James Allen Olson Memorial Lecture

Carotenoids and Breast Cancer

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Key messages

- Carotenoids are hypothesized to have an anticarcinogenic role, via immunoenhancement, antioxidant action, and/or their influence on cellular differentiation; they have been shown to inhibit tumor progression *in vitro*, in breast cancer cells.
- Epidemiological studies thus far have generally observed inverse associations between circulating carotenoid concentrations and breast cancer risk, though significant carotenoids have varied between studies.
- A recent pooled analysis of eight previously published studies found significant inverse associations between quintile of circulating carotenoid concentration and breast cancer risk for α-carotene, β-carotene, lutein and zeaxanthin, lycopene, and total carotenoids.
- Carotenoids appear to reduce risk of recurrent and lethal breast cancers, highlighting a potential role for dietary intervention to reduce the burden of disease.

Carotenoids and cancer

Carotenoids are a group of over 600 fat-soluble plant pigments ranging in color from yellow to red that are essential for plant photosynthesis.[1] In humans, they serve as key micronutrients in development and disease prevention.[1] Just six represent 90% of carotenoids found in circulation,[2,3] all of which can be obtained from the diet: α-carotene (carrots), β-carotene (sweet potatoes and leafy greens), lutein and zeaxanthin (leafy greens), lycopene (tomatoes), and β-cryptoxanthin (citrus fruits). Given the prominent role of oxidative stress and damage in carcinogenesis,[4] the antioxidant properties of carotenoids are thought to lend them an anticarcinogenic role.[5] Further, the provitamin A carotenoids, α- and β-carotene, and β-cryptoxanthin, may protect against carcinogenesis through their metabolism to retinoids, which regulate cell growth, differentiation, and apoptosis.[6] Immune surveillance is also enhanced through carotenoid action, potentially improving cellular responses to block tumorigenesis.[7,8] Driven by biological plausibility, studies have investigated the role of carotenoids in various cancers, most often including lung,[9] colorectal,[10] prostate,[11] and breast cancers.[12]

Risk factors for breast cancer – why carotenoids?

Breast cancer is the most common cancer among women worldwide.[13] Major identified risk factors for breast cancer are either not modifiable or else not favorably modifiable, including age, menopausal status, family history, parity, age at first menstruation, and age at first birth. However, studies of offspring of immigrants who move from areas with low rates of breast cancer, such as China, to areas with higher rates of breast cancer, such as the United States, found that they acquired breast cancer at similar rates to the population of the new country, indicating additional lifestyle risk factors in this disease.[14] Modest harmful associations have been noted between breast cancer and alcohol consumption,[15] smoking,[16] and high body mass index (BMI).[17] High fruit and vegetable consumption has been suggested to reduce

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the risk of developing breast cancer,[18,19] and it is hypothesized that carotenoids are responsible for this protection. In fact, early studies using human breast cancer cells in culture demonstrated the ability of carotenoids, including β-carotene and lycopene, to inhibit tumor progression and reduce proliferation in breast cancer cells.[20]

"Although many risk factors for breast cancer are not modifiable, carotenoid consumption is one modifiable lifestyle factor that may reduce risk of breast cancer"

Epidemiologic evidence for carotenoids as protective agents in breast cancer

Measurement of circulating carotenoids via serum or plasma provides the most accurate way to explore carotenoids as an exposure in studies of disease. This method resolves flaws of dietary data including recall errors,[3] seasonal food variation, altered bioavailability based on cooking methods,[21] and inability of diet records to capture individual differences in nutrient absorption.

Consistent with the reported risk reduction from fruit and vegetable intake uncovered via dietary data, most prospective studies evaluating the association between circulating levels of carotenoids and subsequent breast cancer observed inverse associations between at least one of the primary carotenoids and breast cancer, though specific carotenoids differ.[22–31] While demographics may account for some differences found between cohorts, nested case-control studies conducted within demographically similar cohorts have also found inconsistent results. For example, a study of 969 women with breast cancer and matched controls, drawn from the Nurses' Health Study (NHS), a large prospective cohort primarily composed of Caucasian women, reported a 25–35% decreased risk of breast cancer when comparing the highest to lowest quintiles of α- and β-carotene, lutein/zeaxanthin, and total carotenoids, but no change in risk with increasing quintile of β-cryptoxanthin concentration.[26] In contrast, a study conducted in the New York University Women's Health Study (NYUWHS), a similar cohort of primarily Caucasian women living in New York, reported a non-null, inverse association for β-cryptoxanthin, with a 40% decreased risk comparing high to low quintiles of concentration.[24] Yet another study of Caucasian women living in Missouri found a significant inverse association for lycopene, but null associations for α- and β-carotene, in conflict with observations of NYUWHS and NHS.[22]

To resolve inconsistencies between studies, data from eight previously published nested case-control studies, all with carotenoids measured before disease onset, were combined in a pooled analysis. Evidence of potential measurement error based on inexplicably large variations in carotenoid levels among demographically similar cohorts led to standardization of all laboratory-obtained carotenoid samples following re-assay and recalibration of plasma or serum samples.

Combining the evidence: pooled study results

In total, 3,055 women with breast cancer diagnosed after blood collection, and 3,956 matched controls, between the ages of 51 and 66 years, were included in the analysis, from eight prospective studies: Columbia, Missouri;[22] Umea, Sweden;[23] New York University Women's Health Study (NYUWHS), New York, NY;[24] CLUE I and CLUE II, Washington County, Maryland;[25] Nurses' Health Study (NHS), United States;[26] Women's Health Study (WHS), United States;[27] Shanghai Women's Health Study (SWHS), Shanghai, China;[28] and Multiethnic Cohort Study (MEC), California and Hawaii.[29] To ensure accurate comparisons, the pooled analysis was adjusted for established breast cancer risk factors: menopausal status, age at menarche, parity, age at first birth, exogenous hormone use, BMI, current smoking status, race, personal history of benign breast disease, and family history of breast cancer.[32]

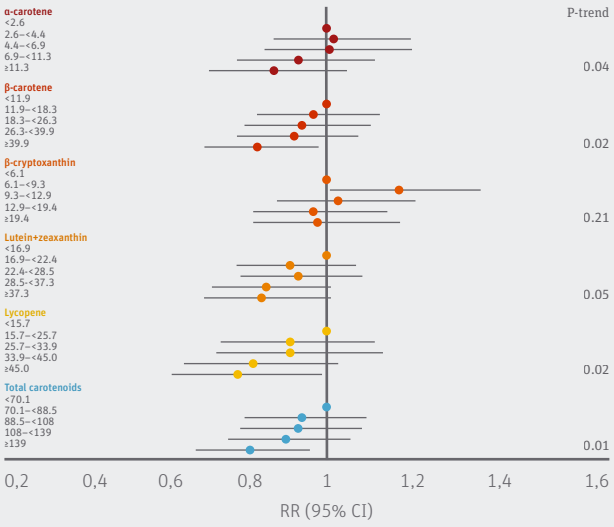
Comparing the highest quintile to the lowest quintile of carotenoid concentration, significant inverse associations were observed for α-carotene (RR=0.87, 95% CI=0.71 to 1.05), β-carotene (RR=0.83, 95% CI: 0.70 to 0.98), lycopene (RR = 0.78, 95% CI = 0.62 to 0.99), and total carotenoids (RR = 0.81, 95% CI = 0.68 to 0.96) (**Figure 1**). Trends in the association were significant when moving across the concentration continuum from the first to last quintile for each carotenoid, with the exception of β-cryptoxanthin. These results agree with inverse associations, either significant or suggestive, reported in studies published after this pooled analysis.[30–31, 33–34]

"Most prospective studies observed inverse associations between at least one of the primary carotenoids and breast cancer risk"

Disease heterogeneity and risk assessment

Breast cancer is a heterogeneous disease, often described by five primary tumor molecular subtypes.[35] Because each subtype of breast cancer acts uniquely in disease initiation and progression,[35] it is best to evaluate exposure-outcome relationships

FIGURE 1: Relative risk of breast cancer according to quintile of plasma carotenoids (µg/dL)



Lines indicate 95% confidence intervals. P-trend tests significance of increasing quintiles.

within tumor subtypes, though it is not always possible to do so based on rarity of certain subtypes. For simplification purposes, tumors are categorized as either estrogen receptor positive (ER+) or estrogen receptor negative (ER-). Breast cancers that are ER- typically occur in younger women and have a poorer prognosis than ER+ breast cancers,[36] in part due to the inability to treat these subtypes with hormonal therapies.

Following stratification by ER expression, the inverse associations between circulating carotenoid levels and breast cancer observed in the pooled analysis appeared much stronger for ER- versus ER+ breast cancers. For example, the relative risk comparing the highest quintile with the lowest quintile of β-carotene was 0.52 (95% CI = 0.36 to 0.77, p-trend = 0.001) for ER- breast cancers. The same comparison was only suggestive of an inverse association in ER+ breast cancers (RR=0.83, 95% CI=0.66 to 1.04, p-trend=0.06).[32] A large analysis of 1,502 breast cancer cases and matched controls within the European Prospective Investigation into Cancer and Nutrition cohort similarly found that carotenoids were associated with ER- but not ER+ breast cancers.[34] It is possible that carotenoids are protective in both subtypes, though because other hormonal risk factors play a stronger role in determining risk of ER+ versus ER- breast cancer,[37] the additional reduction in risk from carotenoid intake is simply too small to detect in the ER+ subtypes.

Interaction with other lifestyle factors

Women with higher levels of oxidative stress are hypothesized to benefit more from higher carotenoid intake due to the antioxidant properties of carotenoids. Investigation of common lifestyle risk factors that induce oxidative stress, including alcohol consumption, smoking, and high BMI,[38,39] revealed modification of associations between carotenoid levels and breast cancer by smoking and BMI.[32] As expected, stronger inverse associations were seen among current smokers. In conflict with this hypothesis, women with higher BMI did not experience protection from increased carotenoid intake. Animal models have demonstrated the possibility that carotenoids act as pro-oxidants if in very high concentrations, which may account for this contradictory result in women with high BMI, as carotenoids are stored in adipose tissue.[40] However, the validity of this theory has not been investigated, leaving the influence of BMI in the carotenoid–breast cancer association unclear.

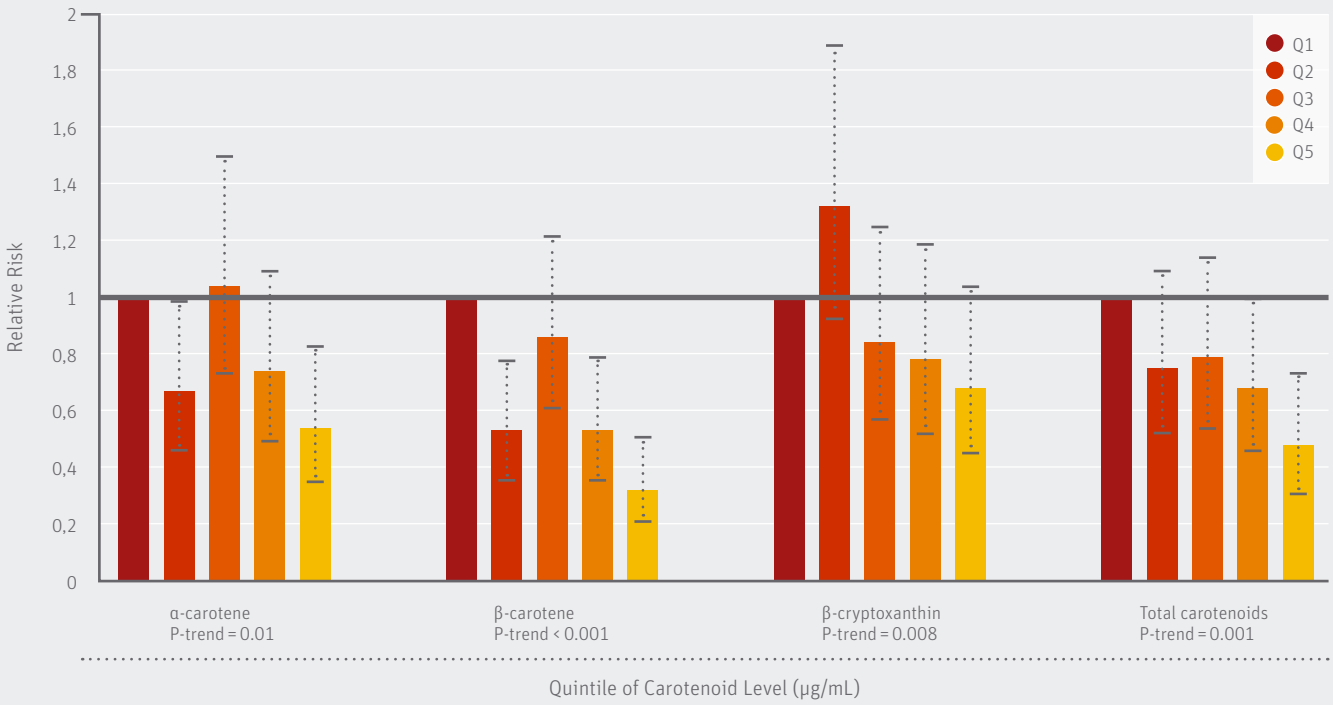
Exploring mechanistic action: gene scores and exposure timing

Use of a genetic marker as a measure for exposure is advantageous in epidemiologic analyses to (a) avoid the potential of unmeasured factors mixing with and altering the exposure-outcome relationship, and/or (b) parse apart the biological mechanism responsible for an observed association. The enzyme β-carotene 15,15'-monooxygenase, BCMO1, cleaves provitamin A carotenoids as a first step in vitamin A production.[41,42] Because single nucleotide polymorphisms (SNPs) in this gene are responsible for poor conversion of carotenoids to retinol, gene scores can predict carotenoid levels based on the presence or absence of such SNPs. This technique was applied to 9,226 breast cancer cases and 10,420 controls within the National Cancer Institute's Breast and Prostate Cancer Cohort Consortium (BPC3). Five weighted gene scores were created for separate carotenoids, based on SNPs with confirmed associations with circulating carotenoid levels, rs12934922 and rs654851.[43,44]

Despite the ability of the gene score to predict carotenoid levels, there was no association between quintile of gene score and breast cancer risk in BPC3.[44] While this null finding does not clarify mechanistic action of carotenoids, it also does not disprove the primary hypothesis. The distribution of carotenoid levels by proxy of genetic scores was limited compared with the much wider distribution of directly measured serum or plasma carotenoids, which may inhibit the ability of the genetic score to capture the relatively modest association seen among studies using plasma carotenoids.

Menopausal status at the time of carotenoid measurement can also reveal details about the timing of exposure. Among cases and controls who were premenopausal at blood collection, from the Nurses' Health Studies, no clear associations between carotenoid levels and breast cancer risk were observed.[47] However, there were significant or suggestive inverse associations between lycopene, α-carotene and total carotenoids, measured

FIGURE 2: Relative risk of lethal or recurrent breast cancer by quintile of plasma carotenoid. Bars represent 95% CIs.



prior to menopause, and breast cancer diagnosed after menopause. This may support the notion that carotenoids are more influential in the early stages of breast cancer given the time difference between premenopausal collection and postmenopausal diagnosis; on the other hand, more nuanced hormonal interactions with carotenoid intake may be responsible for this influence on postmenopausal, but not premenopausal, breast cancer risk.

Carotenoids reduce risk of aggressive and deadly disease

Improved survival due to advancements in screening and surgical treatments, alongside continued high prevalence of disease, emphasizes a need to examine how to improve breast cancer outcomes, including recurrence and death. In an extended analysis in the Nurses' Health Study, carotenoids appeared to protect against these adverse outcomes. Inverse associations were stronger when evaluating pre-diagnostic carotenoid levels with respect to risk of lethal or recurrent breast cancer, than those observed for risk of non-lethal breast cancer.[47] For example, β-carotene levels corresponding with the highest quintile resulted in a 68% reduction in the risk of lethal or recurrent breast cancer, compared with levels corresponding with lowest quintile (RR=0.32, 95% CI: 0.21, 0.51, p-trend=0.001). The inverse trend for risk of lethal or recurrent breast cancer by quintile of intake was also significant for α-carotene (RR=0.61, 95% CI=0.40, 0.93, p-trend=0.04), β-cryptoxanthin (RR=0.68, 95% CI=0.45, 1.04, p-trend=0.008), and total carotenoids (RR=0.48, 95% CI=0.31, 0.73, p-trend=0.001) (**Figure 2**). In addition to these analyses, which were based on pre-diagnostic carotenoid levels, other studies have reported lower risk of recurrence and death among women with higher carotenoid levels at the time of diagnosis and after diagnosis,[48,49] suggesting a role for carotenoids in prognostic improvement as well.

> "Evidence points to a consistent inverse relationship between circulating carotenoids and risk of incident breast cancer"

Conclusion

Overall, current evidence points to a consistent inverse relationship between circulating carotenoids and risk of incident breast cancer, including aggressive and lethal tumors. While direct supplementation of carotenoids is not advocated given harmful effects of high-dose β-carotene supplementation, especially among smokers,[50] breast cancer risk reduction may be possible through dietary changes. Further studies are needed to

uncover intricacies behind the timing of carotenoid action and the distinct role of carotenoids in ER+ versus ER- breast cancers. Additionally, investigators should continue to explore carotenoids measured at diagnosis and after diagnosis, in relation to subsequent prognosis. Future research targeted in these areas will enable a better understanding of the mechanistic action of carotenoids in breast cancer initiation and development.

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