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Carotenoids and cervical, breast, ovarian, and colorectal cancer. Epidemiology and clinical trials*

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Abstract: Recent observational studies and clinical trials that have investigated the relationship between carotenoids (or diets rich in these compounds) and cervical, breast, ovarian, and colorectal cancer have increased knowledge in this area. Although epidemiological studies suggest a protective association, five randomized controlled trials testing the effect of beta-carotene supplementation on regression of cervical dysplasia, a preneoplastic lesion, did not find an effect on rate of regression. In the Women's Healthy Eating and Living (WHEL) Study, the effects of a high-vegetable carotenoid-rich diet on disease-free survival following treatment for breast cancer is being examined in a randomized multicenter diet intervention trial. Few epidemiological studies of dietary factors and risk for ovarian cancer have been conducted, with mixed results. Early case-control and cohort studies of colorectal cancer have generally suggested a protective effect of vegetable consumption, although a recent large cohort study did not confirm this relationship. In two randomized trials, beta-carotene supplementation was not observed to reduce risk of adenoma recurrence. The Polyp Prevention Trial (PPT), which tested the effect of prescribing increased fruit, vegetable, and fiber intake, and reduced dietary fat, revealed no effect of these efforts on adenoma recurrence in the intent to treat analysis. However, serum carotenoid concentrations were associated with decreased risk of recurrence in that study. To move this area of study forward, more research on mechanisms, surrogate biomarkers, and diet–gene interactions is needed.

Carotenoids exhibit several biological activities that could prevent or slow the progression of cancer, including the inhibition of growth and malignant transformation and the promotion of apoptosis in transformed cells [1]. Although initial interest in the link between carotenoids and cancer focused primarily on the antioxidant activities of these compounds, current evidence suggests that the primary mechanisms by which carotenoids influence carcinogenesis relate to cell growth regulation, similar to the effects of retinoids [2]. At this point in time, however, the specific mechanisms by which carotenoids reduce risk and progression of human cancers have not yet been firmly established or demonstrated.

Carcinogenesis is a multistage process that results from several genetic and epigenetic events, involving protooncogenes, tumor suppressor genes, and antimetastasis genes throughout progression [3]. The cancer continuum extends from the earliest cellular changes, to a preneoplastic lesion, to a malignant tumor, and finally, to metastasis. At various stages of the development and progression of

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cancer, carotenoids may influence this process. In general, the specific stages at which intervention involving the biological activities of carotenoids may be efficacious in human cancers is unknown. Nonetheless, a specific point in the cancer continuum is necessarily the focus in observational and analytic epidemiological studies and in clinical trials that test the relationship between carotenoids and cancer. For example, observational studies may examine the relationship between carotenoid status and the incidence of precursor lesions, or diagnosis of a clinical cancer, or cancer deaths. Among the intervention trials, most have tested whether a carotenoid supplement or carotenoid-rich diet intervention can reduce the recurrence or promote regression of a precursor lesion or reduce the incidence of cancer. Clinical trials targeting effects on cancer incidence typically involve high-risk groups, so that the number of end points needed to demonstrate an effect will be observed within a fundable span of time. Without knowledge of the specific mechanism or the point in the process at which carotenoids may exert a beneficial effect, the interpretation of the results of these epidemiological and clinical studies is constrained.

In the majority of the epidemiological studies that examine the relationship between carotenoids and cancer, self-reported dietary data are the focus. Even when the most well-developed instruments and methods are used, these data are subject to substantial error and have many limitations, and the food content data that are used to estimate carotenoid intakes are of very limited quality compared with data for most established micronutrients [4]. Vegetables and fruits are the major contributors of carotenoids in the diet, so intakes of these foods serve as a reasonable proxy for carotenoid intake, recognizing that other phytochemicals, micronutrients, and fiber are also provided by these foods, in addition to carotenoids. In fact, data on carotenoid intakes or tissue concentrations should not be assumed to represent a specific relationship between these compounds and cancer risk or progression in observational studies or in diet intervention trials. These levels of intake and tissue concentrations are also markers of vegetable and fruit intakes, and other constituents of these foods (or an overall dietary pattern) may be the more important influencing factors. This review of recent major epidemiological studies and clinical trials provides updated information on the relationship between carotenoids (or major food sources of these compounds) and the risk and progression of cervical, breast, ovarian, and colorectal cancer.

CAROTENOIDS AND CERVICAL CANCER

Cervical cancer is the second most common cancer for women worldwide. However, death rates from this cancer in women in developed countries are lower than many other common cancers due to the promotion and availability of screening procedures. Nonetheless, the human suffering and costs linked to concern with this cancer remain high even in developed countries, because for every case of invasive cervical cancer, there are an estimated 50 cases of abnormal cervical smears that require monitoring, follow-up, and often, ablative treatment procedures [5]. Invasive cervical cancer arises from a progression of epithelial cell changes across a continuum of lesions classified as cervical intraepithelial neoplasia (CIN) I, II, III, and carcinoma in situ, which are earlier stages of this disease. Human papilloma virus (HPV) is now recognized as the causal agent for cervical cancer and the precursor lesions, although a number of other factors, including dietary factors, are believed to be important determinants of whether the HPV virus persists, disrupts cellular function, and enables progression of disease in the exposed individual.

Evidence for an association between carotenoids and risk for cervical neoplasia or cancer is relatively consistent in the early observational epidemiological studies, although HPV status was not considered in these earlier studies. As reviewed in 1996 [6], dietary carotenoids were inversely associated with risk for cervical neoplasia in 5 of 10 case-control studies, serum carotenoids were inversely associated with risk in 4 of 5 studies, and serum carotenoids were found to be protective in one cohort study. Recent epidemiological studies, in which HPV status is considered in the assessment of risk, have found mixed results. Ho et al. [7] did not observe a significant relationship between plasma beta-carotene and risk for CIN in a large case-control study (378 cases, 366 controls), when adjusted for HPV status. In a

smaller case-control study (147 cases, 191 controls) in which plasma carotenoids were quantified, adjusted plasma cryptoxanthin concentration was inversely associated with risk for cervical dysplasia [odds ratio (OR) 0.3, 95 % confidence interval (CI) 0.1, 0.8 for highest vs. lowest quartiles] [8]. In a nested case-control study of dietary factors and risk for cytological abnormalities of the cervix in HPV-positive women (251 cases, 806 controls), a nonsignificant lower risk with higher dietary beta-carotene intake was observed [9]. A case-control study of Native American women (81 cases, 160 controls) revealed that increasing adjusted tertiles of serum alpha-carotene (OR 0.46, 95 % CI 0.21, 1.00), beta-cryptoxanthin (OR 0.39, 95 % CI 0.17, 0.91) and lutein (OR 0.40, 95 % CI 0.17, 0.95) were associated with increased risk of CIN.

Another approach in the examination of the relationship between carotenoid status and cervical cancer focuses on an earlier point in the cervix cancer continuum. The relationship between persistent HPV infection (rather than cytological abnormalities of the cervix) and serum carotenoids was examined in 123 low-income Hispanic women [10]. In this cohort, adjusted mean concentrations of serum beta-carotene, beta-cryptoxanthin, and lutein were on average 24 % lower ($p < 0.05$) among women who were HPV positive at two time points as compared with those who were HPV negative at both time points or positive at only one time point.

Based on the strength and consistency of the earlier observational studies, five randomized controlled trials testing whether beta-carotene supplements could increase the rate of regression of cervical dysplasia were initiated, and all have been completed [11–15]. As shown in Table 1, none of these studies found a beneficial effect compared with placebo.

Table 1 Randomized controlled trials of beta-carotene supplements and regression of CIN.

Investigators	No. of subjects	Targeted group	Amount of beta-carotene	Length of follow-up	Results
De Vet et al. 1991 [11]	278	CIN I, II, and III	10 mg/d	3 mos	Same response as placebo
Fairley et al. 1996 [12]	111	Atypia, HPV, CIN I, and II	30 mg/d	12 mos	Same response as placebo
Romney et al. 1997 [13]	69	CIN I, II, and III	30 mg/d	9 mos	Same response as placebo
Mackerras et al. 1999 [14]	141	Atypia, CIN I	30 mg/d ± 500 mg/d vitamin C	2 yrs	Same response as placebo
Keefe et al. 2001 [15]	103	CIN II and III	30 mg/d	2 yrs	Same response as placebo

A better test of the associations observed in epidemiological studies, in which the carotenoids that are consumed are from food rather than supplements, involves testing the effect of a carotenoid-rich diet, which would provide the various carotenoids in addition to other micronutrients (e.g., vitamin C, folate) [16]. This approach allows for additive effects of different protective dietary factors and potential synergy of biological interactions. In a clinical trial of this type, 149 women with cervical dysplasia (63 % CIN I, 37 % CIN II) were enrolled and randomized to the diet intervention arm or control arm and followed for one year. The diet intervention efforts resulted in a substantial increase in plasma carotenoid and peripheral tissue concentrations [16], with plasma concentrations of total carotenoids increasing nearly twofold in the intervention group. The overall regression rate to normal was 53 % based on cytological data and 48 % based on biopsy results, with no statistically significant difference in response rate observed across the two groups in the intent to treat analysis. Analysis of response after

adjustment for HPV status, identification of factors associated with regression of dysplasia in these women, and other secondary analysis procedures in that study are ongoing.

An important issue in the interpretation of clinical trials targeting women with CIN is that the stage at which carotenoids may influence the progression of cervical cancer is unknown. In vitro studies suggest that carotenoids can induce growth retardation in cervical dysplasia cell lines and apoptosis in HPV-infected cells [17]. However, a carotenoid-rich diet may have a more meaningful clinical effect earlier in the HPV exposure and infection process, and thus, the earlier part of the continuum may be a more appropriate target for intervention. Overall, most intervention studies conducted to date in this area have been constrained by limited statistical power. Screening, confirmation of histopathologic status, and the availability of ablative treatments substantially reduce the pool of subjects who are eligible and willing to participate in clinical trials. Also, the spontaneous regression rate for this condition typically falls in the range at which the number of subjects needed to detect a treatment effect is very high.

CAROTENOIDS AND BREAST CANCER

Breast cancer is the most common invasive cancer among women in developed countries. Evidence from cell culture studies is strongly suggestive of a specific beneficial effect of these compounds on the development and progression of breast cancer [1,18,19]. Several epidemiological studies have examined the association between dietary intake of carotenoids or the major food sources, vegetables and fruits, on risk for primary breast cancer. In the past few years, two large observational epidemiological studies have addressed this relationship using combined and pooled data. These two pooled analysis studies were based on previous observational studies with different study designs, and they produced somewhat divergent results. In a meta-analysis based on 26 studies (21 case-control and 5 cohort studies) published from 1982–1997, the relationships between risk for breast cancer and intakes of vegetables, fruit, beta-carotene, and vitamin C were examined [20]. High (vs. low) consumption of vegetables exhibited the strongest protective effect (relative risk [RR] 0.75, 95 % CI 0.66, 0.85 for higher vs. lower intakes), while the relationship with fruit consumption was not significant (RR 0.94, 95 % CI 0.74, 1.11 for higher vs. lower intakes). Data from 11 of these studies allowed analysis of beta-carotene intake, which was significantly inversely associated with risk (RR 0.82, 95 % CI 0.76, 0.91 for approximately >7000 vs. <1000 μg/day). In a pooled analysis of 7377 incident breast cancer cases from women enrolled in eight prospective cohort studies, the protective effect of total fruit and vegetable intake was found to be small and nonsignificant (RR 0.93, 95 % CI 0.86, 1.00 for highest vs. lowest quintiles) [21]. Differences in the designs of the studies used in the pooled analysis, and high variability in the instruments used to estimate intake, likely contribute to these inconsistent results.

Fewer studies have examined the relationship between tissue concentrations of carotenoids, an objective measure of carotenoid status and a marker of vegetable and fruit intake, and risk for breast cancer. In the most recent prospective cohort study that examined this relationship [22], the odds ratio for the lowest vs. highest quartile of total serum carotenoids was 2.31 (95 % CI 1.35, 3.96), with serum concentrations of beta-carotene (OR 2.21, 95 % CI 1.29, 3.79), alpha-carotene (OR 1.99, 95 % CI 1.18, 3.34), and lutein (OR 2.08, 95 % CI 1.11, 3.90) inversely associated with risk.

An area of current interest is the effect of carotenoids or their major food sources, vegetables and fruits, on overall survival following the diagnosis of breast cancer. Earlier diagnosis and improvements in initial treatments have resulted in an increasing number of women in the population who are breast cancer survivors and are at risk for breast cancer recurrence or second primary cancers. The relationship between overall survival or recurrence and diet composition has been examined in 13 studies involving cohorts of women who had been diagnosed with breast cancer. Of the eight studies that examined associations between vegetable intake (or nutrients provided by vegetables and fruits, such as carotenoids and vitamin C), three found a significant inverse association with risk of death, one found a trend for an association, and one found a significant inverse association in women with node negative disease, who comprised 62 % of that cohort (but not in the total group that included all stages of inva-

sive breast cancer) [23]. In the studies that found an inverse relationship with survival and intakes of vegetables, fruit, and associated nutrients (beta-carotene, vitamin C), the magnitude of the protective effect was a 20–90 % reduction in risk for death.

Two large multicenter randomized controlled trials are currently testing the effect of diet modification on survival following the diagnosis of breast cancer, and one of them, the WHEL Study, specifically aims to increase intake of phytochemical- and micronutrient-rich vegetables and fruits in the intervention arm.

In the WHEL Study, plasma carotenoid concentrations are the primary dietary biomarkers of vegetable and fruit intake used in the study. Also, a specific effect of carotenoids on mammary cellular function and carcinogenesis, based on evidence from in vitro studies, is one of several possible mechanisms hypothesized as the rationale for proposed beneficial effects of the intervention. The WHEL Study participants are 3109 women who have been diagnosed with Stage I (40 %), Stage II (55 %), or Stage IIIA (5 %) invasive breast cancer and who were randomized into an intervention group or comparison group, following completion of initial therapies and within 48 months of diagnosis [24]. The primary emphasis of the WHEL Study diet intervention is on increased vegetable and fruit intake, with daily dietary goals of five vegetable servings, 16 ounces of vegetable juice, three fruit servings, 15–20 % energy from fat, and 30 g dietary fiber. Feasibility study reports and preliminary trial data from this study indicate excellent adherence [25–27]. Plasma carotenoids are being quantified in serial blood samples from selected subsets and a representative sample of the total study population. At 30 months, geometric means in the 12 % representative random sample indicate that plasma alpha-carotene is increased by 126 %, beta-carotene is increased by 63 %, and lutein is increased by 24 % in the intervention group. The WHEL Study has 80 % power to detect an 18 % difference in event rates within an average of 8 years follow-up, and study end is expected after 2005.

CAROTENOIDS AND OVARIAN CANCER

Ovarian cancer is the fifth most common cancer in U.S. women, but is the fourth most common cause of cancer death in this group, because it is an aggressive cancer. Compared with the number of studies that have examined the associations between dietary factors and risk for cervical or breast cancer, relatively few epidemiological studies have addressed these associations in ovarian cancer. Of the case-control studies in which the relationships between dietary intakes and risk for ovarian cancer have been examined, six studies found protective effects of vegetable and fruit intake [28–33] and four studies found protective effects of carotenoid intake [29,34–36].

The most recent case-control study (549 cases, 516 controls) that examined the relationship between risk for ovarian cancer and dietary carotenoid intakes was a population-based study in which intakes of the individual carotenoids were estimated [36]. Adjusted total "carotene" intake was significantly inversely related to risk (OR 0.55, 95 % CI 0.36, 0.84 for highest vs. lowest quintile). Among the individual dietary carotenoids examined, intakes of alpha-carotene (OR 0.60, 95 % CI 0.39, 0.90), beta-carotene (OR 0.58, 95 % CI 0.38, 0.89), and lycopene (OR 0.53, 95 % CI 0.35, 0.82) exhibited significant inverse relationships with risk.

To date, the relationship between serum carotenoids and ovarian cancer risk has been examined in only one very small prospective study [37]. In that study, serum micronutrients from 35 women who had been diagnosed with ovarian cancer over a 14-year period were compared with values from 67 control subjects from the cohort. Serum carotenoids were not associated with risk. No significant relationships between risk for ovarian cancer and adult dietary intakes of beta-carotene and fruits and vegetables were found in a recent large cohort study [38], although adolescent intake of vegetables and fruits was found to be protective [RR 0.54, 95 % CI 0.29, 1.03 ($p = 0.04$ for linear trend) for women who consumed ≥2.5 servings/day vs. lower intakes]. No clinical trials have tested whether carotenoid supplementation or dietary modification can influence the risk and progression of ovarian cancer.

CAROTENOIDS AND COLORECTAL CANCER

Colon cancer is the third most common cancer in men and women and also the third most common cause of cancer death in developed countries. Similar to cervical cancer, colon and rectal cancers have a well-established and defined continuum of cellular changes and associated lesions that appear to occur in the stepwise process of developing an invasive tumor. Adenomatous polyps are considered the precursors of most large bowel cancers, and the major clinical trials that tested the effect of dietary factors on the development and progression of colon cancer have focused on this point in the continuum, with the outcome being recurrent polyps. However, most adenomas do not develop into colon carcinomas, and the point at which the most important and modifiable molecular changes occur is not well established.

As previously reviewed [39,40], the majority of the case-control studies that have examined the association between dietary carotenoids or their major food sources (vegetables and fruits) and the risk for colon cancer found intakes of carotenoids, vegetables, and fruits to be associated with reduced risk. The majority of studies based on prediagnosis serum carotenoid concentrations also found this relationship. However, a recent prospective study of the relationship between vegetable and fruit intake and incidence of colon and rectal cancers did not find a protective effect [41]. In the largest and most recent case-control study (1993 cases, 2410 controls) that examined the relationship between dietary carotenoids and risk for colon cancer, dietary intakes of the individual carotenoids were estimated [42]. In that study, lutein was inversely associated with colon cancer in both men and women [OR 0.83, 95 % CI 0.66, 1.04 ($p = 0.04$ for linear trend) for upper quintile relative to lowest quintile], while associations with the other carotenoids were not significant.

Two randomized controlled trials have tested the effect of beta-carotene supplementation on the risk for recurrence of polyps in individuals with a history of adenomatous polyps [43,44], as summarized in Table 2. A beneficial effect of beta-carotene was not observed in either of these trials.

Table 2 Randomized controlled trials of beta-carotene supplements and recurrence of colorectal adenomatous polpys.

Investigators	No. of subjects	Targeted group	Amount of beta-carotene	Length of follow-up	Results
Greenberg et al. 1994 [43]	864	Previous adenoma diagnosed within 3 months and removed	25 mg/d ± 1000 mg/d vitamin C and 400 μg/d vitamin E	4 yrs	No treatment effect on recurrent polyps
MacLennan et al. 1995 [44]	306	History of adenomatous polyps that were removed	20 mg/d ± low-fat diet (<25 % energy) ± 25 g/d wheat bran	4 yrs	No effect of beta-carotene on recurrent polyps

Increased vegetable and fruit intake was among the dietary goals in the PPT, a large multicenter study that aimed to test the effect of multifaceted diet modification on the recurrence of colorectal adenomas. In the PPT, 2079 men and women with a history of adenomatous polyps were randomized to the diet intervention arm or control arm [45]. The goals of the intervention were a diet low in fat (<20 % of energy), high in fiber (18 g/1000 kcal/day), and high in vegetables and fruits (3.5 servings/1000 kcal/day). At study end, the intervention group had increased vegetable and fruit intake by an average of 1.1 servings/1000 kcal/day, and average reported intake of total carotenoids increased on average approximately 50 %. However, total plasma carotenoids were increased by only 5 % on average at study end, which is considerably lower than has been observed in response to high-vegetable and -fruit diets in other studies and constrains the interpretation of the self-reported dietary data. No effect on adenoma

recurrence was observed in the PPT. In a secondary analysis of a subcohort of study participants, average serum alpha-carotene, beta-carotene, lutein, and total carotenoid concentrations at four time points during the study were found to be associated with decreased risk of polyp recurrence (OR 0.71, 0.76, 0.67, 0.61, respectively, $p < 0.05$) ($n = 701$) [47].

SUMMARY AND CONCLUSIONS AND FUTURE DIRECTIONS

Epidemiological evidence of the associations between carotenoid status and the risk and progression of cervical, breast, ovarian, and colorectal cancer is overwhelmingly based on intakes of carotenoids from food sources. Serum carotenoid concentrations are indicative of vegetable and fruit intake or the overall dietary pattern, and a causal relationship with carotenoids should not be assumed on the basis of these studies. Beta-carotene supplement trials conducted to date have not been shown to affect the selected outcomes in cervical or colorectal cancers, compared to placebo.

Increased knowledge of mechanisms and the identification of appropriate surrogate biomarkers that are specifically responsive to carotenoid intake could improve the interpretation of results from epidemiological studies and clinical trials. Knowledge of the stages of carcinogenesis at which intervention could affect molecular activities also would be useful in designing clinical trials. Limited resources have restricted the capability of these trials to advance knowledge in this area, with more questions than answers being the usual result of these efforts.

Although carotenoids and other constituents of food likely comprise a major component of the environmental influences that contribute to risk for cancer, not all persons exposed to the same nutritional or dietary factors will develop the associated disease. Differential genetic susceptibility is believed to explain the variations in response and outcome among individuals with similar dietary intakes, and the examination of the interaction between nutritional and genetic factors also would substantially refine the conduct and interpretation of epidemiological studies and clinical trials in this area.

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