Original Article

Dietary carotenoids and risk of breast cancer in Chinese women

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There has been considerable interest in the role of carotenoids in the chemoprevention of cancer. However, the protective effect of carotenoids on breast cancer has been inconclusive. To investigate whether intake of lycopene, α-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin is inversely associated with breast cancer risk, a case-control study was conducted in China during 2004-2005. The cases were 122 female patients aged 24-87 years with histopathologically confirmed breast cancer. 632 healthy women age-matched were randomly recruited from outpatient clinics. Habitual dietary intake and lifestyle were collected by face-to-face interview using a validated and reliable food frequency questionnaire. The USDA nutrient composition database was used to calculate intake of the specific carotenoids. Unconditional logistic regression analyses were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), accounting for age, locality, education, body mass index, smoking, passive smoking, physical activity, number of children breastfed, menopausal status, oral contraceptive use, biopsy-confirmed benign breast diseases, family history of breast cancer, and total energy intake. Compared with the highest versus lowest quartile of intake, the adjusted ORs were 0.26 (95% CI 0.14-0.46) for lycopene, 0.38 (95% CI 0.21-0.71) for β-carotene, 0.43 (95% CI 0.23-0.82) for β-cryptoxanthin, and 0.37 (95% CI 0.20-0.68) for total carotenoids, with statistically significant tests for trend. There was no association with breast cancer for α-carotene and lutein/zeaxanthin. It is concluded that higher intake of lycopene, β-carotene and β-cryptoxanthin is associated to a lower risk of breast cancer among Chinese women. More research to examine the relationship between carotenoids and breast cancer risk is warranted.

Key Words: breast cancer, case-control study, dietary carotenoids, risk factor, Chinese women

Introduction

Breast cancer is the most common cancer among women in the world and it is ranked the second overall when both sexes are considered together.[1] The rates of breast cancer are still increasing in both developed and developing countries. The geographic differences of incidence rates in breast cancer exist. The rates in China is 18.7 per 100,000 women, which is 4 to 5 folds lower than the rates typically found in developed countries,[2] however, it has increased 50.5 % from 1972 to 1994 in southeast China.[3] Because of its increasing incidence, breast cancer is a significant burden for women worldwide.

There has been considerable interest in the protective role of carotenoids against breast cancer in experimental studies past two decades. Many epidemiologic evidence have showed inverse associations between fruit and vegetable consumption and breast cancer risk,[4,5] suggesting the potential importance of carotenoids contained in these foods. However, not all studies found associations.[6,7] Studies examining relations between specific carotenoids and breast cancer risk have increased because database for individual carotenoid only has been available recently.[8] Some studies suggest that higher intake of dietary carotenoids reduce the risk of breast cancer,[9-11] but others could not find inverse association.[12,13] Therefore, dietary carotenoids in relation to breast cancer risk remain unclear.

In view of the increasing incidence of breast cancer and the possible protective effect of dietary carotenoids on this malignancy, a case-control study was conducted in southeast China to examine the association between the risk of breast cancer and intake of dietary carotenoids, namely lycopene, α-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin, which are predominant in the human diet.

Materials and methods

A hospital-based case-control study was conducted during 2004-2005 in Hangzhou, a capital city of Zhejiang Province, China. All participants were Chinese women resided in Zhejiang Province between the ages of 24 and 87 years. Cased were identified from medical records in two teaching hospitals, School of Medicine, Zhejiang University.

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The hospitals are public hospitals with 500-2000 beds and receive patients from all over the province. A total of 122 incidence cases were recruited for the study. These patients were diagnosed with invasive ductal carcinomas or in situ carcinoma of the breast confirmed by histopathology after surgery. The patients were excluded if breast cancer was neither the primary nor final diagnosis. All relevant hospital and laboratory pathology reports were daily reviewed to ensure the completion of recruitment. The proportion of lost or non-responding patients among the cases was 1.6%. During the same period of data collection, 632 healthy women were selected consecutively in the participating hospitals as controls to match each case's age within 5-year age group using a daily update of the list of cases. Each control was recruited as the first in the matched age group to attend the outpatient breast clinics and who consented to participate. The proportion of participation by selected controls was 99.1%. Potential control women were excluded if they had a previous diagnosis of either breast cancer or another malignant disease. The project received ethics clearance from both the Human Research Ethics Committee of The University of Western Australia and the Chinese hospital authorities.

Subjects were briefed regarding the aims of the study, confidentiality and anonymity issues. An appointment for interview was made after obtaining their consent via an initial contact. A face-to-face interview was conducted in the hospital setting using a structured questionnaire and usually took 30-40 minutes. The cases were interviewed in breast surgery wards and most of them (91.8%) were recruited within 3 months after diagnosis, while the controls were interviewed in the outpatient clinic of the same hospital. A valid and reliable questionnaire was used to collect the required information. The structured questionnaire consists of three components: (a) demographic and lifestyle characteristics, e.g. resident area, education, occupation, physical activity; (b) food consumption assessed by a food frequency questionnaire (FFQ); and (c) factors relevant to hormonal status and others, including menstrual cycles, marriage and menopausal status, reproductive and lactation history, family history of breast cancer, benign proliferation breast disease, contraceptive history, and oral contraceptive usage. The FFQ was modified from our previous one used for studying cancers in Hangzhou.[14] The questionnaire was prepared in English and translated into Chinese and checked (back translated) by professional Chinese translators. The reproducibility of the food frequency questionnaire has been assessed in a test-retest study, and intraclass correlation coefficients for the intake of total energy, alcohol, soybean, vegetables and fruits were 0.84, 0.88, 0.78, 0.75 and 0.88 respectively.[15]

The FFQ composed of 87 foods, 8 beverages, and 5 vitamin supplements. These foods included in the FFQ were the most frequently consumed foods in a pretrial study of Zhejiang residents.[15] The food frequency variables were categorized into never or hardly ever, once a month, 2-3 times a month, once a week, 2-3 times a week, 4-6 times a week, once a day, twice a day, and 3 times or more a day. To increase the accuracy of estimation, standard containers (small 200 ml, medium 400 ml, and large 600 ml bowls, and a 400 ml cup) were displayed during the interview. The quantity of each food consumed per meal was estimated in terms of a standard Chinese measure, the *liang* (equivalent to 50 grams). For seasonal vegetables and fruits, only the frequencies consumed during the available period were sought. For cooking oil, salt, and sugar, the total household consumption was divided by the number of individuals sharing the meals. For some sweets and commercial items, the respondent was asked to report the number of units of food consumed on each occasion. Information on usual methods of food preparation or cooking such as steaming, boiling, stir-frying, and deep-frying was also sought. Food consumption measured in the participants was based on their habitual diet and a "reference" recall period was set as one year prior to diagnosis (cases) or interview (controls). If there was any change in their habits recently, only information on the habits before the change was used in data analysis. After interview, an anthropometric measurement was requested of all participants.

All data were reviewed for completeness at the end of each interview. Data were coded and analyzed using the SPSS version 11.0. The frequency and quantity variables derived from the FFQ were converted into daily food consumption, adjustments for the edible portions of foods, cooking methods used, seasonal factors, and market availability.[16,17] Total energy intake was obtained using Chinese Food Composition Tables.[16] Intake (in μg) of lycopene, α-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin were calculated based on daily food consumption derived from the FFQ using a USDA nutrient database, which had been developed specifically for Chinese immigrants in America.[8] We created a variable for total carotenoid intake (referred to as total carotenoid score), which was designated as mean quartile score of each specific carotenoid. We chose this method, rather than using intake in micrograms, because each carotenoid is consumed in varying quantities and it is untenable that any biochemical actions of diverse carotenoids would be identical on a gram basis in a biologically complex system such as a cell. Some category variables were defined as: a total of 20 packs of cigarettes or more in a lifetime for tobacco smoking; regularly inhaled at home or workplace for passive smoking; a total of 26 drinks or more per year for alcohol consumption (beer 285 ml, wine 100 ml, or liquor 30 ml equivalent to one drink); and any recreational physical activity one hour or more per week during the past year for physical activity. Soy intake was assigned as total isoflavones intake based on soy foods consumed.

Demographic characteristics and potential risk factors were compared between cases and controls using a *t*-test for continuous variables and Chi-square test for categorical variables. The mean daily intakes of specific carotenoids were tabulated separately for cases and controls. To facilitate analysis, the quantitative variables of specific carotenoids and total corotenoid score were divided into quartiles based on the corresponding empirical distribution of controls, and the lowest level was defined as reference group. Odds ratios (ORs) and associated 95% confidence intervals (CIs) and *p*-values associated with the quartile daily intake of specific carotenoids and total corotenoid score were estimated using unconditional logistic regression analyses. Univariate analysis was undertaken to screen potential explanatory variables for subsequent multivariate analysis. We firstly evaluated the risk of breast cancer associated with dietary carotenoids adjusting for age, locality, and education. We further assessed breast cancer risk by adjusting for body mass index (BMI, calculated as current weight in kilograms divided by square of height in meters), tobacco smoking, passive smoking, physical activity, number of children breastfed, menopausal status, oral contraceptive use, biopsy-confirmed benign breast diseases, family history of breast cancer, and total energy intake. These variables were included in the models because they were either emerged as significant risk factors for breast cancer in previous studies[9-11] or potential confounders based on the univariate analysis. Each quantitative variable of specific carotenoids and total carotenoid score was subjected to a linear trend test in terms of breast cancer risk. Finally, model adequacy was assessed using the Hosmer and Lemeshow goodness-of-fit statistic.

Results

Selected characteristics of cases and controls are shown in Table 1. There were no differences between cases and controls in terms of age at interview, menarche at age before 13 years, menopause status, hormone replacement therapy, family history of breast cancer in the first degree relatives, tobacco smoking, BMI, physical activity, intake of soy, vegetables and fruits. Compared to the controls, the patients with breast cancer tended to have higher education, more resident in urban area, higher energy intake, more passive smoking and biopsy-confirmed benign breast diseases, but less of them were oral contraceptive use and children breastfed.

Table 2 summarizes the mean daily intake of carotenoids in subjects with and without breast cancer. Com-

Table 1. Selected characteristics of subjects with and without breast cancer

	Case subjects (n=122)	Control subjects (n=632)	*p*-value
Age at interview (years)	47.7 ± 10.1	48.1 ± 9.8	≥0.05
Locality of resident			<0.001
Urban	93 (76.2)	361 (57.1)	
Rural	29 (23.8)	271 (42.9)	
Education			<0.05
No formal education	10 (8.2)	83 (13.1)	
Primary	24 (19.7)	181 (28.6)	
Secondary	60 (49.2)	249 (39.4)	
Tertiary	28 (22.9)	119 (18.9)	
Age at menarche <13 years	3 (2.5)	7 (1.1)	≥0.05
Postmenopause	39 (32.0)	215 (34.0)	≥0.05
Number of children breastfed	1.31 ± 1.1	1.63 ± 1.2	<0.01
Biopsy-confirmed benign breast diseases	22 (17.2)	40 (6.3)	<0.001
Oral contraceptive users	29 (23.8)	212 (33.5)	<0.05
Hormone replacement therapy	6 (4.9)	33 (5.2)	≥0.05
Family history of breast cancer	2 (1.6)	13 (2.1)	≥0.05
Tobacco smoking	1 (0.8)	6 (0.9)	≥0.05
Passive smoking	84 (68.9)	336 (53.2)	<0.01
Physical activity	41 (33.6)	253 (40.0)	≥0.05
Body mass index (kg/m²)	22.4 ± 2.8	22.3 ± 3.0	≥0.05
Energy intake (g/day)	2143.6 ± 671.9	1994.2 ± 492.4	<0.01
Vegetables intake (g/day)	375.1 ± 195.4	389.3 ± 193.1	≥0.05
Fruits intake (g/day)	322.4 ± 244.9	359.6 ± 224.1	≥0.05
Soy intake (mg isoflavones/1000 kcal)	9.7 ± 7.2	10.3 ± 7.0	≥0.05

Values expressed as mean ± SD or number (percent). *p*-value two-sided; *t*-test for continuous variables and Chi-Square test for categorical variables in difference between case and control subjects.

Table 2. Mean daily intake of carotenoids in subjects with and without breast cancer

	Case subjects (n=122)	Control subjects (n=632)	*p*-value
Lycopene (μg)	7117.2 ± 6727.7	9251.3 ± 6425.1	<0.01
α-carotene (μg)	281.5 ± 387.3	226.7 ± 282.4	≥0.05
β-carotene (μg)	3378.5 ± 2129.1	3803.5 ± 2085.4	<0.05
β-cryptoxanthin (μg)	465.7 ± 392.3	509.0 ± 375.8	≥0.05
Lutein/zeaxanthin (μg)	1457.5 ± 998.1	1509.0 ± 1084.8	≥0.05

Values expressed as mean ± SD. *p*-value two-sided; *t*-test for the difference between case and control subjects.

Table 3. Adjusted ORs and 95% CIs of breast cancer for quartile daily intake of carotenoids

	No. of subjects (case/control)	OR (95% CI)†	OR (95% CI)‡
Lycopene (μg)			
<4243.1	59/158	1.0 (referent)	1.0 (referent)
4243.1-8522.8	29/159	0.44 (0.26-0.74)	0.42 (0.25-0.73)
8522.9-12670.9	12/156	0.17 (0.09-0.33)	0.17 (0.08-0.34)
≥12670.1	22/159	0.30 (0.17-0.53)	0.26 (0.14-0.46)
p for linear trend§		*<0.001*	*<0.001*
α-carotene (μg)			
<88.2	26/158	1.0 (referent)	1.0 (referent)
88.2-155.8	33/158	1.11 (0.62-1.96)	1.21 (0.67-2.20)
155.9-266.2	29/158	0.88 (0.49-1.60)	0.98 (0.53-1.82)
≥266.3	34/158	0.90 (0.56-1.77)	0.90 (0.49-1.67)
p for linear trend§		*0.25*	*0.62*
β-carotene (μg)			
<2415.8	46/158	1.0 (referent)	1.0 (referent)
2415.9-3491.5	34/158	0.71 (0.43-1.17)	0.63 (0.37-1.09)
3419.6-4686.9	21/158	0.42 (0.24-0.75)	0.36 (0.20-0.66)
≥4687.0	21/158	0.48 (0.27-0.85)	0.38 (0.21-0.71)
p for linear trend§		*0.008*	*0.01*
β-cryptoxanthin (μg)			
<232.4	36/158	1.0 (referent)	1.0 (referent)
232.5-422.9	34/158	0.81 (0.47-1.38)	0.80 (0.46-1.41)
423.0-674.9	31/158	0.72 (0.42-1.25)	0.73 (0.41-1.30)
≥675.0	21/158	0.46 (0.25-0.85)	0.43 (0.23-0.82)
p for linear trend§		*0.08*	*0.03*
Lutein/zeaxanthin (μg)			
<826.0	33/158	1.0 (referent)	1.0 (referent)
826.1-1252.2	32/158	0.87 (0.50-1.50)	0.81 (0.46-1.45)
1252.3-1831.0	26/158	0.69 (0.39-1.22)	0.62 (0.34-1.13)
≥1831.1	31/158	0.88 (0.51-1.52)	0.72 (0.40-1.31)
p for linear trend§		*0.69*	*0.30*
Total carotenoid score			
<2.0	39/162	1.0 (referent)	1.0 (referent)
2.0-2.5	37/149	0.94 (0.57-1.58)	0.73 (0.42-1.26)
2.6-3.0	21/150	0.48 (0.27-0.87)	0.44 (0.23-0.82)
≥3.1	25/171	0.51 (0.29-0.89)	0.37 (0.20-0.68)
p for linear trend§		*0.001*	*<0.001*

†Estimates from separate unconditional logistic regression models included terms for age at interview (years, continuous), locality (urban, rural), and education (none, primary, secondary, tertiary). ‡Further adjusted for BMI (continuous), tobacco smoking (no, yes), passive smoking (no, yes), physical activity (no, yes), number of children breastfed (continuous), menopausal status (no, yes), oral contraceptive use (never, ever), biopsy-confirmed benign breast diseases (no, yes), family history of breast cancer (no, yes), and total energy intake (kilocalories, continuous). §Two-sided test for trend across the quantitative variable.

pared with the controls, the mean daily intake of lycopene and β-carotene were significantly lower in the cases. There was no statistical difference between cases and controls in terms of the mean daily intake of α-carotene, β-cryptoxanthin, and lutein/zeaxanthin.

Table 3 presents the adjusted odds ratios (OR) and 95% confidence intervals (CI) of breast cancer according to quartile daily intake of specific carotenoids and total carotenoid score from multivariate logistic regression analysis. The risk of breast cancer tended to decline with increasing intake of dietary carotenoids. Compared with the highest versus lowest quartile of intake, adjusted ORs were 0.26 (95% CI 0.14-0.46) for lycopene, 0.38 (95% CI 0.21-0.71) for β-carotene, 0.43 (95% CI 0.23-0.82) for β-cryptoxanthin, and 0.37 (95% CI 0.20-0.68) for total carotenoid. The corresponding linear trends were also statistically significant. There is no relationship between intake of α-carotene and lutein/zeaxanthin and breast cancer risk found in the study. Finally, the Hosmer and Lemeshow goodness-of-fit statistic ranged between 1.72 (p= 0.99) and 12.76 (p = 0.12), indicating no lack of fit for the logistic regression models.

Discussion

The study of Chinese women, a population with high consumption of fruit and vegetable,[18] was conducted to investigate the hypothesis whether intake of lycopene, α-carotene, β-carotene, β-cryptoxanthin, and lutein / zeaxanthin is inversely associated with breast cancer risk. We found that higher intake of dietary carotenoids was associated a lower risk of breast cancer. The results from Chinese women are consistent with the previous findings in western populations.[9-11] This study evaluated the relationship between breast cancer risk and intake of the most common carotenoids in the human diet, and total carotenoids as well. Total carotenoids might be more important than any single carotenoid studied in isolation because the various carotenoids appear to neutralize different free radicals at different locations within membranes,[19-21] and therefore they may work synergistically to reduce cancer risk. Carotenoids might also have other antimutagenic and anticarcinogenic properties.

Many epidemiologic evidence have showed inverse associations between fruit and vegetable consumption and breast cancer risk,[4,5] suggesting the potential importance of carotenoids contained in these foods. However, not all studies found associations.[6,7] It may reflect the fact that total fruit and vegetable consumption may not accurately rank individuals according to micronutrients that are abundant in some, but not all, fruit and vegetables.[12] There has been considerable interest in the protective role of carotenoids against breast cancer in experimental studies past two decades. However, studies examining relations between specific carotenoids and breast cancer risk in human were few until recent years. Information on individual carotenoid content of various foods has become available in the past few years,[8] and consequently the number of epidemiological studies examining dietary carotenoids has increased. Although some studies reported that higher intake of dietary carotenoids reduce the risk of breast cancer,[9-11] others could not find inverse association.[12,13] Therefore, dietary carotenoids in relation to breast cancer risk remain inconclusive. More research to examine the relationship between dietary carotenoids and breast cancer risk is warranted.

Several issues of the study strengths and limitations should be considered when interpreting the findings. A major feature of this study is that detailed information on food intake and dietary patterns as well as lifestyle and factors relevant to hormonal status was obtained. A validated and reliable instrument specifically targeted on adult Chinese women was used to collect the required information. Case-control studies are subjected to several potential biases. Selection bias appeared to be minimal in our study in view of the low refusal rate and random selection for controls. The majority of cases were newly diagnosed and the recruitment procedure used was designed to ascertain all cases. Recall bias was minimized by reporting habitual diet and by using a “reference” recall period. Since Chinese women are typically responsible for buying foods and cooking for the household, the participants could reasonably provide information on the frequency and quantity of each food consumed per meal, using reference containers to estimate the weight of food consumed. The high intraclass coefficient for test-retest reliability suggested that the FFQ may be relied upon in assessing food consumption. The association between dietary carotenoids and breast cancer has not been firmly established and there had been no mention of the association in popular media at the time of the interview, any information bias would be minor. It must be acknowledged, however, that relative small sample size of study did not allow precise estimation for breast cancer risk associated to intake of carotenoids and this may explain our insignificantly inverse association results for α-carotene and lutein/zeaxanthin.

In conclusion, our study suggests that higher intake of lycopene, β-carotene, β-cryptoxanthin, and total carotenoids was associated with a lower risk of breast cancer among Chinese women. Consumption of more vegetables and fruits, which are rich in carotenoids, may provide benefit in the prevention of breast cancer. More research to examine the relationship between dietary carotenoids and breast cancer risk is warranted.

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