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Plasma carotenoids, tocopherols, retinol and breast cancer risk: results from the Shanghai Women Health Study (SWHS)

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Abstract

Background—Evidence from some previous studies suggests that lipophilic antioxidants, particularly carotenoids, may reduce the risk of breast cancer. We prospectively investigated the associations of plasma levels of tocopherols, retinol, carotenoids with the risk of developing breast cancer among Chinese women.

Methods—We conducted a study of 365 incident breast cancer cases and 726 individually-matched controls nested within a large cohort study of women aged 40−70 years at baseline.

Results—We observed no associations between breast cancer risk and any of the tocopherols, retinol, and most carotenoids. However, high levels of plasma lycopene other than *trans*, 5-*cis* and 7-*cis* or *trans* α-cryptoxanthin were inversely associated with the risk of developing breast cancer.

Conclusions—Our results do not support an overall protective effect of lipophilic antioxidants on breast cancer risk. The few inverse associations observed for subtype of carotenoids may need to be confirmed in future studies.

Keywords

Lipophilic antioxidants; breast cancer; Plasma

Introduction

Intake of fruits and vegetables has been linked to a reduced risk of breast cancer in some epidemiologic studies [1-3]. Lipophilic antioxidant constituents of fruits and vegetables, such as carotenoids, retinol, and tocopherols, have received great attention in cancer prevention. These lipophilic antioxidants have been shown to inhibit oxidative processes involved in carcinogenesis, carcinogen metabolism, and cell proliferation, while also enhancing the cellular immune system [4,5]. Dietary intake and supplemental use of carotenoids, tocopherols, and vitamin A have been associated with a reduction in breast cancer risk in numerous investigations [3,6-8], although the observations were not consistent across all studies [9-11].

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A few prospective epidemiologic studies have examined the association between breast cancer risk and plasma or serum levels of antioxidants, with mixed results [12-15]. All of these cohort studies were conducted among Caucasian populations in developed countries with high incidence of breast cancer and generally high intake levels of these antioxidants [16]. The uniformly high levels of antioxidant exposure may have limited the opportunity to detect a significant association in some studies.

In a previous comparative study, we observed that the plasma levels of the most common antioxidants were highest among the US population and lowest among the Chinese population [17]. In particular, the Chinese population had one-seventh the levels of lycopene, one third of α-carotene, and 59% of β- carotene compared to their counterparts in the United States. These findings were consistent with a subsequent study conducted among Chinese living in Shanghai [18]. The relatively low but varied levels of antioxidant exposures in the Chinese population could enhance the opportunity to detect an association with disease risk. To our knowledge, no study has been conducted to investigate the association of serum or plasma level of antioxidant vitamins and risk of breast cancer in China, where the breast cancer incidence rates traditionally have been low but are rapidly increasing [19].

In a nested case-control study within the prospective, population-based Shanghai Women's Health Study (SWHS) cohort, we comprehensively investigated the associations of breast cancer risk with plasma levels of total, α-, γ/β- and δ-tocopherols, retinol, and total carotenoids, including specific carotenes, lycopenes, zeaxanthins, lutiens and cryptoxanthins.

Materials and Methods

Study population

Details on the establishment of the Shanghai Women's Health Study (SWHS) have been reported elsewhere [20]. In brief, at the baseline from March 1997 to May 2000, a cohort of 74,942 Chinese women between the ages of 40 and 70 years was formed from seven urban communities in Shanghai, with a 92% participation rate. Participants were interviewed by trained interviewers using structured questionnaires to obtain information on demographic characteristics, disease and surgery histories, personal habits, occupational history, family history of cancer, dietary habits, reproductive history and hormone use, physical activity and weight history. The average of two measurements was used for weight, standing and sitting height, and circumferences of the waist and hips. A third measurement was conducted if the difference between the first two measurements was larger than 1 kg for weight, 1 cm for height, and 0.5 cm for circumferences. The study was approved by all relevant institutional review boards in the People's Republic of China and in the United States. All participants provided informed written consent.

Cohort follow-up and outcome ascertainment

The SWHS was tracked for occurrence of cancer and other chronic diseases by a combination of active surveys conducted every two years and annual record linkage of the study population to cancer case data collected by the population-based Shanghai Cancer Registry and death certificates collected by the Shanghai Municipal Center for Disease Control and Prevention. Nearly all cohort members were successfully followed, with the response rates for first in-person follow-up being 99.8% (2000−2002), second 98.7% (2002−2004), and third 96.7% (2004−2007). All possible incident cancer cases were verified by home visits. Medical charts from the referral hospitals were reviewed to verify the diagnosis, and pathological characteristics of the tumor were recorded. Breast cancer cases were defined as women for whom breast cancer was the first cancer diagnosis (ICD-9, code of 174) [21].

Nested case-control design

The nested case control study was conducted among women who donated a blood sample at baseline, about 76% of the cohort. Among them, 365 cases were indentified during an average 7.5 years follow up. Controls were selected among the study participants who were cancer free at the time of cancer diagnosis of matched cases. Two controls were randomly selected and matched with each case based on age at baseline (± 2 years), date (≤ 30 days), time (morning or afternoon) of blood collection, interval since last meal (≤ 2 hours), menopausal status (pre- or post-), and antibiotic use (yes/no) in the past week. Two controls were successfully matched with each of 365 cases, while 4 cases were matched with only one control each, yielding a total of 726 controls.

Sample collection, storage and processing

A 10 ml blood sample was drawn from each subject who provided consent, into ethylene diamine tetraacetic acid Vacutainer® tubes (Becton, Dickinson and Company, Franklin Lakes, New Jersey). When the samples were procured a biospecimen collection form was filled out for each sample [20]. The blood samples were processed to separate plasma within 6 hours of collection, and the plasma specimens were immediately stored at −80°C. During thawing and aliquoting, processing of plasma samples was performed in a darkroom equipped with a red light, because lipophilic antioxidants, particularly carotenoids in plasma are light-sensitive and thus, may be degraded after exposure to the light.

Laboratory assays of plasma carotenoids, tocopherols and retinol

Samples for each case-control pair were assayed within the same batch to avoid batch-to-batch variation. Technicians who performed the assays were blinded on any information of the study subjects. A total of 22 types of plasma lipophilic antioxidants were assayed, including total tocopherols, α-tocopherol, β/γ-tocopherol, δ-tocopherol, retinol, total carotenoids, both *cis* and *trans* isomeric forms of β-carotene, *trans* α-carotene, total lycopene, *trans*, *5-cis* and *7-cis* lycopene, geometric isomers other than *trans*, *5-cis* and *7-cis* lycopene, both *cis* and *trans* isomers of lutein/zeaxanthin, both *cis* and *trans* isomers of anhydrolutein, α- cryptoxanthin, both *trans* and *cis* isomers of β-cryptoxanthin, and *cis* isomer of α-cryptoxanthin. Sample extracts were analyzed by isocratic reverse-phase high-performance liquid chromatography methodology with photo-diode array detection, and absorption spectra and retention times for each peak were compared with those of known standards. The quality of all laboratory analyses was periodically evaluated by performance in round-robin trials organized by the U.S. National Institute for Standards and Technologies (Gaithersburg, MD) [22,23]. Inter-batch coefficient of variation were 9% for *trans* lutein, 11% for *trans* zeaxanthin, 9% for *trans* lutein/zeaxanthin, 10% for *trans* anhydrolutein, 8% for *cis* anhydrolutein, 8% for alpha cryptoxanthin, 10% for *trans* beta cryptoxanthin, 8% for *cis* beta cryptoxanthins, 15% for all-*trans* lycopene, 14% for *5-cis* lycopene, 14% for *7-cis* lycopene, 15% for dihydro−/other *cis* lycopenes, 12% for alpha carotene, 14% for *trans* beta carotene, 14% for *cis* beta carotene, 9% for beta+gamma tocopherol, 9% for alpha tocopherol, and 6% for *trans* beta carotene. Intra-batch coefficients of variation were one half to one third of the inter-batch coefficients.

Statistical Analysis

In data analysis, twenty-two plasma lipophilic antioxidants were classified into three main groups (tocopherols, retinols, and carothenoids). Tocopherols and carotenoids were further categorized by their specific types or geometric isomers (Table 2). The percentage of difference between the median levels of these vitamins in cases and controls was obtained by subtraction, and then this difference was divided by the median level in controls [($median_{cases}$ - $median_{controls}$)/$median_{controls}$], which was further expressed in percentage. The paired Wilcoxon rank test was used to compare the levels of lipophilic antioxidants between cases and controls. Conditional logistic regression was used to analyze the association between concentration of each antioxidant vitamin and risk of breast cancer. The levels of plasma lipophilic antioxidants (ng/mL) were categorized based on quartile distribution in controls within each batch because all samples were assayed in the two batches (82.7% and 17.3%, respectively).

To evaluate the potential confounding factors, known breast cancer risk factors in this population and characteristics of study participants were compared between cases and controls. We examined the association between plasma lipophilic antioxidants and breast cancer risk in conditional logistic regression model adjusting for potential confounding factors. Furthermore, we performed mutual controlling for other plasma lipophilic antioxidants (continuous variables). For example, plasma levels of total retinol and total carotenoids were additionally adjusted for and *vice-versa*, when we analyzed the association for total tocopherols. In the analyses for single carotenoid, other carotenoids were similarly adjusted for both total tocopherols and retinol. Moreover, stratified analyses by menopausal status and body mass index (BMI <25.0 vs. ≥25.0 kg/m^2) at blood sample collection were performed to evaluate whether risk of breast cancer differed according to these factors. In addition, sensitivity analyses were conducted by excluding those whose blood samples were collected within two years of cancer diagnosis. *P* values of <0.05 (2 sided probability) were interpreted as being statistically significant. Tests for trend were performed by entering the categorical variables as a continuous variable in the model. Statistical analyses were conducted using SAS statistical software (version 9.1; SAS Institute, Cary, NC).

Results

Shown in Table 1 are known breast cancer risk factors and selected characteristics for cases and controls at baseline. Almost half of the cases were postmenopausal. The median age of cases at diagnosis was 51.0 years. Compared to controls, cases were more likely to have a college education or above, a professional career, earlier age at menarche, later age at first live birth, a history of breast fibroadenoma, and a family history of breast cancer. Cases and controls did not differ significantly on use of oral contraceptives or hormone replacement therapy. Controls were more likely to smoke cigarettes, drink alcohol, and have a higher intake of red meat compared with cases; however, the difference was significant for the intake of red meat only.

Among the controls, the correlation coefficients between plasma lipophilic antioxidants were low (r =0.21 between total carotenoids and total tocopherols, r =0.23 between retinol and total tocopherols, and r =0.14 between total carotenoids and retinol). The correlations were weak to moderate between subgroups of tocopherols (r ranged from 0.15 to 0.57) or isomeric forms of carotenoids (r ranged from 0.13 to 0.44). On average, cases had higher concentrations of α-tocopherol and carotenes (*trans*- and *cis* β-carotene) than controls (p ≤0.05) (Table 2). No other significant case-control differences were observed.

Overall, breast cancer risk was not significantly associated with total tocopherols, retinol, total carotenoids, or their subgroups (Table 3). After adjusting for potential confounding variables, no statistically significant association was found for α-tocopherol and carotenes (*trans*- and *cis* β-carotene). We also found that the ratio of α to γ tocopherol was not related to the risk of breast cancer (data not shown). Among postmenopausal women, breast cancer risk was positively associated with total tocopherols, α-tocopherol, total carotenoids, and β-carotenes with borderline significance (Table 4). However, after adjusting for levels of other lipophilic antioxidants, the associations were diminished and none of the ORs was statistically significant for the highest quartile concentration of these antioxidants.

Plasma level of total lycopenes was not associated with breast cancer risk. However, an inverse association was suggested for the lycopene isomers other than *trans,* 5-*cis,* and 7-*cis* (OR: 0.70, 95%CI: 0.43−1.14 for the highest quartile level compared to the lowest), which was further reduced to 0.56 (0.32−0.97) after adjusting for other lipophilic antioxidants. Similarly, after additional adjustments for other lipophilic antioxidants, we found *trans* α-cryptoxanthin significantly associated with a reduced risk of breast cancer in a dose-response manner, with an OR of 0.59 (95%CI: 0.34−1.01) for the highest quartile level compared to the lowest (P for trend, 0.02) (Table 3). In stratified analyses by menopausal status at blood draw, the inverse association for lycopene isomers other than *trans,* 5-*cis,* and 7-*cis* primarily appeared in premenopausal women with an corresponding OR (95%CI) of 0.36(0.16−0.80) while the inverse association for *trans* α-cryptoxanthin appeared in both pre- and post- menopausal women (Table 4). Furthermore, we have conducted sensitivity analysis by excluding cases diagnosed within two years of blood collection and found similar results for *trans* α-cryptoxanthin and lycopene isomers other than *trans,* 5-*cis,* and 7-*cis* (data not shown).

Discussion

In this nested case-control study, we prospectively evaluated plasma levels of lipophilic antioxidants in relation to subsequent breast cancer risk. In addition to the lipophilic antioxidants that were investigated in previous nested case-control studies [4,12-14,24] (α-, β-carotene, total lycopenes, total lutein, α- and γ-tocopherol, β-cryptoxanthin, and retinol), we examined additional subtypes of antioxidant vitamins, including *cis* and *trans* isomers of α- and β-carotene, lycopenes, lutein, zeaxanthin, and α- and β-cryptoxanthins.

In this study, we found an inverse association between plasma levels of *trans* α-cryptoxanthin (one xanthophyll group of carotenoid) and subsequent breast cancer risk, particularly among premenopausal women. *Trans* α-cryptoxanthin has not been investigated in previous studies because it is scarce in traditional Western diets [25], thus leading to a low plasma level [26]. The inverse association observed in our study became significant only after adjusting for other lipophilic antioxidants. Therefore, we cannot exclude the possibility that the effect of α-cryptoxanthin may be through interacting with other antioxidant vitamins. Most previous studies found a reduced breast cancer risk associated with increased concentration of *trans* β-cryptoxanthin either in pre- or post menopausal women, but not all associations reached statistical significance [4,12-14,24]. However, we did not find such an inverse association. The possible biological mechanism of anti-cancer activity of α-cryptoxanthin is poorly understood. On the other hand, β-cryptoxanthin was proposed to suppress the cyclin D1 and cyclin E expression by up-regulating the cancer-suppressor genes, p21 and retinoic acid receptor β (RAR-β) [27]. Further studies are needed to clarify the associations and the underlying mechanisms between breast cancer and cryptoxanthin and its types or isomers.

We also found a reduced risk of breast cancer among premenopausal women with the highest quartile of plasma levels of lycopene isomers other than *trans* or 5-*cis* and 7-*cis,* after controlling for other lipophilic antioxidants. No study has investigated these specific lycopene isomers in relation to breast cancer risk and the mechanism for the inverse association is unclear. Laboratory and epidemiological studies found that *cis* isomer of lycopene, a metabolite of *trans* lycopene (predominant form of natural lycopene) may possess a stronger cancer inhibiting effect than *trans* isoforms of lycopene [28-30]. It is also possible that lycopene isomers other than *trans* or 5-*cis* and 7-*cis* may interact with other lipophilic antioxidants. Several studies reported a non-significantly reduced risk of breast cancer with a higher circulating level of total lycopenes [12,24], while other studies found a null association [13, 14,31].

We found higher median levels of β-carotenes (*trans*- and *cis* β-carotenes), the most abundant carotenoid, among cases compared with controls. However, no significantly elevated associations were found for these antioxidants in multivariable models. The null associations were consistent with some previous studies [4,31-34], but inconsistent with several prospective studies which found a reduction in risk of breast cancer associated with higher levels of serum β-carotene [12-15,32]. Similarly, levels of total carotenoids, α-carotene and lutein (*trans*- or *cis*-lutein/zeaxanthin) were not associated with breast cancer risk. Our results also do not suggest an association between anhydrolutein and risk of breast cancer. To the best of our knowledge, no study has previously evaluated such an association for breast cancer, although one study found a null association with bladder cancer [35]. The null association observed in this study for plasma retinol [4,24] and tocopherols [4,13,24] was in agreement with most previous studies. Our results for α-tocopherols were also consistent with those found in clinical trial [36]. It has been reported that α-tocopherol supplementation provided no overall benefit for total mortality, and for incidence and mortality of major cardiovascular diseases or cancer [36], including breast cancer [10,11].

The findings from this study do not support plasma levels of total tocopherols, retinol, and total carotenoids being associated with a reduced risk of breast cancer. However, it is possible that these antioxidants may show protective effects against breast cancer only among subgroups of women, such as those with genotypes favoring low activity of manganese superoxide dismutase (MnSOD) [37]. For the two significant novel findings on *trans* α-cryptoxanthin and lycopene isomers other than *trans* or 5-*cis* and 7-*cis*, we cannot exclude the possibility that the inverse associations are due to chance given multiple comparisons involved.

The present study has several notable strengths. This is a nested case-control study within a population-based cohort study with high rates of baseline participation and follow-up, which minimized selection bias. Antioxidants were measured through blood samples that were collected before cancer diagnosis, which avoids the potential modifying effect of cancer treatment and changes in lifestyle and dietary habits after cancer diagnosis. We have also conducted sensitivity analyses by excluding those who were diagnosed with breast cancer within two years from blood collection and found similar results. Our study is limited by using only measure from one baseline spot sample, which may lead to non-differential misclassification and bias the result to the null. However, in previous studies using repeated measurements, one spot measure reasonably represents long-term levels of plasma or serum antioxidants [31,32,38].

In summary, we found no overall associations between breast cancer risk and plasma levels of total carotenoids, total tocopherols, and total retinol. The novel observations of reduction in risk associated with *trans* α-cryptoxantin and lycopene isomers other than *trans*, 5-*cis*, and 7-*cis* need further evaluation and confirmation in future studies.

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Table 1

Comparison of breast cancer cases and controls by selected baseline demographic and risk factors, the Shanghai Women's Health Study (SWHS), 1997−2006

	Cases, n=365	Controls, n=726	*P* -value*
Demographic and reproductive factors			
Age, years (mean ± SD)	52.5 ± 9.0	52.6 ± 9.0	0.87
Education college and above (%)	15.7	10.5	0.001
Occupation, professional (%)	35.9	26.7	0.006
Family income group, high (%)	29.0	29.3	0.86
Age at menarche, years (mean ± SD)	14.8 ± 1.8	15.0 ± 1.8	0.03
Nulliparity (%)	0.8	0.5	0.60
Number of live births § (mean ± SD)	1.7 ± 1.1	1.8 ± 1.2	0.12
Age at first live birth, years § (mean ± SD)	25.7 ± 4.2	24.8 ± 4.1	0.01
Ever breastfed§ (%)	81.0	85.0	0.10
Postmenopausal at baseline (%)	49.6	50.7	0.73
Oral contraceptive use (%)	21.1	22.1	0.68
Hormone replacement therapy use (%)	3.8	1.6	0.07
History of breast fibroadenoma (%)	7.4	4.4	0.04
First degree family history of breast cancer (%)	4.7	1.5	0.002
Life style and dietary factors			
Body mass index (mean ± SD)	23.9 ± 3.5	24.2 ± 3.3	0.39
Waist to hips ratio (mean ± SD)	0.810 ± 0.05	0.813 ± 0.05	0.82
Exercised regularly in past 5 years (%)	35.3	35.1	0.94
Ever smoked cigarette regularly (%)	1.4	3.0	0.10
Ever consumed alcohol regularly (%)	1.9	3.2	0.23
Regular tea consumption (%)	31.8	28.5	0.26
Ginseng used regularly (%)	28.5	25.8	0.33
Dietary factors (mean ± SD)			
Total energy intake (kcal/day)	1633.5 ± 363.1	1672.4 ± 393.9	0.22
Total fat intake (g/day)	27.6 ± 11.1	28.8 ± 13.0	0.19
Total vegetables intake (g/day)	304.8 ± 163.8	306.9 ± 172.7	0.69
Total fruit intake (g/day)	259.7 ± 175.4	257.8 ± 171.3	0.89
Total red meat intake (g/day)	45.0 ± 31.3	50.0 ± 36.6	0.03
Total fish intake (g/day)	46.7 ± 41.0	48.6 ± 49.1	0.67

*Derived from t-test for continuous variables and chi-square test for categorical variables

§Among parous women

Table 2

Comparison of plasma levels of carotenoids, tocopherols, and retinol between breast cancer cases and controls: a nested case-control study within the SWHS (n=1 091)

	Median (25th, 75th percentile)			
Lipophilic antioxidants (ng/mL)	**Cases (n=365)**	**Controls (n=726)**	**% difference***	***P*-value****
Total tocopherols	11111.6 (9355.3, 13218.1)	10762.0 (9168.7, 12951.9)	3.2	0.16
α- tocopherol	8593.9 (7110.5, 10322.7)	8113.4 (6817.0, 10178.4)	5.9	0.04
β/γ- tocopherol	1894.2 (1452.7, 2568.0)	2013.9 (1511.4, 2613.3)	−5.9	0.24
δ- tocopherol	346.5 (244.9, 456.0)	350.0 (253.3, 457.1)	−1.0	0.79
Retinol	626.4 (520.2, 727.2)	602.9 (509.2, 714.3)	3.9	0.10
Total carotenoids	1325.5 (1024.1, 1627.9)	1250.9 (1012.5, 1560.9)	6.0	0.09
Carotenes:				
β- carotenes	248.5 (162.0, 347.0)	226.0 (152.3, 313.2)	10.0	0.02
trans β- carotene	232.5 (150.8, 324.5)	210.7 (140.9, 291.4)	10.3	0.02
cis β- carotene	16.6 (10.4, 23.8)	14.8 (10.1, 21.4)	12.2	0.03
trans α- carotene	23.5 (15.3, 34.4)	21.5 (15.1, 32.6)	9.3	0.17
Lycopenes	113.5 (75.0, 174.6)	109.7 (68.8, 182.5)	3.5	0.49
trans, 5cis, 7cis lycopene	78.0 (49.7, 120.0)	74.8 (46.8, 125.5)	4.3	0.43
Lycopene other than *trans, 5-cis, 7-cis*	34.5 (22.9, 50.3)	34.4 (21.4, 53.4)	0.3	0.60
Other carotenoids:				
Trans lutein/zeaxanthin	390.6 (308.0, 484.8)	389.6 (313.3, 476.2)	0.3	0.98
trans lutein	251.3 (198.5, 317.6)	253.2 (198.5, 318.1)	−0.7	0.90
trans zeaxanthin	136.0 (106.3, 167.0)	133.9 (107.6, 163.1)	1.6	0.86
Cis lutein/zeaxanthin	104.9 (87.9, 126.9)	103.8 (85.8, 126.8)	1.1	0.62
Trans anhydrolutein	67.5 (50.2, 86.3)	65.5 (48.1, 83.3)	3.0	0.25
Cis anhydrolutein	31.6 (24.1, 41.5)	31.1 (24.2, 40.2)	1.6	0.29
Trans α- cryptoxanthin	24.5 (19.7, 32.3)	25.3 (19.9, 32.0)	−3.2	0.77
Trans β- cryptoxanthin	142.8 (74.8, 255.4)	122.1 (71.1, 241.2)	16.9	0.19
Cis β- cryptoxanthin	49.4 (30.1, 72.5)	42.9 (30.8, 71.2)	15.1	0.20

* Expressed as: $(\text{median}_{\text{cases}} - \text{median}_{\text{controls}}) / \text{median}_{\text{controls}}$

** Derived from the Wilcoxon two-sample paired signed rank test

Table 3

Odds ratios (ORs) and 95% confidence intervals (CI) for risk of breast cancer associated with plasma carotenoids, tocopherols, and retinol: a nested case-control study within the SWHS (n=1 091)

Lipophilic antioxidants (ng/mL)		Plasma lipophilic antioxidants in quartile level (ng/mL)‡			$P_{for\ trend}$
		Q2	Q3	Q4	
		OR_{adj} (95% CI)	OR_{adj} (95% CI)	OR_{adj} (95% CI)	
Total tocopherols	Model 1	1.19 (0.80−1.78)	1.25 (0.83−1.89)	1.15 (0.74−1.76)	0.51
	Model 2	1.16 (0.77−1.75)	1.19 (0.77−1.83)	1.07 (0.67−1.71)	0.93
α- tocopherol	Model 1	1.14 (0.75−1.73)	1.47 (1.00−2.17)	1.19 (0.77−1.82)	0.25
	Model 2	1.15 (0.75−1.76)	1.40 (0.93−2.12)	1.15 (0.72−1.85)	0.56
β/γ- tocopherol	Model 1	1.00 (0.69−1.45)	0.85 (0.58−1.25)	0.94 (0.63−1.40)	0.54
	Model 2	1.01 (0.68−1.46)	0.86 (0.57−1.26)	0.97 (0.65−1.45)	0.59
δ- tocopherol	Model 1	0.81 (0.55−1.20)	0.88 (0.57−1.37)	1.03 (0.64−1.65)	0.74
	Model 2	0.83 (0.56−1.23)	0.91 (0.58−1.43)	1.09 (0.66−1.79)	0.66
Retinol	Model 1	0.99 (0.66−1.47)	1.48 (1.01−2.17)	1.20 (0.80−1.81)	0.18
	Model 2	0.95 (0.64−1.42)	1.44 (0.98−2.13)	1.17 (0.77−1.78)	0.20
Total carotenoids	Model 1	0.92 (0.62−1.37)	1.08 (0.73−1.58)	1.29 (0.88−1.89)	0.12
	Model 2	0.93 (0.61−1.39)	1.08 (0.72−1.59)	1.30 (0.87−1.93)	0.14
Carotenes:					
β- carotenes	Model 1	1.12 (0.75−1.67)	0.94 (0.63−1.41)	1.44 (0.97−2.15)	0.11
	Model 2	1.11 (0.74−1.69)	0.96 (0.62−1.49)	1.47 (0.92−2.35)	0.19
trans β- carotene	Model 1	1.13 (0.76−1.67)	0.92 (0.61−1.37)	1.43 (0.96−2.14)	0.13
	Model 2	1.12 (0.75−1.70)	0.93 (0.60−1.44)	1.46 (0.91−2.34)	0.24
cis β- carotene	Model 1	0.88 (0.59−1.31)	0.98 (0.67−1.44)	1.22 (0.82−1.81)	0.21
	Model 2	0.85 (0.56−1.28)	0.96 (0.62−1.47)	1.17 (0.70−1.96)	0.54
trans α- carotene	Model 1	0.78 (0.53−1.15)	0.97 (0.67−1.42)	1.08 (0.73−1.59)	0.52
	Model 2	0.74 (0.50−1.11)	0.89 (0.60−1.34)	0.98 (0.62−1.54)	0.95
Lycopenes	Model 1	1.09 (0.73−1.64)	1.38 (0.92−2.08)	0.91 (0.55−1.50)	0.93
	Model 2	1.03 (0.68−1.57)	1.26 (0.83−1.94)	0.83 (0.49−1.39)	0.76
trans, 5cis, 7cis lycopene	Model 1	1.03 (0.69−1.46)	1.27 (0.84−1.90)	0.98 (0.60−1.59)	0.83
	Model 2	0.96 (0.63−1.45)	1.17 (0.77−1.78)	0.89 (0.54−1.49)	0.91
lycopene other than *trans, 5-, 7-cis*	Model 1	1.06 (0.72−1.56)	1.14 (0.76−1.71)	0.70 (0.43−1.14)	0.25

Lipophilic antioxidants (ng/mL)		**Plasma lipophilic antioxidants in quartile level (ng/mL)‡**			**$P_{for\ trend}$**
		Q2	**Q3**	**Q4**	
		OR_{adj} (95% CI)	**OR_{adj} (95% CI)**	**OR_{adj} (95% CI)**	
	Model 2	1.00 (0.67−1.49)	0.98 (0.63−1.52)	0.56 (0.32−0.97)	0.08
<u>*Other carotenoids:*</u>					
Trans lutein/zeaxanthin	Model 1	0.86 (0.58−1.26)	1.03 (0.70−1.50)	1.07 (0.72−1.59)	0.60
	Model 2	0.80 (0.54−1.19)	1.00 (0.68−1.47)	1.02 (0.67−1.54)	0.71
trans lutein	Model 1	1.07 (0.74−1.57)	1.02 (0.69−1.50)	1.07 (0.72−1.59)	0.83
	Model 2	1.02 (0.69−1.51)	1.00 (0.67−1.49)	1.01 (0.67−1.54)	0.97
trans zeaxanthin	Model 1	1.01 (0.68−1.49)	1.01 (0.67−1.48)	1.21 (0.81−1.81)	0.46
	Model 2	1.00 (0.67−1.52)	0.97 (0.65−1.45)	1.14 (0.74−1.76)	0.67
Cis lutein/zeaxanthin	Model 1	1.11 (0.75−1.64)	1.07 (0.72−1.57)	1.17 (0.80−1.73)	0.49
	Model 2	1.12 (0.74−1.68)	1.04 (0.67−1.62)	1.10 (0.65−1.85)	0.86
Trans anhydrolutein	Model 1	1.10 (0.76−1.61)	0.97 (0.65−1.45)	1.17 (0.79−1.72)	0.46
	Model 2	1.11 (0.74−1.63)	1.01 (0.59−1.70)	1.07 (0.68−1.68)	0.87
Cis anhydrolutein	Model 1	0.80 (0.53−1.21)	0.98 (0.67−1.44)	0.97 (0.64−1.45)	0.71
	Model 2	0.74 (0.48−1.13)	0.86 (0.56−1.32)	0.77 (0.45−1.31)	0.58
Trans α- cryptoxanthin	Model 1	1.02 (0.70−1.48)	0.77 (0.52−1.14)	0.85 (0.57−1.26)	0.28
	Model 2	0.92 (0.62−1.37)	0.62 (0.40−0.97)	0.59 (0.34−1.01)	0.02
Trans β- cryptoxanthin	Model 1	0.80 (0.53−1.22)	1.23 (0.81−1.85)	1.31 (0.81−2.09)	0.09
	Model 2	0.79 (0.51−1.22)	1.19 (0.77−1.83)	1.25 (0.75−2.09)	0.17
Cis β- cryptoxanthin	Model 1	0.58 (0.38−0.88)	1.20 (0.81−1.78)	1.07 (0.68−1.68)	0.30
	Model 2	0.53 (0.34−0.83)	1.10 (0.70−1.73)	0.94 (0.53−1.67)	0.64

Model1: Conditional logistic regression model controlling for covariates included age at entry (continuous), education, occupation, age at menarche (continuous), age at 1st live birth (categorized), waist to hips ratio (categorized), exercised regularly in past 5 years (yes/no), ever smoke (yes/no), menopausal status, history of breast fibroadenoma (yes/no), 1st degree family history cancer (yes/no), total intakes of energy: vegetables, fruit, red meat and fish, regular tea consumption (yes/no) and batch for assays

Model 2: Additionally and mutually adjusted for other plasma lipophilic antioxidants

Note: The reference group is the lowest quartile in all models

‡Antioxidants were categorized into quartiles according to the distribution in the controls (Table 3)

Table 4

Odds ratios (ORs) and 95% confidence intervals (CI) for risk of breast cancer associated with plasma carotenoids, tocopherols, and retinol by Menopausal status: a nested case-control study within the SWHS (n=1 091)

Lipophilic antioxidants (ng/mL)		Plasma lipophilic antioxidants in quartile level (ng/mL)‡ Q2	Q3	Q4	P_{trend}
		OR_{adj} (95% CI)	OR_{adj} (95% CI)	OR_{adj} (95% CI)	
Premenopausal women, n=542					
Total tocopherols	Model 1	1.68 (0.71–1.93)	0.87 (0.50–1.51)	0.96 (0.50–1.87)	0.80
	Model 2	1.12 (0.67–1.88)	0.80 (0.44–1.47)	0.90 (0.44–1.85)	0.65
α- tocopherol	Model 1	1.08 (0.62–1.66)	1.07 (0.64–1.79)	0.85 (0.44–1.65)	0.91
	Model 2	1.05 (0.60–1.83)	1.01 (0.57–1.78)	0.81 (0.40–1.67)	0.78
Retinol	Model 1	1.05 (0.63–1.75)	1.45 (0.86–2.45)	1.21 (0.64–2.30)	0.28
	Model 2	1.09 (0.65–1.85)	1.54 (0.90–2.64)	1.30 (0.68–2.48)	0.21
Total carotenoids	Model 1	0.95 (0.52–1.73)	1.08 (0.61–1.91)	0.97 (0.57–1.67)	0.96
	Model 2	0.98 (0.53–1.80)	1.12 (0.62–2.01)	1.06 (0.51–1.91)	0.75
Carotenes:					
β- carotenes	Model 1	0.98 (0.54–1.78)	1.06 (0.60–1.90)	1.22 (0.69–2.16)	0.37
	Model 2	1.03 (0.56–1.91)	1.18 (0.63–2.20)	1.44 (0.73–2.82)	0.22
Lycopenes	Model 1	0.81 (0.46–1.43)	1.30 (0.72–2.32)	0.63 (0.31–1.29)	0.73
	Model 2	0.99 (0.54–1.80)	1.22 (0.65–2.30)	0.66 (0.30–1.43)	0.69
lycopene other than *trans, 5-, 7-cis*	Model 1	0.81 (0.47–1.42)	0.94 (0.52–1.70)	0.42 (0.21–0.87)	0.08
	Model 2	0.78 (0.44–1.38)	0.84 (0.44–1.58)	0.36 (0.16–0.80)	0.06
Trans α- cryptoxanthin	Model 1	0.88 (0.51–1.53)	0.73 (0.40–1.34)	0.68 (0.38–1.22)	0.19
	Model 2	0.83 (0.47–1.47)	0.60 (0.30–1.19)	0.50 (0.23–1.12)	0.10
Trans β- cryptoxanthin	Model 1	0.78 (0.41–1.45)	1.34 (0.77–2.73)	1.26 (0.63–2.52)	0.23
	Model 2	0.81 (0.42–1.57)	1.46 (0.74–2.90)	1.36 (0.63–2.94)	0.17
Postmenopausal women, n=549					
Total tocopherols	Model 1	1.36 (0.64–2.92)	2.06 (1.01–4.19)	1.58 (0.80–3.13)	0.20
	Model 2	1.26 (0.58–2.76)	1.88 (0.91–3.88)	1.35 (0.66–2.78)	0.42
α- tocopherol	Model 1	1.23 (0.59–2.54)	2.12 (1.11–4.03)	1.76 (0.90–3.43)	0.06
	Model 2	1.18 (0.68–3.23)	1.98 (1.06–4.38)	1.61 (0.79–3.27)	0.15
Retinol	Model 1	0.86 (0.43–1.72)	1.50 (0.79–2.83)	1.12 (0.60–2.10)	0.55

Lipophilic antioxidants (ng/mL)		Plasma lipophilic antioxidants in quartile level (ng/mL)‡			P_{trend}
		Q2	Q3	Q4	
		OR_{adj} (95% CI)	OR_{adj} (95% CI)	OR_{adj} (95% CI)	
	Model 2	0.82 (0.41−1.65)	1.45 (0.76−2.77)	1.05 (0.56−1.99)	0.69
Total carotenoids	Model 1	0.84 (0.47−1.49)	1.08 (0.62−1.92)	1.82 (1.00−3.30)	0.04
	Model 2	0.84 (0.47−1.49)	1.09 (0.61−1.90)	1.77 (0.96−3.25)	0.05
Carotenes:					
β- carotenes	Model 1	1.27 (0.72−2.25)	0.81 (0.44−1.49)	1.81 (0.99−3.33)	0.20
	Model 2	1.20 (0.67−2.17)	0.74 (0.38−1.43)	1.58 (0.78−3.19)	0.56
Lycopenes	Model 1	1.54 (0.82−2.94)	1.51 (0.79−2.94)	1.35 (0.64−2.84)	0.53
	Model 2	1.50 (0.79−2.86)	1.35 (0.69−2.62)	1.17 (0.54−2.51)	0.85
lycopene other than *trans, 5-, 7-cis*	Model 1	1.43 (0.78−2.64)	1.36 (0.72−2.57)	1.18 (0.56−2.47)	0.81
	Model 2	1.37 (0.73−2.55)	1.17 (0.60−2.27)	0.88 (0.39−2.01)	0.62
Trans α- cryptoxanthin	Model 1	1.17 (0.67−2.06)	0.82 (0.47−1.41)	0.97 (0.53−1.76)	0.79
	Model 2	0.96 (0.53−1.74)	0.58 (0.31−1.08)	0.48 (0.21−1.11)	0.08
Trans β- cryptoxanthin	Model 1	0.82 (0.45−1.50)	1.19 (0.67−2.14)	1.40 (0.70−2.81)	0.32
	Model 2	0.78 (0.42−1.45)	1.10 (0.60−2.03)	1.21 (0.56−2.59)	0.67

Model1: Conditional logistic regression model controlling for covariates included age at entry (continuous), education, occupation, age at menarche (continuous), age at 1st live birth (categorized), waist to hips ratio (categorized), exercised regularly in past 5 years (yes/no), cigarette smoke (yes/no), history of breast fibroadenoma (yes/no), 1st degree family history cancer (yes/no), total intakes of energy: vegetables, fruit, red meat and fish, regular tea consumption (yes/no) and batch for assays

Model 2: Additionally and mutually adjusted for other plasma lipophilic antioxidants

Note: The reference group is the lowest quartile in all models

‡Antioxidants were categorized into quartiles according to the distribution in the controls (Table 3)