groups, including dark green leafy vegetables (bok choy, lettuce, mustard, spinach, water spinach), cruciferous vegetables (Chinese cabbage, cabbage, broccoli, cauliflower), carrots and tomatoes, allium vegetables (onion, garlic, head of garlic), mushrooms and fungi (fresh and fried mushrooms, white and black fungi), and other vegetables (cucumber, eggplant, wax gourd, loofah, pepper, turnip, potato, sweet potato, taro, fresh corn, bean sprouts), and fruit groups, including banana, citrus fruits (orange, grapefruit, lemon, tangerine, pomelo), apple/pear/peach/plum, grape/litchi/longan, and watermelon/papaya/cantaloupe groups, and other fruits (kiwi fruit, strawberry, pineapple, mango, durian).

Potential confounding variables

A structured questionnaire was used to elicit detailed information on several potential confounding factors, including sociodemographic 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 (including a self-reported history of diabetes, hypertension, or high cholesterol). Body mass index (BMI) was calculated by dividing weight (kg) by height (m^2). Menopausal status was defined as at least 12 months since the last menstrual cycle. Women were considered to be premenopausal if they were currently menstruating, or if they were not menstruating because of a hysterectomy and younger than 50 years old. Women were defined as postmenopausal if they had either undergone a natural menopause, or surgery to remove both ovaries, or if their ovarian function was unknown but they were older than 50 years. Oral contraceptive use was classified as the use of oral contraceptives for more than 3 months. Regular smoking was defined as smoking at least one cigarette per day for more than six consecutive months. Regular drinking was defined as alcohol drinking at least once per week over the past year.

Statistical analysis

SPSS 13.0 was used to conduct the data analysis χ^2 or t tests were used to test differences in sociodemographic and reproductive factors between the case and control subjects. Quartiles for each dietary factor were defined based on the distribution among the controls. Unconditional logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CI) for the association of vegetable and fruit and the selected nutrients and breast cancer risk, using the lowest quartile as the reference. The following variables, selected based on comparison of baseline characteristics between cases and controls, were adjusted for as potential confounding factors: age at menarche, BMI, family history of breast cancer in a first-degree relative, history of benign breast disease, physical activity, and passive smoking from a husband. Total energy intake was included in all models. Tests for trend were performed by entering the categorical variables as continuous parameters in the models. Analyses were also stratified by menopausal status. In this paper, all p values are two-sided and statistical significance was determined at the $p < 0.05$ level.

Results

Infiltrating duct 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 of the breast (3, 0.7%), tubular carcinoma (2, 0.5%) and micropapillary carcinoma (1, 0.2%). The average interval between diagnosis and interview was 7.15 days for case subjects.

Compared to controls, case subjects had an earlier age at menarche and higher BMI (Table I). They were also 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. All of the above variables were considered potential confounders and adjusted for in subsequent analyses. No significant differences were found between the case and control subjects in sociodemographic 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 of menopause, and use of an oral contraceptive.

Among control subjects, the median intake of total vegetables and total fruits were 406 and 194 g/day, respectively. More than half of the total vegetable intake was from the dark green leafy vegetable group. Of the total fruit intake, 43.36% was from the apple/pear/peach/plum group (Table II). Total consumption by the control subjects ranged from a median value of 211 g/day in the lowest quartile to 707 g/day in the highest quartile for vegetables and from 57 to 421g/day for fruits.

A strong inverse association was found between total vegetable and total fruit consumption and breast cancer risk. Compared with the lowest quartile, the highest intake quartile showed a risk reduction of 72% for total vegetable and 47% for total fruit. An inverse association was also observed for dark green leafy vegetables, cruciferous vegetables, carrots and tomatoes, mushrooms and fungi, other vegetables, banana, watermelon/papaya/cantaloupe intake. There was a modest negative association between consumption of citrus fruits, grape/litchi/longan and risk of breast cancer. No significant association between allium vegetables, apple/pear/peach/plum and other fruits intake and breast cancer risk was found (Tables III and IV). The inverse association between total vegetable and fruit consumption and breast cancer risk was observed in both pre- and postmenopausal women. The adjusted ORs of the highest *versus* the lowest quartile were 0.24

TABLE I – DEMOGRAPHIC AND SELECTED RISK FACTORS OF BREAST CANCER CASES AND CONTROLS IN A FEMALE CHINESE POPULATION

	Case (n = 438)	Control (n = 438)	p
Age (yr)			
25–30	13	13	
31–35	40	40	
36–40	75	75	
41–45	84	84	
46–50	79	79	
51–55	61	61	
56–60	48	48	
61–65	26	26	
66–70	12	12	
Age (mean ± SD)	47.04 ± 9.53	47.14 ± 9.58	0.875
Residence (n, %)			
Rural	86 (19.6)	87 (19.9)	0.932
Urban	352 (80.4)	351 (80.1)	
Marital Status (n, %)			
Married	409 (93.4)	413 (94.3)	0.574
Unmarried/Divorced/Widowed	29 (6.6)	25 (5.7)	
Educational Level (n, %)			
Primary School or Below	106 (24.2)	127 (29.0)	0.401
Junior High School	127 (29.0)	116 (26.5)	
Senior High School/Secondary Technical School	109 (24.9)	109 (24.9)	
College or Above	96 (21.9)	86 (19.6)	
Occupation (n, %)			
Administrator/Other White Collar Worker	190 (43.4)	166 (37.9)	0.157
Blue Collar Worker	97 (22.1)	118 (26.9)	
Farmer/Other	151 (34.5)	154 (35.2)	
Income (yuan/mo) (n, %)			
<2,000	157 (35.8)	161 (36.8)	0.751
2,001–5,000	152 (34.7)	149 (34.0)	
5,001–8,000	68 (15.5)	59 (13.5)	
>8,001	61 (13.9)	69 (15.8)	
Body Mass Index, 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 Smoking from a 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, %)			
Never	170 (38.8)	139 (31.7)	0.016
Occasionally	46 (10.5)	35 (8.0)	
≥1 time/wk	222 (50.7)	264 (60.3)	
Age at Menarche, yr (mean ± SD)	14.82 ± 1.88	15.11 ± 1.84	0.019
Nulliparous (n, %)	17 (3.9)	19 (4.3)	0.734
Number of Live Births[1] (mean ± SD)	1.98 ± 1.12	2.03 ± 1.20	0.532
Age at First Live Birth[1] (yr) (mean ± SD)	25.58 ± 3.42	25.15 ± 3.45	0.074
Months of Breast Feeding[2] (mean ± SD)	21.56 ± 17.66	22.13 ± 17.70	0.658
Age at Menopause[3] (yr) (mean ± SD)	49.33 ± 3.96	49.06 ± 3.93	0.579
Menopausal Status (n, %)			
Premenopausal	306 (69.9)	295 (67.4)	0.423
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 an Oral Contraceptive (n, %)	27 (6.2)	21 (4.8)	0.373
Ever used a Nutritional Supplement (n, %)	70 (16.0)	80 (18.3)	0.370
Energy Intake, kcal/d (mean ± SD)	1463.68 ± 430.25	1504.47 ± 429.42	0.160
Total Fat Intake, g/d (mean ± SD)	29.40 ± 16.29	30.63 ± 16.09	0.259

[1]Among women who have had a live birth.–[2]Among women who have breast fed.–[3]Among menopausal women.

(95%CI = 0.14–0.40, trend test $p < 0.001$) for total vegetables and 0.72 (95%CI = 0.43–1.21, trend test $p = 0.079$) for total fruits among premenopausal women, 0.32 (95%CI = 0.14–0.73, trend test $p = 0.004$) for total vegetables and 0.27 (95%CI = 0.12–0.62, trend test $p = 0.001$) for total fruits among postmenopausal women (data not shown).

The ORs associated with intake of selected micronutrients are shown in Table V. Significant inverse associations were found between fiber, vitamin A, vitamin E, vitamin C, and carotene intake and breast cancer risk. Retinol had no significant risk-reducing effect.

We next explored whether the effect of vegetables and fruits on breast cancer risk could be explained by antioxidants and fiber. We added each nutrient in the model one at a time and in combination to examine whether the primary association with vegetable or fruit intake could be explained by nutrient intake. The inverse association between the consumption of vegetables and breast cancer risk became attenuated when the model included fiber, vitamin C, carotene, vitamin E, and vitamin A, or all antioxidants and fiber together. The ORs across quartiles of vegetable intake were 1.00, 0.62, 0.46 and 0.40 (trend test $p = 0.032$) in the analysis, adjusting for fiber and all antioxidants. For fruits, however, adjusting for fiber attenuated the risk estimates, with an OR (95% CI) of 0.95 (0.58–1.58) comparing the fourth quartile with the first quartile (trend test $p = 0.521$) (Table VI).

Because patients with diabetes, hypertension, or high cholesterol might have changed their fruit and vegetable intake following their diagnosis, we conducted analyses excluding women with diabetes, hypertension or high cholesterol and found the results were not materially different. Ductal carcinoma was the most fre-

TABLE II – INTAKE OF VEGETABLES AND FRUITS AMONG CONTROL SUBJECTS (G/D), GUANGDONG, CHINA

	Mean	SD	Median (25th, 75th)	Proportion (%)
Total Vegetable	458.49	251.69	406.22 (290.74, 577.38)	
Dark Green Leafy Vegetables[1]	243.79	163.38	207.73 (131.80, 314.66)	53.17
Cruciferous Vegetables[2]	52.96	58.53	33.46 (12.56, 71.29)	11.55
Carrots and Tomatoes	37.93	47.00	26.78 (11.37, 48.48)	8.27
Allium Vegetables[3]	6.99	12.24	2.33 (0.00, 10.00)	1.52
Mushrooms and Fungi[4]	6.18	10.16	2.50 (0.83,7.14)	1.35
Other Vegetables[5]	110.64	83.74	91.98 (50.36, 140.42)	24.13
Total Fruits	225.78	168.33	193.54 (99.47, 301.91)	
Citrus Fruits[6]	31.79	45.26	13.59 (6.75, 38.57)	14.18
Apple/Pear/Peach/Plum	97.91	92.90	72.86 (31.07, 134.17)	43.36
Banana	40.18	61.77	18.75 (5.93, 53.57)	17.80
Grape/Litchi/Longan	13.88	22.39	5.00 (1.81, 15.36)	6.15
Watermelon/Papaya/Cantaloupe	32.46	48.50	15.86 (5.00, 40.92)	14.38
Other Fruits[7]	9.56	21.43	3.31 (1.04, 9.17)	4.23

[1]Dark green leafy vegetables: bok choy, lettuce, mustard, spinach, water spinach.–[2]Cruciferous vegetables: Chinese cabbage, cabbage, broccoli, cauliflower.–[3]Allium vegetables: onion, garlic, head of garlic.–[4]Mushroom and fungi: fresh and fried mushroom, white and black fungi.–[5]Other vegetables: cucumber, eggplant, wax gourd, loofah, pepper, turnip, potato, sweet potato, taro, fresh corn, bean sprouts.–[6]Citrus fruits: orange, grapefruit, lemon, tangerine, pomelo.–[7]Other fruits: kiwi fruit, strawberry, pineapple, mango, durian.

TABLE III – ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (95% CIS) OF BREAST CANCER ACCORDING TO QUARTILES OF TOTAL AND SPECIFIC VEGETABLE INTAKE

	Q1	Q2	Q3	Q4	*p* trend
Total Vegetables					
No. Cases/Controls	195/109	112/110	76/110	55/109	
Crude OR (95% CI)	1.00	0.57 (0.40–0.81)	0.39 (0.27–0.56)	0.28 (0.19–0.42)	<0.001
Adjusted OR (95% CI)[1]	1.00	0.55 (0.38–0.79)	0.37 (0.25–0.55)	0.28 (0.18–0.43)	<0.001
Dark Green Leafy Vegetables					
No. Cases/Controls	162/109	123/110	85/110	68/109	
Crude OR (95% CI)	1.00	0.75 (0.53–1.07)	0.52 (0.36–0.76)	0.42 (0.28–0.62)	<0.001
Adjusted OR (95% CI)[1]	1.00	0.78 (0.54–1.14)	0.52 (0.35–0.77)	0.41 (0.27–0.62)	<0.001
Cruciferous Vegetables					
No. Cases/Controls	149/109	134/110	84/110	71/109	
Crude OR (95% CI)	1.00	0.89 (0.63–1.27)	0.56 (0.38–0.81)	0.48 (0.32–0.70)	<0.001
Adjusted OR (95% CI)[1]	1.00	0.89 (0.61–1.29)	0.57 (0.38–0.85)	0.49 (0.32–0.74)	<0.001
Carrots and Tomatoes					
No. Cases/Controls	148/109	133/110	82/110	75/109	
Crude OR (95% CI)	1.00	0.89 (0.62–1.27)	0.55 (0.38–0.80)	0.51 (0.34–0.74)	<0.001
Adjusted OR (95% CI)[1]	1.00	0.99 (0.68–1.44)	0.56 (0.37–0.84)	0.58 (0.38–0.88)	0.001
Allium Vegetables					
No. Cases/Controls	136/129	106/90	112/125	84/94	
Crude OR (95% CI)	1.00	1.12 (0.77–1.62)	0.85 (0.60–1.21)	0.85 (0.58–1.24)	0.226
Adjusted OR (95% CI)[1]	1.00	1.24 (0.84–1.84)	0.81 (0.56–1.18)	0.92 (0.61–1.38)	0.316
Mushrooms and Fungi					
No. Cases/Controls	132/116	132/117	84/96	90/109	
Crude OR (95% CI)	1.00	0.99 (0.70–1.41)	0.77 (0.52–1.13)	0.73 (0.50–1.06)	0.047
Adjusted OR (95% CI)[1]	1.00	0.95 (0.66–1.38)	0.69 (0.45–1.04)	0.65 (0.43–0.98)	0.018
Other Vegetables					
No. Cases/Controls	167/110	134/109	74/110	63/109	
Crude OR (95% CI)	1.00	0.81 (0.57–1.15)	0.44 (0.30–0.65)	0.38 (0.26–0.56)	<0.001
Adjusted OR (95% CI)[1]	1.00	0.79 (0.54–1.14)	0.44 (0.30–0.67)	0.38 (0.24–0.58)	<0.001

[1]Odds ratio adjusted for age at menarche, BMI, history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking and total energy intake.

quent histologic type (415, 94.7%) and restricting the analysis to these cases yielded very similar results (data not shown).

All case subjects in the present study were inpatients who had to undergo surgery for suspected breast cancer. A total of 76 inpatients were interviewed before the operation and they were treated as cases when the interviews were conducted. Fifty-nine were identified as having primary breast cancer after the diagnostic workup. Consumption of total vegetables and total fruits between the 59 cases before the operation and 379 confirmed cases was not significantly different (mean of 361.11 *vs.* 353.28 g/day for total vegetables; 180.02 *vs.* 187.64 g/day for total fruits).

Discussion

This hospital-based case–control study examined the association between vegetable and fruit intake and breast cancer risk among Guangdong Chinese women. Our results suggest an inverse association between vegetable and fruit intake and breast cancer risk. Among the micronutrients examined, dietary vitamin C, vitamin E, vitamin A, fiber, and carotene were associated with reduced breast cancer risk.

The association between vegetable and fruit consumption and breast cancer risk has been examined in many epidemiological studies.[1–16,18] One case–control study conducted in China reported a 40% reduction in risk in the highest quartile of consumption of vegetables and 66% reduction with a high intake of fruits.[5] Other case–control studies, but not all, have found similar results.[1–4,6] Consistent with these studies, we observed that a high intake of vegetables and fruits was associated with a reduced risk of breast cancer. In contrast, the Shanghai Women Breast Cancer Study reported no association between total fruit and vegetable intake and reduced breast cancer risk.[11] A pooled analysis of eight pro-

TABLE IV – ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (95% CIS) OF BREAST CANCER ACCORDING TO QUARTILES OF TOTAL AND SPECIFIC FRUIT INTAKE

	Q1	Q2	Q3	Q4	*p* trend
Total Fruits					
No. Cases/Controls	132/109	140/110	94/110	72/109	
Crude OR (95% CI)	1.00	1.05 (0.74–1.50)	0.71 (0.48–1.03)	0.54 (0.37–0.81)	0.001
Adjusted OR (95% CI)[1]	1.00	1.09 (0.75–1.59)	0.68 (0.45–1.01)	0.53 (0.34–0.82)	0.001
Citrus Fruits					
No. Cases/Controls	177/155	58/64	102/103	101/116	
Crude OR (95% CI)	1.00	0.79 (0.52–1.20)	0.87 (0.61–1.23)	0.76 (0.54–1.07)	0.141
Adjusted OR (95% CI)[1]	1.00	0.83 (0.54–1.29)	0.98 (0.68–1.42)	0.73 (0.50–1.06)	0.173
Apple/Pear/Peach/Plum					
No. Cases/Controls	128/109	119/110	95/110	96/109	
Crude OR (95% CI)	1.00	0.92 (0.64–1.33)	0.74 (0.51–1.07)	0.75 (0.52–1.09)	0.071
Adjusted OR (95% CI)[1]	1.00	0.89 (0.61–1.31)	0.72 (0.48–1.07)	0.80 (0.53–1.19)	0.161
Banana					
No. Cases/Controls	137/109	113/111	111/110	77/108	
Crude OR (95% CI)	1.00	0.81 (0.56–1.16)	0.80 (0.56–1.16)	0.57 (0.39–0.83)	0.007
Adjusted OR (95% CI)[1]	1.00	0.82 (0.56–1.21)	0.84 (0.57–1.23)	0.57 (0.37–0.86)	0.015
Grape/Litchi/Longan					
No. Cases/Controls	136/109	111/111	105/109	86/109	
Crude OR (95% CI)	1.00	0.80 (0.56–1.15)	0.77 (0.53–1.12)	0.63 (0.43–0.92)	0.020
Adjusted OR (95% CI)[1]	1.00	0.77 (0.52–1.13)	0.81 (0.55–1.19)	0.66 (0.44–0.99)	0.067
Watermelon/Papaya/Cantaloupe					
No. Cases/Controls	136/111	125/108	95/110	82/109	
Crude OR (95% CI)	1.00	0.94 (0.66–1.35)	0.71 (0.49–1.02)	0.61 (0.42–0.90)	0.004
Adjusted OR (95% CI)[1]	1.00	1.01 (0.69–1.48)	0.74 (0.50–1.09)	0.62 (0.41–0.94)	0.009
Other Fruits					
No. Cases/Controls	116/109	109/110	119/110	94/109	
Crude OR (95% CI)	1.00	0.93 (0.64–1.35)	1.02 (0.70–1.47)	0.81 (0.55–1.18)	0.393
Adjusted OR (95% CI)[1]	1.00	0.85 (0.58–1.26)	1.03 (0.70–1.52)	0.80 (0.54–1.21)	0.493

[1]Odds ratio adjusted for age at menarche, BMI, history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking and total energy intake.

TABLE V – ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (95% CIS) OF BREAST CANCER ACCORDING TO QUARTILES OF SELECTED NUTRIENTS INTAKE

	Q1	Q2	Q3	Q4	*P* trend
Vitamin A					
No. Cases/Controls	174/109	120/110	82/110	62/109	
Crude OR (95% CI)	1.00	0.68 (0.48–0.97)	0.47 (0.32–0.68)	0.36 (0.24–0.53)	<0.001
Adjusted OR (95% CI)[1]	1.00	0.64 (0.44–0.93)	0.42 (0.28–0.63)	0.31 (0.20–0.48)	<0.001
Retinol					
No. Cases/Controls	120/110	105/109	110/109	103/110	
Crude OR (95% CI)	1.00	0.88 (0.61–1.28)	0.92 (0.64–1.34)	0.86 (0.59–1.25)	0.863
Adjusted OR (95% CI)[1]	1.00	0.76 (0.51–1.14)	0.85 (0.57–1.27)	0.76 (0.50–1.15)	0.511
Carotene					
No. Cases/Controls	182/109	112/110	86/110	58/109	
Crude OR (95% CI)	1.00	0.61 (0.43–0.87)	0.47 (0.32–0.68)	0.32 (0.21–0.47)	<0.001
Adjusted OR (95% CI)[1]	1.00	0.59 (0.41–0.86)	0.46 (0.31–0.69)	0.30 (0.19–0.46)	<0.001
Vitamin C					
No. Cases/Controls	187/109	107/110	83/110	61/109	
Crude OR (95% CI)	1.00	0.57 (0.40–0.81)	0.44 (0.30–0.64)	0.33 (0.22–0.48)	<0.001
Adjusted OR (95% CI)[1]	1.00	0.56 (0.38–0.82)	0.43 (0.29–0.64)	0.30 (0.19–0.46)	<0.001
Vitamin E					
No. Cases/Controls	167/109	108/110	100/110	63/109	
Crude OR (95% CI)	1.00	0.64 (0.45–0.92)	0.59 (0.41–0.85)	0.38 (0.26–0.56)	<0.001
Adjusted OR (95% CI)[1]	1.00	0.62 (0.42–0.92)	0.50 (0.33–0.76)	0.31 (0.19–0.50)	<0.001
Fiber					
No. Cases/Controls	175/110	115/108	86/111	62/109	
Crude OR (95% CI)	1.00	0.67 (0.47–0.95)	0.49 (0.34–0.70)	0.36 (0.24–0.53)	<0.001
Adjusted OR (95% CI)[1]	1.00	0.64 (0.44–0.94)	0.42 (0.28–0.64)	0.26 (0.16–0.44)	<0.001

[1]Odds ratio adjusted for age at menarche, BMI, history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking and total energy intake.

spective studies did not find any protection from vegetables or fruit.[22] In a meta-analysis, 15 case–control studies and 10 cohort studies were analyzed separately. From the analysis of case–control studies it was concluded that the relative risk of breast cancer was 14% lower for each additional 100 g/day intake of vegetables and 8% lower for each additional 100 g/day intake of fruits. However, the analysis of cohort studies did not show any relationship between vegetable or fruit intake and breast cancer risk.[23]

There are several possible explanations for these inconsistent results. The level and range of vegetable and fruit intake differ among different populations. The median vegetable intake in our population was 406 g/day, which was greater than 132 g/day in Korean women,[14] 158 g/day in the Sweden Diet and Cancer cohort,[12] 164 g/day in the Denmark Diet Cancer and Health cohort,[24] and 234 g/day in the Shanghai Women Breast Cancer Study.[11] There might also be a lack of variation in vegetable and

TABLE VI – ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (95% CIS) OF BREAST CANCER ACCORDING TO QUARTILES INTAKE OF TOTAL VEGETABLES AND FRUITS, ADJUSTING FOR OTHER RELATED NUTRIENTS

	Q1	Q2	Q3	Q4	*P* trend
Total Vegetables					
No. Cases/Controls	132/109	140/110	94/110	72/109	
OR (95% CI)[1]	1.00	0.55 (0.38–0.79)	0.37 (0.25–0.55)	0.28 (0.18–0.43)	<0.001
OR (95% CI)[2]	1.00	0.59 (0.37–0.96)	0.40 (0.21–0.73)	0.31 (0.14–0.68)	0.002
OR (95% CI)[3]	1.00	0.57 (0.38–0.85)	0.43 (0.26–0.68)	0.37 (0.21–0.65)	<0.001
OR (95% CI)[4]	1.00	0.56 (0.35–0.90)	0.37 (0.21–0.68)	0.30 (0.14–0.64)	0.001
OR (95% CI)[5]	1.00	0.62 (0.37–1.05)	0.46 (0.23–0.92)	0.40 (0.17–0.98)	0.032
Total Fruits					
No. cases/controls	132/109	140/110	94/110	72/109	
OR (95% CI)[1]	1.00	1.09 (0.75–1.59)	0.68 (0.45–1.01)	0.53 (0.34–0.82)	0.001
OR (95% CI)[2]	1.00	1.20 (0.82–1.77)	0.76 (0.50–1.15)	0.72 (0.46–1.14)	0.048
OR (95% CI)[3]	1.00	1.31 (0.88–1.95)	0.92 (0.59–1.43)	0.95 (0.58–1.58)	0.521
OR (95% CI)[4]	1.00	1.20 (0.81–1.76)	0.74 (0.49–1.11)	0.67 (0.43–1.05)	0.019
OR (95% CI)[5]	1.00	1.33 (0.88–2.00)	0.86 (0.54–1.35)	0.91 (0.54–1.53)	0.356

[1]Odds ratio adjusted for age at menarche, BMI, history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking and total energy intake.–[2]Adjusted for 1 plus vitamin C.–[3]Adjusted for 1 plus fiber.–[4]Adjusted for 1 plus carotene.–[5]Adjusted for 1 plus vitamin C, fiber, carotene, vitamin A and vitamin E.

fruit intake in some populations and the intake is relatively homogeneous in Western society. In the current study, the median intake in the highest quartile group among control subjects was threefold that in the lowest quartile group for vegetables (707 *vs.* 211 g) and sevenfold for fruits (421 *vs.* 57 g). These variations were greater than that in the European Prospective Investigation Into Cancer and Nutrition study which did not observe an association of breast cancer risk with consumption of vegetables or fruits.[13] The use of an FFQ with comprehensive fruit and vegetable items ($n = 30$) also contributed to the ability to reflect the variations among study subjects. Moreover, differences in study designs may also partially explain the discrepancy in findings among different studies. Prospective studies generally provide weaker association between vegetable and fruit consumption and breast cancer risk than case–control studies.[23] Case–control studies are vulnerable to selection and recall bias possibly resulting in a spurious inverse association. On the other hand, dietary changes over time can lead to misclassification of long-time exposures in cohort studies resulting in an attenuation of the association between vegetable and fruit consumption and cancer risk.

The mechanisms through which vegetables and fruits protect against breast cancer are likely to be numerous. The postulated beneficial constituents in fruits and vegetables include antioxidant vitamins, fiber and folate. Vitamin C, vitamin E, and the carotenoids act as antioxidants, which protect DNA from oxidative damage.[25] The function of vitamin C may also be related to its action on the immune system.[25] Vitamin E has been found to inhibit tumors and reduce cell proliferation in animal models.[25] In addition, vitamin C, vitamin E and the carotenoids have other chemopreventive actions.[25] Dietary fiber may affect breast cancer risk by decreasing reabsorption in the gut of estrogen excreted in the biliary system.[26,27] The results of our study regarding the association between nutrients and breast cancer risk support this hypothesis. We found inverse associations across quartiles of intake of vitamin C, vitamin E, vitamin A, fiber, and carotene. These findings are consistent with those of two studies conducted in China[11,28] and other studies conducted elsewhere.[1,4,29–31] However, some studies have not found a protective effect of nutrients on breast cancer.[32,33] The present study showed that the inverse association between vegetable intake and breast cancer risk persisted after adjusting for vitamin C, vitamin E, vitamin A, carotene and fiber. It seems that, whereas each of the examined components may affect risk, there probably remains some unexplained protection attributable to total consumption of vegetables. Fiber intake may explain in part the protective effect of fruit intake. Other unmeasured factors in these foods may also affect risk.

Reports from Sweden[10] and the United States (premenopausal women)[15] suggest an association between a reduction in breast cancer risk and cruciferous vegetable intake. Some studies show that green leafy and yellow vegetables, tomato, pepper, spinach, white turnip, and mushroom are associated with a lower incidence of breast cancer.[3,11,14,16–18] Our study also found that consumption of cruciferous vegetables, dark green leafy vegetables, carrots and tomatoes, and mushroom and fungi were inversely related with breast cancer risk. Like other vegetables, cruciferous vegetables contain a number of nutrients and phytochemicals with cancer chemopreventive properties, including folate, fiber, carotenoids, and chlorophyll. Moreover, cruciferous vegetables are an especially rich source of glucosinolates, which may be important anticarcinogens.[34] Dark green leafy vegetables and carrots and tomatoes contain high level of carotenes, folate, vitamin C, vitamin E, lycopene and numerous other beneficial phytochemicals. Lycopene has been reported to inhibit the proliferation of mammary human cancer cells[35] and suppress insulin-like growth factor.[36] Mushrooms are considered excellent sources of nutrition, and in many species, a number of bioactive compounds have been identified, such as polysaccharides, which have antitumor and immunomodulating properties.[37,38]

A few studies have examined the association between individual fruit intake and the risk of breast cancer. Intake of bananas, citrus fruits, peaches and grapes has been associated with lower risk of breast cancer.[11,14] Similar to these studies, we observed an inverse association between breast cancer risk and high consumption of banana, grape/litchi/longan and watermelon/papaya/cantaloupe. Bananas are known for their high content of anticarcinogenic substances, including vitamin A, vitamin C and dietary fiber. Grapes are rich in flavonoids such as catechins, resveratrol and anthocyanin, which may act through antioxidant, pro-oxidant, antiestrogenic and cell signaling pathways, modulation or mitochondrial toxicity to inhibit breast carcinogenesis.[39] Watermelon and papaya contain antioxidants such as lycopene, carotene and β-cryptoxanthin which exert an antioxidant effect via scavenging free radicals.[40]

Our study has several limitations. Selection bias is a potential limitation in hospital-based case–control studies. The use of hospital-based controls with conditions potentially related to diet is a major concern though 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 this potential bias, consumption of nutrients and food groups by the hospital-based controls was compared with that by participants in the validation of the FFQ. The results showed that there was no significant difference in 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 sociodemographic factors between the two groups indicated that selection bias should not be a serious problem.[41,42]

Recall bias is another limitation. Patients with cancer may recall dietary practices in different ways than do controls, or change their dietary behavior after cancer diagnosis. To minimize this bias, we tried to interview patients as soon as diagnosis was made. The average interval between diagnosis and interview was 7.15 days for case subjects. In addition, in our study, great effort was taken to interview cases before their surgery. Consumption of vegetables and fruits was not different for the case subjects interviewed pre and postoperatively. We also provided food photographs with usual intake portions to assist participants with quantification of intake. Moreover, the comparability of the recall between case and control subjects was improved by interviewing all of the subjects in a hospital setting.[43]

To minimize interviewer bias, we introduced 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.

Random measurement error in the estimation of usual intake is also of concern. However, this misclassification is most likely nondifferential regarding case–control status, which would tend to attenuate any association between dietary intake and breast cancer risk.[44] Therefore, the ~47–72% reduction in risk associated with a high intake of vegetables and fruits observed in our study may be a conservative estimate.

In conclusion, our study found an inverse association between the consumption of vegetable, fruit and antioxidant nutrients and breast cancer risk and the findings add to the existing evidence on the protective role of vegetable and fruit in breast cancer.

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