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Dietary carotenoids and risk of hormone receptor-defined breast cancer in a prospective cohort of Swedish women

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ABSTRACT

Carotenoids have antioxidant and antiproliferative properties and may reduce the risk of breast cancer. We examined the association between dietary carotenoids and risk of invasive breast cancer in the Swedish Mammography Cohort, a population-based cohort of 36,664 women who completed a questionnaire in 1997. During a mean follow-up of 9.4 years, 1008 women were diagnosed with incident breast cancer. Dietary carotenoids were not significantly associated with the risk of breast cancer overall or with any subtype defined by oestrogen receptor (ER) and progesterone receptor (PR) status. However, dietary α-carotene and β-carotene were inversely associated with the risk of ER–PR-breast cancer among ever smokers. Among ever smokers, the multivariable relative risks of ER–PR-breast cancer comparing the highest with the lowest quintile of intake were 0.32 (95% confidence interval (CI): 0.11–0.94; P_{trend} = 0.01) for α-carotene and 0.35 (95% CI: 0.12–0.99; P_{trend} = 0.03) for β-carotene. The risk of breast cancer also decreased with increasing intakes of α-carotene (P_{trend} = 0.02) and β-carotene (P_{trend} = 0.01) among women who did not use dietary supplements. These findings suggest that dietary α-carotene and β-carotene are inversely associated with the risk of breast cancer among smokers and among women who do not use dietary supplements.

1. Introduction

Carotenoids are yellow to red fat-soluble pigments found in fruits and vegetables and have been postulated to reduce the risk of cancer. Carrots are a rich source of α-carotene and β-carotene, whereas oranges and orange juice contain high amounts of β-cryptoxanthin. Lycopene is found mainly in tomatoes and tomato products, and lutein and zeaxanthin in broccoli and dark green leafy vegetables. Carotenoids may lower the risk of cancer through their antioxidant properties by reducing oxidative DNA damage[1] and thereby may protect against breast carcinogenesis. Some carotenoids (α-carotene, β-carotene and β-cryptoxanthin) have provitamin A activity. Vitamin A and its derivates are involved in cellular differentiation and proliferation and may enhance immune function.[2] Moreover, β-carotene and lycopene have been shown to inhibit oestrogen signalling of 17β-estradiol, and attenuate the adverse effect in hormone-dependent breast cancer.[3]

Epidemiologic studies of dietary or blood levels of carotenoids in relation to breast cancer risk have yielded inconsistent results. An inverse association between certain carotenoids and risk of overall breast cancer has been observed in several case-control[4–7] and prospective studies.[8–14] However, in some of these studies the inverse association was confined to specific subgroups, e.g., smokers,[10] premenopausal women,[6,9] or postmenopausal women who used

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exogenous hormones.[14] Other case-control[15] and prospective studies[16–20] have not supported an association between carotenoids and breast cancer risk.

Only two previous studies have, to our knowledge, examined carotenoids in association with the risk of breast cancer defined jointly by oestrogen receptor (ER) and progesterone receptor (PR) status,[5,11] although the subtypes defined by ER/PR status may have different etiologies.[21] One of those studies showed that the inverse association of dietary α-carotene and β-carotene with breast cancer risk might be restricted to ER+PR+ tumours.[11]

The aim of this study was to examine the association between major dietary carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin and lycopene) and the incidence of invasive breast cancer in a population-based prospective cohort of Swedish women. We evaluated whether the associations varied according to ER and PR status. In addition, we examined the associations stratified by breast cancer risk factors and dietary supplement use.

2. Materials and methods

2.1. Study population

Data used in the present study were obtained from participants of the Swedish Mammography Cohort. Details of this population-based cohort study have been reported previously.[22] In brief, the cohort was established between 1987 and 1990, when all women born between 1914 and 1948 and living in central Sweden (Västmanland and Uppsala Countries) received a mailed questionnaire on diet and other risk factors for breast cancer. In the late autumn of 1997, all participants who were still alive and residing in the study area received a new questionnaire that was expanded to include about 350 items concerning diet and other lifestyle factors as well as dietary supplement use; 39,227 women (70%) completed the second questionnaire.

For the present analyses, we used information from the 1997 questionnaire because this expanded questionnaire contained more questions on carotenoid-rich fruits and vegetables than the baseline questionnaire. In addition, data on some potential effect modifiers, including family history of breast cancer, smoking and dietary supplement use were obtained first in 1997. We excluded women with an incorrect or missing National Registration Number, those with implausible values for total energy intake (i.e. 3 SDs from the $\log_e$-transformed mean energy intake) and those with a history of cancer other than non-melanoma skin cancer, leaving 36,664 women for analysis. The study was approved by the Ethical Review Board at the Uppsala University Hospital (Uppsala, Sweden) and the Karolinska Institutet (Stockholm, Sweden).

2.2. Assessment of diet

A food-frequency questionnaire (FFQ) with 96 food items was used to assess diet in 1997. In this FFQ, participants were asked to indicate how often, on average, they had consumed each food item during the past year. The FFQ had eight mutually exclusive predefined categories for frequency of consumption, ranging from 'never/seldom' to 'three or more times per day'. Nutrient intakes were calculated by multiplying the frequency of consumption by the nutrient content of age-specific (<53, 53–65, ⩾66 years) portion sizes, using composition values from the Swedish Food Administration Database.[23] We adjusted carotenoid intake for total energy intake by using the residual method.[24] Participants also provided information about use of dietary supplements, including multivitamins and specific vitamin and mineral supplements. The FFQ has been validated, and the Spearman correlation coefficient between estimates from the questionnaire and the mean of fourteen 24-h recall interviews was 0.5 for dietary β-carotene intake.[25]

2.3. Case ascertainment and follow-up

Histologically confirmed incident cases of invasive breast cancer were ascertained by linkage of the study cohort with the national and regional Swedish Cancer registers. The completeness of cancer follow-up was estimated to be almost 100%.[26] Information on ER and PR status of the breast tumours was obtained by linkage with the clinical database (Quality Register) at the Regional Oncology Centre in Uppsala, which was based on the patients' original medical records. ER and PR status was evaluated using an immunohistochemical method. Cases were considered as receptor-positive when the percentage of positive cells was ⩾10%, and receptor-negative when the percentage of positive cells was <10%. Information on dates of death for deceased participants was obtained from the Swedish Death Registry.

2.4. Statistical analysis

Person-time of follow-up for each participant was calculated from January 1, 1998 to the date of breast cancer diagnosis, death, or December 31, 2007, whichever came first. We used Cox proportional hazard models to estimate relative risks (RRs) with corresponding 95% confidence intervals (CIs). The covariates chosen for inclusion in the multivariable model were based on previously identified risk factors for breast cancer and factors associated with breast cancer risk in the Swedish Mammography Cohort. Multivariable models were adjusted for age, education (primary school, high school, university), family history of breast cancer (yes/no), history of benign breast disease, parity (nulliparous, 1–2, ⩾3 years), age at first birth (nulliparous, <26, 26–30, ⩾31 years), age at menarche (⩽12, 13, ⩾14 years), age at menopause (<51, ⩾51 years), use of oral contraceptives (never, ⩽3, 4–9, ⩾10 years), use of postmenopausal hormones (never, <5, ⩾5 years), body mass index (<18.5, 18.5–24.9, 25–29.9, ⩾30 kg/m^2), total physical activity (in quartiles of metabolic equivalent h/d), smoking status (never, past, current), multivitamin use (yes/no), total energy intake (in kcal/d; continuous variable), and alcohol intake (non-drinkers, <3.4, 3.4–9.9, ⩾10.0 g/d).

Stratified analyses were performed according to family history of breast cancer (yes, no), history of benign breast disease (yes, no), parity (nulliparous, ⩾1 child), use of postmenopausal hormones (ever, never), body mass index (<25, ⩾25 kg/m^2), physical activity (below or above median), smoking status (never, ever), dietary supplement use (yes, no), and

alcohol intake (<5, ⩾5 g/d). To test the statistical significance of interactions, we entered the main effect term for carotenoid intake (as a continuous variable) and the covariate of interest along with a term for their product into the multivariable model. To test for trend, we assigned the median value to each quintile of carotenoid intake and treated this value as a continuous variable. All statistical analyses were conducted with SAS version 9.1 (SAS Institute Inc., Cary, NC). All *P*-values were two-sided.

3. Results

Baseline characteristics of the study population by the intake of dietary carotenoids are shown in Table 1. Compared with women with a low carotenoid intake, those with a high intake were more likely to have a postsecondary education and to use multivitamins but were less likely to be current smokers. Dietary α-carotene, β-carotene, and lutein and zeaxanthin were positively associated with age, whereas β-cryptoxanthin and lycopene were inversely associated with age. Women with a high intake of β-cryptoxanthin, lutein and zeaxanthin, and lycopene were less likely to be nulliparous compared with women with low intakes of these carotenoids. Pearson correlations between the carotenoids ranged from 0.91 for α-carotene and β-carotene to 0.10 for α-carotene and β-cryptoxanthin. Only 2.6% of participants reported use of specific β-carotene supplements.

During a mean follow-up of 9.4 years (346,163 person-years) a total of 1008 incident cases of breast cancer were ascertained among the 36,664 women in the cohort. Of these breast cancers, 562 were ER+PR+, 244 were ER+PR–, nine were ER–PR+, 110 were ER–PR– and 83 were undefined. We observed no significant association between intake of any carotenoid and risk of breast cancer overall or of specific subtypes defined by ER and PR status (Table 2). Because the age- and multivariable-adjusted RRs were similar, only the multivariable RRs are presented in Table 2. For example, for total breast cancer the RRs comparing the highest with the lowest quintile of β-carotene intake were 0.87 (95% CI: 0.71–1.05) after adjustment for age only and 0.87 (95% CI: 0.71–1.06) in multivariable-adjusted analysis. Further adjustment for other dietary variables (fat, fibre, and lignans) did not change the results materially.

The association between dietary carotenoids and breast cancer did not vary appreciably by major risk factors for breast cancer, including family history of breast cancer, history of benign breast disease, parity, use of postmenopausal hormones, body mass index, physical activity, or alcohol intake. However, α-carotene and β-carotene intakes were inversely related to the risk of ER–PR-breast cancer among the ever smokers but not among the never smokers (Table 3). Among the ever smokers, women in the highest quintile of α-carotene or β-carotene intake had a 68% and a 65% lower risk, respectively, of developing ER–PR-breast cancer compared with the women in the lowest quintile of intake. Among the never smokers, women in the highest four quintiles of lutein/zeaxanthin intake had lower risk of ER–PR-breast cancer compared with those in the lowest quintile.

Dietary α-carotene and β-carotene were inversely associated with overall breast cancer risk among women who did not use dietary supplements (Table 4). Tests for interaction with supplement use was statistically significant for α-carotene ($P = 0.01$) and β-carotene ($P = 0.03$). The inverse associations of α-carotene and β-carotene with the risk of breast cancer were somewhat stronger for ER+PR– and ER–PR– tumours than for ER+PR– tumours but a test for difference in the association among the subtypes was not statistically significant ($P = 0.28$ for α-carotene and $P = 0.14$ for β-carotene). Intakes of lutein/zeaxanthin, lycopene and β-cryptoxanthin were not associated with reduced risk of overall breast cancer

Table 1 – Age-standardised characteristics of 36,664 women in the Swedish Mammography Cohort by quintiles of dietary carotenoids in 1997.

Characteristic	α-Carotene		β-Carotene		β-Cryptoxanthin		Lutein and zeaxanthin		Lycopene	
	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5
Age (years)	60.8	63.8	61.7	63.0	65.4	60.4	62.2	63.6	67.2	58.1
Postsecondary education (%)	17.7	19.2	14.5	19.9	11.2	25.1	12.0	23.7	15.6	19.3
Family history of breast cancer (%)	9.4	9.0	9.2	8.9	8.4	8.6	9.0	8.9	8.5	8.8
History of benign breast disease (%)	12.9	12.3	13.1	12.2	12.6	13.0	12.7	12.9	12.1	12.6
Age at menarche (years)	13.2	13.1	13.2	13.1	13.2	13.2	13.2	13.1	13.2	13.1
Age at menopause (years)	50.9	51.0	50.8	51.0	50.8	51.2	50.7	51.2	50.8	51.1
Age at first birth (years)[a]	24.3	24.2	24.1	24.1	23.7	24.6	23.8	24.3	23.8	24.3
Nulliparous (%)	10.4	11.2	10.6	10.3	12.2	9.2	11.6	10.0	13.0	8.2
Oral contraceptive use (%)	58.9	56.6	57.8	56.7	54.9	59.2	56.2	57.2	55.3	59.0
Postmenopausal hormone use (%)	50.9	50.9	48.7	51.4	47.9	52.9	47.1	53.7	48.7	51.7
Body mass index (kg/m^2)	24.9	25.1	25.0	25.2	25.2	24.8	25.1	25.1	24.9	25.3
Total physical activity (MET h/d)	41.7	42.8	41.9	42.9	42.7	42.3	42.2	42.8	42.8	42.2
Current smoker (%)	28.3	19.9	28.9	20.6	28.5	21.5	29.8	21.2	27.1	23.0
Multivitamin use (%)	22.2	26.3	21.4	26.2	20.6	27.2	20.9	26.2	22.4	23.4
Total energy intake (kcal/d)	1660	1630	1728	1672	1796	1613	1742	1681	1816	1534
Alcohol intake (g/d)	4.5	3.5	4.0	3.6	3.3	4.6	3.5	4.1	3.6	4.2

Q = quintile; MET = metabolic equivalent.
a Among parous women.

Table 2 – Multivariable relative risks[a] for the association between dietary carotenoids and breast cancer, overall and by hormone-receptor status, among 36,664 women in the Swedish Mammography Cohort, 1998–2007.

Carotenoid intake (μg/d)	Total breast cancer		ER+PR+ tumours		ER+PR− tumours		ER−PR− tumours	
	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
α-Carotene								
<318	212	1.00	110	1.00	62	1.00	28	1.00
318–592	219	1.03 (0.85–1.25)	110	1.02 (0.78–1.34)	54	0.87 (0.60–1.26)	24	0.77 (0.44–1.35)
593–1026	194	0.92 (0.76–1.12)	116	1.05 (0.81–1.37)	38	0.62 (0.41–0.93)	25	0.87 (0.51–1.50)
1027–1649	201	0.95 (0.78–1.16)	123	1.13 (0.87–1.47)	47	0.76 (0.52–1.12)	13	0.39 (0.20–0.76)
⩾1650	182	0.86 (0.71–1.06)	103	0.94 (0.71–1.24)	43	0.72 (0.49–1.08)	20	0.61 (0.34–1.10)
P_{trend}		0.10		0.71		0.25		0.05
β-Carotene								
<1774	211	1.00	114	1.00	52	1.00	31	1.00
1774–2516	202	0.92 (0.76–1.12)	104	0.88 (0.67–1.15)	58	1.04 (0.70–1.50)	19	0.62 (0.35–1.11)
2517–3445	206	0.96 (0.79–1.16)	116	1.00 (0.77–1.30)	46	0.84 (0.56–1.25)	20	0.63 (0.36–1.12)
3446–4782	202	0.91 (0.75–1.11)	119	1.00 (0.77–1.31)	46	0.79 (0.53–1.19)	21	0.64 (0.36–1.13)
⩾4783	187	0.87 (0.71–1.06)	109	0.93 (0.71–1.22)	42	0.79 (0.52–1.19)	19	0.57 (0.31–1.02)
P_{trend}		0.20		0.90		0.12		0.11
β-Cryptoxanthin								
<80	183	1.00	110	1.00	36	1.00	23	1.00
80–180	209	1.10 (0.90–1.35)	124	1.11 (0.85–1.43)	53	1.30 (0.84–2.00)	17	0.74 (0.39–1.41)
181–317	189	0.97 (0.79–1.19)	99	0.86 (0.65–1.14)	46	1.07 (0.68–1.68)	24	1.12 (0.62–2.02)
318–591	224	1.13 (0.92–1.39)	119	1.03 (0.78–1.34)	57	1.29 (0.84–1.99)	27	1.19 (0.66–2.13)
⩾592	203	1.02 (0.82–1.26)	110	0.95 (0.72–1.26)	52	1.12 (0.72–1.76)	19	0.90 (0.47–1.71)
P_{trend}		0.99		0.65		0.95		0.87
Lutein and zeaxanthin								
<1422	206	1.00	114	1.00	45	1.00	32	1.00
1422–1901	203	0.96 (0.79–1.17)	116	1.00 (0.77–1.29)	49	0.99 (0.64–1.47)	21	0.79 (0.46–1.37)
1902–2410	196	0.90 (0.74–1.10)	102	0.86 (0.65–1.13)	57	1.10 (0.74–1.64)	19	0.64 (0.36–1.14)
2411–3159	197	0.87 (0.71–1.16)	109	0.90 (0.68–1.17)	48	0.87 (0.57–1.33)	16	0.50 (0.27–0.93)
⩾3160	206	0.95 (0.78–1.16)	121	1.02 (0.78–1.33)	45	0.86 (0.56–1.32)	20	0.63 (0.35–1.13)
P_{trend}		0.56		0.94		0.35		0.07
Lycopene								
<1061	184	1.00	96	1.00	49	1.00	24	1.00
1061–1658	201	1.01 (0.82–1.24)	125	1.22 (0.94–1.62)	37	0.65 (0.42–1.02)	24	0.92 (0.52–1.68)
1659–2228	208	1.03 (0.84–1.27)	111	1.07 (0.81–1.42)	50	0.85 (0.56–1.28)	21	0.85 (0.46–1.56)
2229–2972	231	1.15 (0.94–1.41)	135	1.34 (1.02–1.78)	52	0.83 (0.55–1.26)	24	1.03 (0.57–1.88)
⩾2973	184	0.91 (0.73–1.14)	95	0.93 (0.68–1.26)	56	0.88 (0.57–1.34)	17	0.79 (0.41–1.55)
P_{trend}		0.66		0.59		0.96		0.62

a Adjusted for age, education, family history of breast cancer, history of benign breast disease, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, body mass index, physical activity, smoking, multivitamin use, total energy intake, and alcohol intake.

(Table 4) among non-users of supplements. There was no association between any of the carotenoids and breast cancer risk among women who used supplements (data not shown).

Consumption of carrots, the predominant source of dietary α-carotene and β-carotene, was not associated with breast cancer risk. The multivariable RRs of breast cancer for women who consumed carrots one or more times per day compared with those who consumed carrots 1–2 times per week or less were 0.88 (95% CI: 0.70–1.12; P_{trend} = 0.30).

4. Discussion

In this population-based prospective cohort, we observed no overall association between dietary carotenoids and breast cancer risk. However, dietary α-carotene and β-carotene were inversely associated with the risk of ER–PR– tumours among smokers and with overall breast cancer risk among women who did not use dietary supplements.

An interaction between carotenoids and supplement use in relation to breast cancer risk is plausible. If the potential protective effect of α-carotene and β-carotene against breast cancer is mediated through their antioxidant properties, an association may be stronger or limited to women who do not obtain other antioxidants from dietary supplements. A protective effect of carotenoids may also be more pronounced among smokers because tobacco smoke induces oxidative stress. In our study, dietary α-carotene and β-carotene were significantly inversely associated with the risk of ER–PR– tumours among smokers but not among the never smokers. Our findings are consistent with those of two previous prospective studies in which dietary α-carotene and β-carotene appeared to confer the greatest protection against breast cancer among smokers.[6,10] Given the large number of subgroup analyses in the present study, we cannot exclude the possibility that the results observed among non-users of supplements and smokers are due to chance.

Table 3 – Multivariable relative risks[a] for the association between dietary carotenoids and breast cancer by hormone-receptor status stratified by smoking status among women in the Swedish Mammography Cohort, 1998–2007.

Carotenoid intake (μg/d)	ER+PR+ tumours[b]		ER+PR− tumours[b]		ER−PR− tumours[b]	
	Never (288 cases)	Ever (268 cases)	Never (118 cases)	Ever (125 cases)	Never (63 cases)	Ever (46 cases)
α-Carotene						
<318	1.00	1.00	1.00	1.00	1.00	1.00
318–592	1.19 (0.80–1.76)	0.85 (0.57–1.25)	0.97 (0.55–1.71)	0.73 (0.43–1.22)	0.72 (0.30–1.72)	0.74 (0.33–1.67)
593–1026	0.98 (0.65–1.47)	1.14 (0.80–1.63)	0.70 (0.38–1.29)	0.49 (0.27–0.86)	1.31 (0.60–2.83)	0.57 (0.23–1.39)
1027–1649	1.21 (0.82–1.78)	1.01 (0.69–1.48)	0.88 (0.49–1.55)	0.60 (0.34–1.06)	0.48 (0.19–1.20)	0.26 (0.08–0.82)
⩾1650	0.94 (0.63–1.41)	0.89 (0.60–1.33)	0.66 (0.36–1.23)	0.81 (0.48–1.39)	0.84 (0.37–1.91)	0.32 (0.11–0.94)
P_{trend}	0.63	0.71	0.22	0.63	0.47	0.01
β-Carotene						
<1774	1.00	1.00	1.00	1.00	1.00	1.00
1774–2516	0.84 (0.57–1.24)	0.87 (0.60–1.28)	0.90 (0.50–1.59)	1.15 (0.68–1.93)	0.57 (0.23–1.41)	0.61 (0.26–1.42)
2517–3445	1.08 (0.74–1.58)	0.95 (0.65–1.38)	0.80 (0.44–1.44)	0.80 (0.45–1.43)	0.80 (0.36–1.78)	0.51 (0.20–1.29)
3446–4782	1.05 (0.73–1.53)	0.87 (0.59–1.28)	0.91 (0.52–1.58)	0.62 (0.33–1.16)	0.84 (0.38–1.85)	0.45 (0.18–1.14)
⩾4783	0.86 (0.58–1.27)	0.95 (0.65–1.40)	0.56 (0.29–1.06)	1.07 (0.61–1.87)	0.66 (0.29–1.50)	0.35 (0.12–0.99)
P_{trend}	0.71	0.89	0.10	0.71	0.58	0.03
β-Cryptoxanthin						
<80	1.00	1.00	1.00	1.00	1.00	1.00
80–180	1.37 (0.96–1.97)	0.92 (0.61–1.38)	1.57 (0.82–3.00)	1.04 (0.57–1.89)	0.64 (0.28–1.44)	1.09 (0.32–3.74)
181–317	0.86 (0.57–1.28)	0.93 (0.62–1.40)	1.34 (0.69–2.59)	0.80 (0.42–1.52)	0.74 (0.34–1.63)	1.87 (0.62–5.61)
318–591	1.07 (0.72–1.57)	1.07 (0.72–1.58)	1.67 (0.88–3.19)	0.99 (0.54–1.81)	0.88 (0.41–1.89)	2.09 (0.71–6.22)
⩾592	0.94 (0.63–1.41)	1.02 (0.68–1.53)	1.04 (0.51–2.11)	1.03 (0.57–1.87)	0.54 (0.22–1.34)	1.78 (0.58–5.49)
P_{trend}	0.35	0.66	0.53	0.78	0.35	0.33
Lutein and zeaxanthin						
<1422	1.00	1.00	1.00	1.00	1.00	1.00
1422–1901	0.73 (0.50–1.06)	1.28 (0.88–1.85)	0.86 (0.47–1.58)	1.12 (0.63–1.99)	0.42 (0.19–0.96)	1.44 (0.60–3.46)
1902–2410	0.73 (0.50–1.07)	0.95 (0.64–1.42)	1.14 (0.64–2.00)	1.07 (0.60–1.93)	0.42 (0.19–0.96)	1.15 (0.46–2.91)
2411–3159	0.82 (0.56–1.18)	0.86 (0.57–1.29)	1.03 (0.58–1.82)	0.71 (0.37–1.36)	0.43 (0.21–0.94)	0.54 (0.18–1.67)
⩾3160	0.87 (0.61–1.26)	1.16 (0.78–1.71)	0.46 (0.23–0.92)	1.45 (0.82–2.57)	0.43 (0.20–0.92)	0.85 (0.31–2.33)
P_{trend}	0.90	0.98	0.06	0.33	0.03	0.34
Lycopene						
<1061	1.00	1.00	1.00	1.00	1.00	1.00
1061–1658	1.26 (0.87–1.81)	1.19 (0.77–1.82)	0.80 (0.43–1.49)	0.51 (0.27–0.97)	0.73 (0.35–1.56)	1.73 (0.59– 5.09)
1659–2228	0.84 (0.56–1.26)	1.35 (0.89–2.06)	0.94 (0.52–1.70)	0.77 (0.43–1.38)	0.65 (0.28–1.49)	1.28 (0.44–3.73)
2229–2972	1.47 (1.00–2.13)	1.24 (0.81–1.90)	1.22 (0.69–2.19)	0.52 (0.28–0.97)	0.90 (0.41–1.94)	1.45 (0.49–4.30)
⩾2973	0.90 (0.58–1.38)	0.94 (0.60–1.48)	1.06 (0.55–2.02)	0.71 (0.40–1.27)	0.43 (0.15–1.17)	1.41 (0.46–4.35)
P_{trend}	0.82	0.53	0.50	0.59	0.19	0.77

a Adjusted for age, education, family history of breast cancer, history of benign breast disease, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, body mass index, physical activity, smoking, total energy intake, and alcohol intake.

b Information on smoking status was missing for eight cases.

Only two studies have examined carotenoids in relation to breast cancer stratified jointly by ER and PR status.[5,11] In the Women's Health Initiative Observational Study of 84,805 postmenopausal women, dietary α-carotene and β-carotene were significantly inversely associated with the risk of ER+PR+ tumours only (highest versus lowest quintile: RR = 0.78; 95% CI: 0.66–0.94).[11] Other carotenoids were not significantly associated with any breast cancer subtype. In a population-based case-control study, β-carotene intake was inversely associated with ER+PR+ (high versus low intake: odds ratio (OR) = 0.76; 95% CI: 0.58–0.99), ER+PR− (OR = 0.71; 95% CI: 0.46–1.09) and ER−PR− (OR = 0.67; 95% CI: 0.44–1.02) tumours in postmenopausal women.[5] In that case-control study there were also inverse associations between dietary lutein and ER+PR+ tumours and between lycopene and ER−PR− tumours.[5] In our study, the inverse associations of α-carotene and β-carotene with the risk of breast cancer among the non-users of supplements were slightly stronger for ER+PR− tumours.

The strengths of this study include its prospective and population-based study design, the detailed dietary information, essentially complete follow-up of participants by linkage with various population-based Swedish registers, and information on hormone-receptor status of the tumour. A further strength was the ability to adjust for various factors that might potentially confound the association between dietary carotenoids and breast cancer risk.

A limitation of this study is that diet was assessed by using a self-administered food-frequency questionnaire. Measurement error in our assessment of carotenoid intake would most likely lead to attenuated relative risk estimates. Another limitation is the observational design. Although we controlled

Table 4 – Multivariable relative risks[a] for the association between dietary carotenoids and breast cancer, overall and by hormone-receptor status, among 14,393 women in the Swedish Mammography Cohort who do not use dietary supplements, 1998–2007.

Carotenoid intake (μg/d)	Total breast cancer		ER+PR+ tumours		ER+PR− tumours		ER−PR− tumours	
	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
α-Carotene								
<318	95	1.00	46	1.00	32	1.00	12	1.00
318–592	79	0.92 (0.67–1.24)	44	1.04 (0.68–1.60)	15	0.54 (0.28–1.04)	10	0.89 (0.36–2.23)
593–1026	67	0.79 (0.57–1.09)	38	0.94 (0.60–1.47)	13	0.43 (0.22–0.85)	9	0.73 (0.28–1.88)
1027–1649	66	0.86 (0.62–1.19)	40	1.01 (0.71–1.71)	17	0.62 (0.33–1.17)	5	0.32 (0.10–0.99)
⩾1650	49	0.63 (0.44–0.90)	27	0.72 (0.44–1.16)	10	0.35 (0.17–0.75)	7	0.53 (0.19–1.49)
P_{trend}		0.02		0.26		0.02		0.09
β-Carotene								
<1774	86	1.00	40	1.00	26	1.00	15	1.00
1774–2516	90	1.08 (0.80–1.47)	52	1.39 (0.81–2.14)	24	0.90 (0.50–1.63)	9	0.61 (0.25–1.51)
2517–3445	67	0.86 (0.62–1.19)	37	1.03 (0.64–1.63)	13	0.56 (0.28–1.12)	5	0.28 (0.10–0.85)
3446–4782	65	0.91 (0.65–1.27)	39	1.26 (0.79–1.99)	14	0.58 (0.29–1.16)	8	0.48 (0.18–1.25)
⩾4783	48	0.65 (0.45–0.95)	27	0.84 (0.50–1.40)	10	0.39 (0.18–0.84)	6	0.34 (0.12–1.96)
P_{trend}		0.01		0.32		0.01		0.05
β-Cryptoxanthin								
<80	66	1.00	40	1.00	14	1.00	8	1.00
80–180	74	1.11 (0.79–1.57)	43	1.11 (0.71–1.74)	20	1.47 (0.70–3.07)	7	0.92 (0.31–2.70)
181–317	68	1.00 (0.70–1.44)	34	0.83 (0.51–1.35)	20	1.29 (0.61–2.71)	11	1.46 (0.53–4.04)
318–591	83	1.24 (0.88–1.74)	48	1.23 (0.79–1.93)	16	1.15 (0.53–2.50)	9	1.18 (0.40–3.44)
⩾592	65	1.02 (0.71–1.48)	30	0.80 (0.48–1.33)	17	1.23 (0.57–2.67)	8	1.19 (0.41–3.45)
P_{trend}		0.94		0.43		0.63		0.78
Lutein and zeaxanthin								
<1422	81	1.00	42	1.00	20	1.00	15	1.00
1422–1901	81	1.02 (0.74–1.40)	41	1.03 (0.61–1.62)	21	0.96 (0.50–1.83)	12	0.71 (0.31–1.64)
1902–2410	64	0.81 (0.57–1.14)	34	0.90 (0.56–1.44)	16	0.78 (0.38–1.58)	7	0.39 (0.15–1.04)
2411–3159	68	0.94 (0.67–1.31)	42	1.27 (0.81–2.00)	15	0.71 (0.34–1.45)	3	0.18 (0.05–0.64)
⩾3160	62	0.87 (0.62–1.23)	36	1.03 (0.65–1.65)	15	0.73 (0.35–1.53)	6	0.36 (0.12–1.03)
P_{trend}		0.41		0.67		0.31		0.02
Lycopene								
<1061	64	1.00	28	1.00	20	1.00	10	1.00
1061–1658	74	0.97 (0.69–1.38)	42	1.28 (0.78–2.11)	17	0.63 (0.31–1.25)	9	0.70 (0.26–1.93)
1659–2228	84	1.13 (0.80–1.59)	49	1.55 (0.95–2.53)	19	0.63 (0.31–1.25)	8	0.51 (0.17–1.50)
2229–2972	80	1.01 (0.71–1.44)	49	1.47 (0.89–2.42)	14	0.52 (0.25–1.11)	11	0.75 (0.28–2.04)
⩾2973	54	0.67 (0.46–1.01)	27	0.77 (0.43–1.36)	17	0.53 (0.25–1.12)	5	0.43 (0.13–1.47)
P_{trend}		0.05		0.28		0.12		0.26

a Adjusted for age, education, family history of breast cancer, history of benign breast disease, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, body mass index, physical activity, smoking, total energy intake, and alcohol intake.

for known breast cancer risk factors, we cannot rule out the possibility that our findings may be due to residual or uncontrolled confounding. Carrots are the principal source of α-carotene and β-carotene and it might be some other factor in carrots that is responsible for the inverse association in this study. Finally, we had limited statistical power in the analyses of breast cancer subtypes, especially in the subgroup analyses.

In summary, findings from this prospective study do not support an overall association between dietary carotenoids and breast cancer risk but suggest that high intakes of α-carotene and β-carotene may be protective among women who do not use dietary supplements and among smokers. Further studies are needed to clarify whether carotenoids confer more protection among non-users of supplements and smokers, and whether the association varies by hormone-receptor status.

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Conflict of interest statement

None declared.

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