Invited Commentary: Serum Carotenoids and Breast Cancer

Thomas E. Rohan

A vast amount of epidemiologic evidence suggests that a relatively high fruit and vegetable intake is associated with reduced risk of cancer (1). Although findings for breast cancer are less consistent than those for cancers at several other anatomic sites, including the mouth and pharynx, esophagus, stomach, and lung (1), a recent meta-analysis suggested that women with a relatively high vegetable consumption have a 25 percent reduction in breast cancer risk, and those with a relatively high fruit consumption have approximately a 6 percent reduction in risk (2).

Vegetables and fruits contain numerous bioactive and potentially anticarcinogenic substances, including carotenoids, thiols, flavonoids, indoles, isothiocyanates, phenols, folic acid, and vitamins C and E (3). The many possible mechanisms by which these substances might inhibit carcinogenesis include antioxidant effects, increases in cell-to-cell communication, activation of enzymes involved in carcinogen detoxification, alteration of estrogen metabolism, effects on DNA methylation and repair, and antiproliferative effects (3).

Much attention has been devoted to study of the association between carotenoids and cancer risk (1). Although more than 600 carotenoids have been identified in nature, diets in the United States typically include only about 40 carotenoids, and only about 20 carotenoids can be measured in human serum and tissues (4). Those carotenoids that have the highest blood concentrations in populations which have been studied in the United States are \( \alpha \)-carotene, \( \beta \)-carotene, \( \beta \)-cryptoxanthin, lutein, lycopene, and zeaxanthin (4). The carotenoids are antioxidants and may therefore exert anticarcinogenic effects by inhibiting the ability of free radicals to induce DNA damage (5). However, some carotenoids might operate by other means as well. For example, \( \alpha \)- and \( \beta \)-carotene and \( \beta \)-cryptoxanthin can be metabolized to retinol and thereby induce epithelial cell differentiation (6), and \( \alpha \)- and \( \beta \)-carotene can also inhibit cell proliferation (7).

There have been many epidemiologic studies of the association between dietary carotenoids and breast cancer risk. Case-control studies have mostly shown inverse associations with carotenoid intake (and, in particular, with intake of \( \beta \)-carotene) (1, 8, 9), whereas the results of cohort studies have been divided fairly evenly between those showing no association and those showing some evidence of inverse associations (1, 10). Of those studies that have reported on breast cancer risk in association with dietary intake of both \( \beta \)-carotene and other carotenoids, one case-control study in premenopausal women showed inverse associations with intake of \( \beta \)-carotene and of lutein plus zeaxanthin but not with intake of \( \alpha \)-carotene (11); one showed an inverse association with lycopene intake but not with intake of \( \alpha \)- and \( \beta \)-carotene, lutein, lycopene, or cryptoxanthin (13). In addition, one cohort study showed weak inverse associations with intake of \( \beta \)-carotene and of lutein plus zeaxanthin but not association with intakes of \( \alpha \)-carotene, \( \beta \)-cryptoxanthin, or lycopene in premenopausal women and no association with intake of any of these carotenoids in postmenopausal women (10). Although, overall, the findings of these studies provide some support for inverse associations between carotenoid intake and breast cancer risk, they are somewhat difficult to reconcile with each other, given that the inverse associations have generally been more evident in case-control studies, the results of which are susceptible to selection and recall bias to a greater extent than those of cohort studies (recall bias is usually not an issue in cohort studies). However, in both the case-control and the cohort studies, misclassification of individual intake might have occurred because of random measurement error, with consequent attenuation of true associations (14).

Given that feeding studies have shown that serum carotenoids are good markers of vegetable and fruit intake (15, 16), the association between blood levels of carotenoids and breast cancer risk has been investigated in several case-control (17–23) and cohort studies (24–28). To date, most studies have reported on the association between blood levels of \( \beta \)-carotene and risk, or they have compared \( \beta \)-carotene levels in individuals with and without breast cancer. The case-control studies have mostly shown no association between \( \beta \)-carotene and risk (17, 18, 20, 21), although one showed an inverse association (22) and two showed lower levels of \( \beta \)-carotene in cases than in controls (19, 23). However, an important concern with respect to interpretation of the results of these case-control studies is the possibility that disease status influenced carotenoid levels. In this regard, cohort studies are potentially more informative, and of those that have been reported, two (27, 28) showed no
association between β-carotene and risk, one (26) showed a positive association, and one (25) showed an inverse association, although the latter finding may have been due to artefact associated with the conditions under which the blood specimens were stored and the frequency with which they were frozen and thawed (29).

To date, only three case-control studies (21–23) and two cohort studies (27, 28) have reported on the relation between serum or plasma carotenoids other than β-carotene and risk of breast cancer. Of these, two case-control studies showed no association with α-carotene and lycopene (21, 22), and one (23) suggested that, when compared with controls, cases had lower levels of lycopene, in particular, but also had lower levels of α-carotene, cryptoxanthin, canthaxanthin, and zeaxanthin and lutein; of the cohort studies, one (27) showed no association with serum lycopene, while the other (28) showed an inverse association with serum lycopene, some suggestion of inverse associations with β-cryptoxanthin and lutein/zeaxanthin, and no association with α-carotene. However, the cohort studies were relatively small, one involving 30 cases (27) and the other involving 105 cases (28). In this regard, the relatively large prospective study reported by Toniolo et al. (30) in this issue of the Journal provides further evidence in support of potential antiproliferative effects of at least several of the carotenoids. Their case-control study was nested within the New York Women’s Health Study, a cohort study of diet, hormones, metabolism, and cancer risk involving 14,275 women recruited between 1985 and 1991 and followed (for the present analysis) until 1994. The study included 270 breast cancer cases (the largest number to date in prospective studies of carotenoids and breast cancer risk) and 270 controls who were free of cancer and matched to the cases on several factors, including age at recruitment, menopausal status at baseline, and date of baseline blood sampling. Cases and controls were compared with respect to baseline levels of serum carotenoids. For serum β-cryptoxanthin and α- and β-carotene (and total carotenoids), there were inverse, dose-dependent associations with breast cancer risk, the odds ratios for the lowest quartile level (using the highest quartile level as the reference category) ranging from about 1.7 for β-cryptoxanthin to about 2.2 for β-carotene. There was also some suggestion of an inverse association between serum lutein and risk, although the relation was not monotonic. Serum zeaxanthin and lycopene were not associated with altered risk.

Interpretation of the results of studies of disease risk in association with dietary factors or serum levels of those dietary factors is beset by several difficulties. First, given the inherent complexity of the diet, which contains thousands of chemicals of which at least some are potentially carcinogenic (activation to the carcinogenic form often depending on methods of food preparation) and some (as indicated earlier) are potentially antiproliferative, considerable uncertainty accompanies any attribution of effect to a particular dietary item or constellation of dietary factors or, indeed, to serum markers of those factors. Essentially, there is always concern about the possibility of confounding by other dietary factors (as well as by nondietary factors). Given the limited adjustment that Toniolo et al. (30) undertook in this regard, it is conceivable that their findings might reflect residual confounding, a possibility acknowledged by the authors. In general, adjustment for overall dietary patterns, or perhaps the representation in blood of overall dietary patterns (assuming that appropriate markers can be identified), might help to establish the independent effect of a given dietary factor or of its levels in the blood (31). Second, interpretation of studies reporting on associations for several potentially highly correlated variables is complicated by the possibility of collinearity between those variables and the difficulty of evaluating their independent effects. Although Toniolo et al. (30) did not report correlations among the various carotenoids that they investigated, Dorgan et al. (28) investigated the same carotenoids as those examined by Toniolo et al. (30) and showed that correlations among their serum levels ranged from 0.35 to 0.55. After mutual adjustment of the estimates in the study of Dorgan et al. (28), the estimates of risk in association with the various carotenoids were not altered markedly, although the trends for lycopene and β-cryptoxanthin were less apparent. This provides some reassurance concerning the findings of Toniolo et al. (30), whose estimates for the associations for the individual carotenoids were not mutually adjusted. Third, an underlying assumption (often implicit) of studies of serum markers of dietary exposures and disease risk is that there is an association between those serum markers and their concentrations in the target tissue. However, as noted by Toniolo et al. (30), currently there are no data on the association between serum carotenoids and carotenoid levels in breast tissue. Finally, a single measurement of blood levels of markers such as carotenoids probably does not provide a time-integrated measure of exposure, but rather reflects relatively recent dietary intake. Nevertheless, Toniolo et al. (30) showed apparently strong correlations among levels of individual serum carotenoids over a 3-year period (they did not present confidence intervals for their point estimates of correlation). Furthermore, two case-control studies have examined the association between levels of carotenoids in adipose tissue and breast cancer risk (32, 33), on the assumption that such levels better reflect intake over a longer period than does a single blood measurement. Of these studies, one (32) showed no association between β-carotene levels in buttock fat samples and breast cancer risk, while the other (33) showed reductions in breast cancer risk in association with relatively high levels of β-carotene and lycopene in breast adipose tissue but no association with lutein/zeaxanthin. Given these caveats, the accumulated data on the relation between carotenoids (in the diet or in blood) and breast cancer risk do not provide unequivocal support for inverse associations. This uncertainty reflects larger issues relating to the difficulty of attributing effect in nutritional epidemiologic studies. Nevertheless, although identification of the individual dietary constituents that are responsible for causing or preventing cancer might continue to elude us given the inherent complexity of diet, this may not matter for cancer prevention efforts. The latter would appear to rely more on the identification of dietary patterns (or food groups) that might modify risk, an approach which has already yielded
much empirical evidence supporting the role of dietary factors in the etiology of cancer, and which forms the basis upon which current dietary recommendations for risk reduction are made (1).

REFERENCES