

Serum Micronutrients and the Subsequent Risk of Oral and Pharyngeal Cancer¹

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ABSTRACT

To investigate the relationship between serum micronutrients and the subsequent risk of oral and pharyngeal cancer, a nested case-control study was conducted within a cohort of 25,802 adults in Washington County, MD, whose blood samples were collected in 1974 and stored at -70°C for subsequent assays. The serum levels of nutrients in 28 individuals who developed oral and pharyngeal cancer during 1975 to 1990 were compared with levels in 112 matched controls. Serum levels of all individual carotenoids, particularly β -carotene, were lower among subjects who developed oral and pharyngeal cancer. The risks of this malignancy decreased substantially with increasing serum level of each individual carotenoid. Persons in the highest tertile of total carotenoids had about one-third the cancer risk as those in the lowest tertile. High serum levels of α -tocopherol also were related to a low oral cancer risk in later years, but the risks were elevated significantly with increasing serum levels of γ -tocopherol and selenium. The findings from this study are consistent with many previous epidemiological investigations of dietary factors for oral and pharyngeal cancer and provide further evidence for the potential role of carotenoids and α -tocopherol in the chemoprevention of these malignancies.

INTRODUCTION

Oral and pharyngeal cancer may serve as an ideal disease model for cancer chemoprevention, since many patients with this disease have had well recognized premalignant lesions, such as leukoplakia (1), and a high proportion of patients with this cancer will subsequently develop second primary malignancy (2). Supplementation with retinol or its synthetic analogues has been shown to inhibit the progression of oral leukoplakia (3, 4) and to reduce the occurrence of second primary cancers in patients with head and neck cancer (5). General application of this nutrient in cancer prevention, however, may be difficult, since long-term and high-dose use may result in some toxic effects (5).

Other nutrients, including carotenoids, vitamin E (tocopherols) and selenium, have also been suggested as promising cancer prevention agents (6). High serum levels of these nutrients, particularly β -carotene, have been linked to a low risk of cancer, notably cancer of the lungs (7), but such evidence for oral and pharyngeal cancer is limited. Some dietary factors, including high consumption of fruits and some carotene-rich vegetables, have been shown to be associated with a low risk of this malignancy, but the effects of specific nutrients are not clear (8). To further evaluate the association between cancer risk and specific nutrients we conducted a nested case-control study of oral and pharyngeal cancer using serum collected prior to cancer diagnosis.

MATERIALS AND METHODS

This nested case-control study was conducted within a cohort of community volunteers in Washington County, Maryland, whose blood samples were col-

lected in 1974 and stored at -70°C for subsequent assays (9). At the time of blood collection, a brief interview was administered to obtain information on demographic characteristics, smoking history, and use of selected medications during the 48 h prior to blood collection. Among the 25,802 individuals who donated blood in 1974, 28 were diagnosed with primary oral and pharyngeal cancer (ICD-9, 141-149) as their first cancer diagnosis during the period of January 1975 to December 1990 and were identified through the population-based Washington County Cancer Registry. These patients served as the case group in the present study and will be simply referred to hereafter as cases of oral cancer.

Four controls were selected for each case from those in the same cohort who were alive and free of diagnosed cancer (except for skin cancer) at the date the case was diagnosed. The controls were matched to the index case on sex, race, year of birth (± 5 years), hours between blood drawing and the previous meal, and the month of serum collection.

Serum from study subjects was withdrawn from the freezers and organized into case-control sets. Each set contained the index case, its four matched controls, and at times one quality control specimen. The serum samples were assayed for levels of retinol, tocopherols, and carotenoids by high-performance liquid chromatography (10) and selenium by neutron activation analysis (11). Serum for each case-control set was assayed on the same day. In addition, serum specimens were masked with regard to case-control or quality control status.

The coefficients of variation for serum assays were 2.1% for selenium, 4.3% for α -tocopherol, 5.1% for γ -tocopherol, 3.1% for retinol, 5.8% for β -carotene, and 3.9-11.3% for other individual carotenoids.

Matched *t* tests were used to evaluate the mean case-control differences of each individual nutrient (12). To normalize the distributions of the set-specific case-control differences for most nutrients, log-transformed data were used in statistical tests. Categorical data analyses were also performed to further examine the dose-response effect of serum nutrients. The nutrient variables were dichotomized or trichotomized according to the median or tertile distributions of controls. Conditional logistic regression was used to derive RO^3 as estimates of risks of oral cancer associated with the individual serum nutrient levels (13). Tests for trends of these risk estimates across tertiles were performed in logistic regression by assigning scores of 1, 2, and 3 to the first, second, and third tertile levels of the variable selected. All statistical tests were based on two-tailed probabilities.

RESULTS

As expected, cases and controls were similar in all matching factors, *i.e.*, sex, race, age, month of blood collection, and hours between blood drawing and the previous meal. Slightly more cases, however, were poorly educated and were taking medication for hypertension, while slightly more controls were taking vitamin pills. Nearly all cases had been smokers, compared to two-thirds of the controls.

The mean values of all individual carotenoids were consistently lower among cases than controls, particularly for β -carotene (Table 1). Although the serum level of α -tocopherol, the most abundant and active form of vitamin E, was somewhat lower among cases, the serum γ -tocopherol level was significantly lower among controls. In addition, cases were found to have higher serum levels of retinol, selenium and cholesterol, but none of these differences were significant at the 0.05 level.

To investigate the dose-response relation between serum nutrients and oral cancer risk, study subjects were categorized according to the

³ The abbreviation used is: RO, relative odds.

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Table 1 Means ± SD of prediagnostic serum nutrients in cases and controls, Washington County (1975-1990)

| Nutrients | Mean ± SD | | % of difference ^a | P ^b (t test) |
|---------------------------|---------------|---------------|------------------------------|-------------------------|
| | Cases | Controls | | |
| Retinol (µg/dl) | 67.33 ± 17.61 | 63.15 ± 16.85 | +15.1 | 0.24 |
| Total carotenoids (µg/dl) | 77.55 ± 37.40 | 93.54 ± 41.65 | -17.1 | 0.04 |
| β-Carotene | 11.39 ± 9.26 | 14.94 ± 11.67 | -23.8 | 0.03 |
| α-Carotene | 2.37 ± 3.06 | 2.86 ± 2.73 | -17.3 | 0.08 |
| Cryptoxanthine | 8.05 ± 8.28 | 9.58 ± 7.83 | -16.0 | 0.07 |
| Lutein | 18.96 ± 9.79 | 23.28 ± 12.32 | -18.6 | 0.10 |
| Lycopene | 23.78 ± 12.70 | 25.57 ± 14.97 | -7.0 | 0.61 |
| Total tocopherol (mg/dl) | 1.42 ± 0.71 | 1.39 ± 0.41 | +2.2 | 0.94 |
| α-Tocopherol | 1.09 ± 0.54 | 1.13 ± 0.36 | -3.4 | 0.42 |
| γ-Tocopherol | 0.32 ± 0.20 | 0.25 ± 0.15 | +27.6 | <0.01 |
| Selenium (µg/ml) | 0.11 ± 0.01 | 0.10 ± 0.01 | +4.0 | 0.06 |
| Cholesterol (mg/dl) | 228 ± 57 | 223 ± 38 | +2.3 | 0.75 |

^a % of difference = 100 × $\frac{\text{mean of cases} - \text{mean of controls}}{\text{mean of controls}}$

^b Matched t test based on log-transformed values.

tertile distribution of controls. As shown in Table 2, high serum levels of each individual carotenoid were consistently associated with a low risk of oral cancer. The risks decreased monotonically with increasing levels of most carotenoids, except for β-carotene, for which the lowest RO of 0.24 (95% confidence interval, 0.07-0.84) was observed in the second tertile group. α-Tocopherol was inversely associated with subsequent risk of oral cancer (trend test, P = 0.07), but the risks were elevated with increasing levels of γ-tocopherol (trend test, P = 0.05). Positive associations of oral cancer risk with serum levels of selenium and retinol were also observed, but the trend test was significant only for selenium. Similar patterns were observed after exclusion of 4 cases who were diagnosed with oral cancer within five years (<5) of follow-up.

Smoking, an established risk factor for oral cancer (8), was found to be associated with reduced serum levels of α-tocopherol and most carotenoids, particularly β-carotene, among the control group. Adjustment for smoking (ever versus never) slightly attenuated the associations of oral cancer with serum levels of most nutrients, except for selenium and cholesterol which became slightly stronger. The smoking-adjusted RO were 1.00, 1.28, and 2.07 for retinol; 1.00, 0.51, and 0.46 for total carotenoids; 1.00, 0.22, and 0.69 for β-carotene; 1.00, 0.92, and 0.33 for α-tocopherol; and 1.00, 4.26, and 5.43 for selenium with increasing tertile levels of serum nutrients. Cholesterol was positively correlated with all other serum nutrients, particularly α-tocopherol (r = 0.60) and total carotenoids (r = 0.39). Adjustment for cholesterol, however, made almost no change in the crude RO of oral cancer with serum nutrients.

To assess the independent effects of major serum nutrients, stratified analyses were performed (Table 3). Due to the small number of cases, study subjects were categorized into only two groups according to the median distribution of controls. High serum levels of total carotenoids, β-carotene, and α-tocopherol were generally related to low risks of oral cancer regardless the serum levels of other nutrients, while the risks were elevated among individuals with high levels of selenium and retinol in each level of the other nutrients.

DISCUSSION

This nested case-control study of oral cancer revealed that individuals with high serum levels of carotenoids and α-tocopherol had reduced risks of developing oral cancer in subsequent years, while the risks were elevated with increasing prediagnostic serum levels of selenium and retinol. Such associations were unchanged after exclusion of patients with cancer diagnosed within 5 years of follow-up,

suggesting little influence of the cancers themselves or their preclinical states in altering the blood levels. The confounding effect of other factors is unlikely to be substantial, since cases and controls were very similar in many baseline characteristics, and adjustments for cholesterol, smoking, and the other nutrients did not materially change the pattern of the association. We did not have information on alcohol consumption, a known risk factor for oral cancer, but adjustment for smoking partially controls for alcohol intake since the two habits are highly correlated (8). The slightly attenuated associations of oral cancer with α-tocopherol and carotenoids following adjustment for smoking were not unexpected, since smoking may act on the putative causal chain between low serum levels of these micronutrients and subsequent risk of cancer (7).

The most marked finding of this study was the strong and consistent protective association of each of the individual carotenoids, which was in line with the putative cancer-inhibiting hypothesis for this group of nutrients. Several carotenoids are known to be efficient antioxidants. They capture singlet oxygen and other free radicals, which would otherwise induce potentially harmful processes, such as chromosome damage and immunosuppression (14). Dietary supplementation with carotenoids, including those without provitamin A function, such as canthaxanthin, has been shown to substantially reduce the incidence of chemical- or physical-induced tumors in experimental animals (15). β-Carotene supplementation has lowered the prevalence of oral leukoplakia in a randomized trial (16). Although, to our knowledge, no prospective serum study of oral cancer has been published, epidemiological investigations for cancers of the other sites have provided strong evidence that β-carotene may be protective against lung cancer and perhaps other epithelial carcinomas in humans (7, 17). Other studies have also suggested a possible protective effect of some other carotenoids, although the evidence is limited (18). For instance, lycopene, another major carotenoid, has been found to be lower in serum among patients with cancers of the bladder, pancreas, rectum, breast (postmenopausal), and prostate in a series of nested case-control studies in Washington County (9).

A case-control study in Pakistan found that patients with oral cancer had a significantly lower serum levels of β-carotene (19), although the reduction may be caused by presence of cancer which may influence the dietary patterns of patients. Many dietary interview studies of oral cancer have provided additional evidence for the protective effect of carotenoids. High consumption of fruits and vegetables, particularly dark yellow and green, leafy vegetables (high carotene content), was repeatedly shown to be associated with a reduced risk of oral cancer (20, 21). Our study thus adds to the cumulative evidence suggesting a protective effect of carotenoids against oral cancer.

Table 2 Relative odds of the development of oral cancer according to prediagnostic serum levels of nutrients, Washington County (1975-1990)

| | No. of cases by tertile | | | Relative odds by tertile ^a | | | P for trend |
|-------------------|-------------------------|----------------|----------------|---------------------------------------|----------------|----------------|-------------|
| | T ₁ (low) | T ₂ | T ₃ | T ₁ (low) | T ₂ | T ₃ | |
| Retinol | 6 | 9 | 13 | 1.00 | 1.65 | 2.51 | 0.14 |
| Total carotenoids | 15 | 7 | 6 | 1.00 | 0.41 | 0.33 | 0.05 |
| β-Carotene | 15 | 4 | 9 | 1.00 | 0.24 | 0.50 | 0.17 |
| α-Carotene | 15 | 7 | 6 | 1.00 | 0.40 | 0.37 | 0.06 |
| Cryptoxanthine | 14 | 8 | 6 | 1.00 | 0.48 | 0.33 | 0.07 |
| Lutein | 12 | 8 | 8 | 1.00 | 0.62 | 0.61 | 0.37 |
| Lycopene | 11 | 9 | 8 | 1.00 | 0.78 | 0.65 | 0.46 |
| Total tocopherol | 12 | 6 | 10 | 1.00 | 0.53 | 0.89 | 0.75 |
| α-Tocopherol | 13 | 11 | 4 | 1.00 | 0.90 | 0.31 | 0.07 |
| γ-Tocopherol | 4 | 11 | 13 | 1.00 | 3.07 | 4.04 | 0.05 |
| Selenium | 3 | 12 | 13 | 1.00 | 3.69 | 4.30 | 0.04 |
| Cholesterol | 11 | 8 | 9 | 1.00 | 0.70 | 0.77 | 0.64 |

^a Cases and controls were categorized according to the tertile distribution of controls. The lowest tertile was treated as reference group in the estimation of relative odds.

Table 3 Relative odds of the development of oral cancer according to the combined prediagnostic serum levels of major nutrients, Washington County (1975-1990)

| | Total carotenoids ^a | | β-Carotene ^a | | α-Tocopherol ^a | | Selenium ^a | |
|--------------------------------|---------------------------------------|-------------|---------------------------|-------------|---------------------------|-------------|--------------------------|---------------------------|
| | Low | High | Low | High | Low | High | Low | High |
| Retinol ^a | | | | | | | | |
| Low | 1.00 ^b (7/33) ^c | 0.63 (3/23) | 1.00 ^b (8/36) | 0.50 (2/19) | 1.00 ^b (8/37) | 0.46 (2/19) | 1.00 ^b (2/29) | 3.88 (8/27) |
| High | 2.73 (11/23) | 1.15 (7/33) | 1.93 (11/34) | 1.74 (7/22) | 2.75 (9/21) | 1.56 (9/35) | 4.00 (4/19) | 7.27 ^d (14/37) |
| Total carotenoids ^a | | | | | | | | |
| Low | | | 1.00 ^b (16/47) | 0.77 (2/9) | 1.00 ^b (12/38) | 1.09 (6/18) | 1.00 ^b (4/27) | 3.00 (14/29) |
| High | | | 0.38 (3/23) | 0.57 (7/33) | 0.72 (5/20) | 0.38 (5/36) | 0.58 (2/21) | 1.23 (8/35) |
| β-Carotene ^a | | | | | | | | |
| Low | | | | | 1.00 ^b (11/42) | 1.06 (8/28) | 1.00 ^b (3/34) | 4.41 ^d (16/36) |
| High | | | | | 1.27 (6/16) | 0.41 (3/26) | 2.14 (3/14) | 2.07 (6/28) |
| α-Tocopherol ^a | | | | | | | | |
| Low | | | | | | | 1.00 ^b (3/26) | 3.36 (14/32) |
| High | | | | | | | 1/13 (3/22) | 1.97 (8/32) |

^a Cases and controls were categorized according to the median level of controls.

^b Reference group.

^c Numbers in parentheses, number of cases/number of controls.

^d $P < 0.05$.

Vitamin E is a strong intracellular antioxidant (14), which has been shown to confer a cancer-inhibiting effect in animal studies (22). Topical application of this nutrient has been reported to inhibit the development of tumors in the hamster buccal pouch (23). Vitamin E has also been linked to human cancers in some epidemiological studies (7). In particular, a recent population-based case-control study of oral cancer in the United States revealed a 50% reduced risk of oral cancer among individuals with high use of vitamin E supplements (24). In addition, lower serum levels of α-tocopherol among oral cancer patients have also been reported in a case-control study in India (25).

We found that α-tocopherol was inversely associated with subsequent risk of oral cancer, while the risk was elevated with increasing serum levels of γ-tocopherol. The reversal of associations is surprising even though similar results have been reported for other cancers (26, 27), since the antioxidant capacity of γ-tocopherol, while less than that of α-tocopherol, is of the same order of magnitude (28, 29). It is possible that serum levels of γ-tocopherol are elevated as a compensation for low α-tocopherol.

The positive association of oral cancer risk with serum selenium level observed in this study was unexpected and in contrast to the results from many previous epidemiological and animal studies (7, 22). Two epidemiological studies have assessed the association of oral cancer with body levels of selenium (30, 31), but both of them were prevalent case-control studies. The serum study conducted in patients with untreated cancer showed a significantly higher serum selenium level among cases, but the erythrocyte levels of selenium were lower among oral cancer patients (30). A recent case-control study in Washington State reported a lower selenium in the nail of the big toe among oral cancer patients than that among controls (31). This association, however, was observed only among men in the youngest age group.

Our finding was consistent with a large lung cancer study in the same Washington County population, which indicated a positive dose-response relationship between lung cancer risk and prediagnostic serum level of selenium, especially among persons with low levels of α-tocopherol (32). This consistency may be of interest, since cancers of the mouth and the lungs originate from epithelial tissue and are strongly related to cigarette smoking. In some other studies, the protective association for selenium was limited to subgroups of the study population with certain characteristics (33-35), such as low levels of α-tocopherol or retinol (33). These inconsistent findings in humans are in line with animal studies, in which selenium has been found to

exert both cancer-inhibiting and -enhancing effects, depending on the cancer sites and carcinogens (22).

The literature regarding the association between retinol and cancer risk is conflicting (36). Supplementation with retinol or 13-*cis*-retinoic acid, a synthetic retinoid, has been shown to inhibit the progression of oral leukoplakia (3, 4) and to reduce the occurrence of second primary cancers in patients with head and neck cancer (5). On the other hand, high dietary intake of retinol has been repeatedly reported to be associated with a number of cancers, including cancers of the oral cavity, pharynx, and esophagus (36). Prospective serum studies provided no clear evidence for the association of this nutrient with a variety of cancers (7). Consistent with most dietary interview studies, we found a positive, although nonsignificant, association of oral cancer risk with prediagnostic serum level of retinol. This finding was in contrast to the observation from a prevalent case-control study in India, which reported a significantly lower serum level of retinol among patients with oral cancer, but the serum retinol level in that study population was very low (29).

In summary, despite the small sample size, this nested case-control study of oral cancer for the first time revealed that high serum levels of carotenoids are strongly associated with a lower risk of future oral cancer. This finding was similar to that observed in many previous lung cancer studies and consistent with the protective effect of fruits and vegetables, particularly dark yellow and green, leafy vegetables. The association of high α-tocopherol with lower subsequent risk of oral cancer was also of interest in view of experimental evidence that vitamin E can inhibit buccal carcinogenesis and the recent epidemiological finding on the protective effect of vitamin E supplements. The study, along with previous epidemiological and experimental studies, provides further evidence that carotenoids and α-tocopherol may be promising agents in the chemoprevention of cancers of the oral cavity and pharynx.

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