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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