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Acute Adverse Effects of Radiation Therapy and Local Recurrence in Relation to Dietary and Plasma Beta Carotene and Alpha Tocopherol in Head and Neck Cancer Patients

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Abstract: *There is a debate concerning the effects of antioxidant vitamins during radiation therapy: Can they reduce the adverse effects of therapy without reducing treatment efficacy? We examined whether dietary and plasma beta carotene and alpha tocopherol were related to severe acute adverse effects of radiation therapy and to cancer local recurrence. We conducted a prospective study of 540 head and neck cancer patients treated by radiation therapy. Dietary intakes of beta carotene and alpha tocopherol were measured by a validated food frequency questionnaire and plasma levels were determined. Acute adverse effects of radiation therapy and local recurrence were documented. A higher beta carotene dietary intake was associated with fewer severe acute adverse effects: odds ratio (OR) = 0.61 [95% confidence interval (CI) = 0.40–0.93]. There was a tendency for a similar effect for plasma beta carotene: OR = 0.73 (95% CI = 0.48–1.11). Participants with higher plasma beta carotene had a significantly lower rate of local recurrence (hazard ratio = 0.67; 95% CI = 0.45–0.99). Alpha tocopherol was not related to severe adverse effects or to cancer recurrence. This study suggests that a higher usual dietary beta carotene intake can reduce the occurrence of severe adverse effects of radiation therapy and decrease local cancer recurrence.*

Introduction

Many cancer patients take antioxidant vitamin supplements during conventional cancer therapy with the hope of enhancing the benefits of treatment and alleviating its adverse effects (1–3). The use of antioxidant supplements during radiation therapy has long been a controversial topic (4). Some scientists believe that antioxidants can reduce the adverse effects of radiation therapy without affecting its efficacy, whereas others fear that they interfere with treatment (5–7). We recently reported the results of a double-blind, placebo-controlled, randomized trial using high dose beta carotene and alpha tocopherol supplements among patients with head and neck cancer (HNC) treated by radiation therapy (8). The supplementation combining beta carotene and alpha tocopherol was able to reduce the frequency of severe acute adverse effects. However, the rate of local recurrence was higher in the supplementation arm of the trial than in the placebo arm. Many studies have documented that antioxidant vitamins do not have the same effects when obtained from the diet and when obtained from supplements at high dosage (9–14). To further investigate the relationships between antioxidant vitamins and radiation therapy outcome, we conducted an exploratory study among our trial subjects to examine whether baseline dietary intakes and plasma levels of beta carotene and alpha tocopherol were related to the occurrence of severe acute adverse effects of radiation therapy and to cancer local recurrence.

Patients and Methods

Study Design

We conducted a multicenter, double-blind, placebo-controlled, randomized chemoprevention trial with alpha tocopherol and beta carotene supplements among patients treated by radiation therapy for stage I or II HNC. The results concerning the main objectives of the trial (occurrence of second primary cancers, occurrence and severity of adverse effects of radiation therapy, and recurrence of the HNC) have been published (8,15). For this report, the trial population was used to conduct an exploratory study assessing prospectively the relationships of dietary intakes of beta carotene and alpha tocopherol over the year preceding randomization and of plasma beta carotene and alpha tocopherol levels at the time of randomization to the occurrence of severe acute adverse

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effects of radiation therapy and to the recurrence of the HNC.

Study Population

Eligible patients were aged 18 years and over, had received a first diagnosis of stage I or II histologically documented squamous cell carcinoma of the head and neck area (tongue, gum or mouth, oropharynx, hypopharynx, pharynx, and larynx), and were scheduled to be treated by radiation therapy between October 1, 1994 and June 6, 2000 in 1 of 5 radiation therapy centers in the province of Quebec, Canada. Among them, patients with any of the following conditions were ineligible: Karnofsky performance score (16) <60; multiple primary HNC or previous cancer; severe cardiovascular disease; inadequate renal, hepatic, or hematological function; anticoagulant therapy; pregnancy; and average daily supplement intake of beta carotene or vitamin E above 6.0 mg and 50 international units (IU), respectively. The institutional review board of each participating center approved the study protocol. All 540 trial subjects gave written informed consent prior to randomization.

Intervention

Patients were randomly assigned to receive a daily supplementation combining alpha tocopherol (400 IU of dl-α-tocopherol) and beta carotene (30 mg) or corresponding placebos during radiation therapy and for 3 yr thereafter. The supplementation began on the 1st day of radiation treatment. This timing was justified by the anticipated beneficial effect of antioxidant supplementation during radiation therapy. During the course of the trial, supplementation with beta carotene was discontinued because of ethical concerns after the release of the CARET trial results showing adverse effects of a supplementation containing beta carotene (12). Throughout the trial, the patients, the study nurses, the treating physicians, the study personnel, and the investigators were kept blind to the patients' intervention group assignment.

Baseline Data Collection

Baseline data collection was completed before patients were randomly assigned and before the initiation of radiation therapy. The study nurses administered several questionnaires on patients' characteristics including socioeconomic data, height and weight, alcohol consumption, smoking, and diet. To assess the dietary intakes of beta carotene and alpha tocopherol over the year preceding randomization, an 84-item, semiquantitative food frequency questionnaire had been designed and validated previously in a population of 73 patients with HNC (17). In this validation study, positive correlations were observed between dietary intakes and plasma levels for both beta carotene (correlation coefficient $r = 0.32$, $P = 0.006$) and alpha tocopherol (correlation coefficient $r = 0.21$, $P = 0.11$). Stronger, statistically significant correlations were observed when the contribution from supplements was also considered. Average daily intakes of beta carotene and alpha tocopherol over the year preceding randomization were calculated using the Canadian food composition table (18). A 10-ml blood specimen was collected at baseline for the measurement of plasma beta carotene, alpha tocopherol, cholesterol, and triglycerides. Plasma beta carotene and alpha tocopherol were analyzed by reverse-phase high performance liquid chromatography according to established methods (19,20).

Acute Adverse Effects of Radiation Therapy

Acute adverse effects of radiation therapy were assessed using the 1st version of the Radiation Therapy Oncology Group "Acute Radiation Morbidity Scoring Criteria" (21). This assessment was made during radiation therapy, at the end of radiation therapy, and 1 mo after the end of radiation therapy. During radiation therapy, patients were seen in the clinic every week by the radiation oncologist who noted the side effects**.** A reference measure was taken with the same instrument before radiation therapy. After taking into account the baseline status, the most severe radiation therapy adverse effect, graded from 0 (no symptom) to 4 (severe symptom), was noted in 6 sites (skin, mucosa, ear, salivary glands, pharynx and esophagus, larynx). In our study, there was no death due to radiation therapy (Grade 5). In addition to the site specific measures, the most severe grade among the 6 sites was taken as an overall (all sites) measure of the severity of radiation therapy acute adverse effects. This overall measure was constructed to take into account the cancer site heterogeneity of the patient population and the potential beneficial effect on multiple sites of the antioxidant vitamin supplementation. In addition, we choose this outcome in accordance with the pragmatic approach used in the clinical setting where the aim is to avoid any severe adverse effect (Grade 3 or 4). For this report, only severe (Grade 3 or 4) acute adverse effects during radiation therapy to the mucosa, to the larynx, and overall were considered because they were observed the most frequently.

Follow-Up

Patient outcome information was obtained by the radiation oncologists and the study nurses at predetermined times during the follow-up: during therapy, immediately at the end of radiation therapy, 1 mo after radiation therapy, every 6 mo during the first 3 yr, and then once a year. During each visit, the radiation oncologists assessed the recurrence of the initial head and neck tumor. A local recurrence had to occur within 2 cm of the initial HNC and be of the same histological

type. Copies of all pathology reports and death certificates were obtained. Follow-up ended when the last patient enrolled had completed the supplementation period on June 30, 2003.

Statistical Analysis

Baseline characteristics of patients were compared according to the occurrence of severe adverse effects of radiation therapy and according to local recurrence of the HNC. The statistical tests used were, respectively, χ^2 tests for categorical data, Student's t-tests for continuous variables that followed a normal distribution, and Wilcoxon 2 sample tests for those that did not. For the multivariate analyses, the 4 exposure variables (dietary and plasma beta carotene and alpha tocopherol) were converted from continuous to dichotomous variables using the median of their distribution as cutoff. Participants with intake or plasma level above the median were compared to those with level below the median (reference category).

The relationships between dietary and plasma beta carotene and alpha tocopherol and occurrence of severe adverse effects of radiation therapy were assessed by logistic regression (22). Covariates included in the regression analysis to control confounding varied but always included intervention assignment in the trial. In addition, we considered as potential confounders both the variables associated with severe adverse effects of radiation therapy with P values <0.25 and the known or suspected determinants of severe adverse effects based on the literature (including age and smoking). When examining the effect of dietary beta carotene or dietary alpha tocopherol, we also assessed the potential confounding effect of total energy intake. When examining the effects of plasma alpha tocopherol, we also considered plasma cholesterol as a potential confounder. If the β coefficient of the exposure variable of interest changed by more than $\pm 10\%$ when a given potential confounder was added to the model, this covariate was considered as a confounder and kept in the model. Stage, site of tumour, dose of radiation therapy, number of fractions, age, sex, smoking either at the time of randomization and in the preceding year, and body mass index did not confound the associations studied. There was no interaction between dietary or plasma beta carotene or alpha tocopherol and intervention arm (P values for interaction ranging from 0.56–0.86). Despite the absence of statistical interaction, analyses were also conducted separately in each intervention arm of the trial to present with more details the results of this exploratory study. The logistic regression models provided estimates for the odds ratios (OR) of severe acute adverse effects of radiation therapy associated with dietary and plasma beta carotene and alpha tocopherol and their 95% confidence intervals (CI).

We assessed whether dietary and plasma beta carotene and alpha tocopherol were associated to the rate of local recurrence of the initial HNC over the entire follow-up period. Follow-up time was calculated from randomization until local recurrence of the initial cancer, death, or date of last visit before June 30, 2003. Cox proportional hazard regression was used to calculate hazard ratios (HR) with their 95% CI (23). The proportionality assumption was verified visually by checking the parallelism of the log cumulative hazard function plotted against the log of follow-up time and tested by the weighted Schoenfeld residual score test. The strategy for model selection in these analyses followed the same logic as for the logistic regression analyses described previously. Covariates included in the Cox regression models to control confounding varied but always included intervention assignment. Stage, site of tumor, dose of radiation therapy, age, and smoking did not confound the associations studied. There was no interaction between dietary or plasma alpha tocopherol and intervention arm (P values of 0.44 and 0.88). For dietary or plasma beta carotene, the HRs for recurrence were not similar in the 2 intervention arms, but the tests for interaction did not reach statistical significance (P values of 0.12 and 0.20). Analyses were also conducted separately in each intervention arm of the trial.

Results

The occurrence of severe acute adverse effects of radiation therapy overall was observed in 117 of the 535 patients (22%) during radiation therapy. Five trial subjects could not be evaluated for radiation therapy acute adverse effects. The patients' baseline characteristics are presented in Table 1 according to the occurrence, or not, of severe acute adverse effects overall (to all sites). Severe acute adverse effects were more often observed in patients with stage II cancer, in female patients, and in subjects with low dietary beta carotene intake. Severe acute adverse effects to specific sites were observed for 65 patients to the mucosa, for 60 patients to the larynx, and for 25 patients to 1 of the 4 other sites.

A higher dietary intake of beta carotene was associated with approximately 40% lower frequencies of severe acute adverse effects of radiation therapy to specific sites and overall (Table 2). The association was statistically significant for severe acute adverse effects to the larynx (OR = 0.56, 95% CI = 0.32–0.99) and overall (OR = 0.61, 95% CI = 0.40–0.93), whereas it was of borderline statistical significance for acute adverse effects to the mucosa (OR = 0.62, 95% CI = 0.36–1.07). Inverse associations tended to be more pronounced in the intervention arm than in the placebo arm of the trial. A similar pattern of inverse relationships was observed between plasma beta carotene and severe acute adverse effects of radiation therapy, although statistical significance level was only achieved for adverse effects to the mucosa (OR = 0.55, 95% CI = 0.32–0.94). Neither dietary alpha tocopherol nor plasma alpha tocopherol was associated with the occurrence of severe adverse effects of radiation therapy.

The median duration of follow-up was 51 mo. During the follow-up, local recurrence of the HNC was diagnosed in 103 of the 540 subjects (19%). Table 3 presents the baseline characteristics of the study participants according to local recurrence. Local recurrence was more often observed in patients treated for cancer in other sites than the larynx, in patients

Table 1. Baseline Characteristics of Patients According to Severity of Adverse Effects Overall (to Any Site) of Radiation Therapy

Characteristic	Severe Adverse Effects of Radiation Therapy (Grade 3 or 4) $N = 117$	No Severe Adverse Effects of Radiation Therapy (Grade 0 to 2) $N = 418$	P Value
Supplementation arm of trial No. of patients (%)	52 (44)	220 (53)	0.12
Laryngeal cancer No. of patients (%)	92 (79)	355 (85)	0.10
Stage II No. of patients (%)	58 (50)	148 (35)	0.005
Total dose of radiation therapy, gy Mean (SD)	62.6 (7.8)	61.3 (7.1)	0.09
Number of radiation therapy fractions Mean (SD)	30.0 (6.6)	28.9 (5.6)	0.09
Age (yr) Mean (SD)	62.0 (9.6)	62.6 (9.8)	0.61
Female sex No. of patients (%)	35 (30)	78 (19)	0.008
Smokers in preceding year No. of patients (%)	76 (65)	263 (63)	0.69
Smokers at time of randomization No. of patients (%)	30 (26)	101 (24)	0.73
Body mass index, kg/m^2 Mean (SD)	26.9 (5.3)	25.9 (4.6)	0.07
Dietary beta carotene intake, mg/day Median	4.10	5.07	0.02
Dietary alpha tocopherol intake, mg/day Median	5.25	5.57	0.37
Dietary energy intake, kcal/day Median	1,869	1,882	0.61
Plasma beta carotene, μmol/l Median	0.14	0.18	0.09
Plasma alpha tocopherol, μmol/l Median	31.5	31.2	0.47
Plasma cholesterol, mmol/l Median	5.37	5.65	0.18

with stage II cancer, in younger participants, and in smokers during the preceding year. HRs of local recurrence associated with baseline dietary or plasma beta carotene or alpha tocopherol are presented in Table 4. Dietary beta carotene was not associated with local recurrence of the HNC (HR = 0.93, 95% CI = 0.63–1.38). On the other hand, patients with plasma beta carotene above the median had a significantly lower rate of local recurrence (HR = 0.67, 95% CI = 0.45–0.99). This effect was particularly marked in the supplementation arm of the trial (HR = 0.54, 95% CI = 0.32–0.91). Neither dietary alpha tocopherol nor plasma alpha tocopherol was associated with local recurrence of the HNC (Table 4).

Discussion

The results of our study suggest that patients undergoing radiation therapy for HNC are at increased risk of severe acute adverse effects and at higher risk of local recurrence when their usual dietary intake of beta carotene is low. Conversely, they provide support to the hypothesis that moderate increases of beta carotene intake, achievable by dietary modification, could reduce the frequency of severe acute effects of radiation therapy without interfering with radiation therapy efficacy.

In our study, we used 2 complementary methods to estimate participants' usual intake of beta carotene. Because patients taking alpha tocopherol or beta carotene supplements were not eligible for randomization in the chemoprevention trial, plasma beta carotene is a good estimate of dietary intake over a few wk preceding blood collection. There is good evidence that plasma carotenoids, including beta carotene, are good indicators of their long-term dietaryintakes (24). The food frequency questionnaire used in our study was especially designed and validated to provide a reliable measure of beta carotene intake (17). Nevertheless, reporting errors from participants about portion sizes or frequency of intakes and potential inadequacy of the food composition table could have affected the estimate of dietary beta carotene. The dietary and plasma measures should be interpreted in complementarity. The dietary measure may overestimate recent intake and be closer to long-term intake, whereas the plasma measure may provide a better estimate of recent intake and underestimate long-term intake. The sources of errors affecting the estimates of beta carotene from plasma and from the food frequency questionnaire are unrelated (25). These measurement errors were comparable for all participants and could only have created nondifferential misclassification. In our study, the results from dietary and plasma beta carotene are consistent and complementary, reflecting the effect of long-term dietary intake of beta carotene.

These results should be compared to those observed with the supplementation in our trial (8). Some participants received a supplementation combining alpha tocopherol (400 IU/day) and beta carotene (30 mg/day) or placebos, and some others received the alpha tocopherol supplement or its placebo only. Patients randomized in the supplement arm who received both beta carotene and alpha tocopherol had fewer severe acute adverse effects during radiation therapy (OR = 0.38, 95% CI = 0.20–0.74). Supplementation with alpha tocopherol only had no effect on acute adverse effects of radiation therapy (OR = 0.92, 95% CI = 0.62–1.38). The rate of local recurrence of the head and neck tumor tended to be higher in the supplement arm of the trial. This adverse effect of supplementation on local recurrence was observed among the participants who received both alpha tocopherol and beta carotene supplements (HR = 1.56, 95% CI = 0.79–

Table 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Severe Adverse Effects of Radiation Therapy to the Mucosa, to the Larynx, and Overall Associated With Dietary and Plasma Beta Carotene and Alpha Tocopherol Among All Patients and by Intervention Arm

	Severe Adverse Effects of Radiation Therapy to the Mucosa		Severe Adverse Effects of Radiation Therapy to the Larynx		Severe Adverse Effects of Radiation Therapy Overall	
	OR	95% CI	OR	95% CI	OR	95% CI
Dietary beta carotene intake						
All patients[a]	0.62	0.36–1.07	0.56	0.32–0.99	0.61	0.40–0.93
Placebo arm[b]	0.85	0.41–1.78	0.68	0.32–1.44	0.68	0.38–1.22
Supplementation arm[b]	0.42	0.18–0.96	0.42	0.17–1.07	0.52	0.28–0.99
Dietary alpha tocopherol intake						
All patients[a]	0.81	0.42–1.55	1.15	0.58–2.27	0.95	0.57–1.59
Placebo arm[b]	0.88	0.36–2.15	0.93	0.37–2.33	0.78	0.38–1.59
Supplementation arm[b]	0.73	0.29–1.89	1.52	0.54–4.25	1.19	0.57–2.51
Plasma beta carotene						
All patients[c]	0.55	0.32–0.94	0.82	0.47–1.42	0.73	0.48–1.11
Placebo arm[d]	0.60	0.29–1.27	0.89	0.43–1.87	0.70	0.39–1.24
Supplementation arm[d]	0.50	0.23–1.09	0.73	0.32–1.66	0.77	0.42–1.40
Plasma alpha tocopherol						
All patients[e]	1.72	0.95–3.13	1.43	0.78–2.61	1.24	0.78–1.97
Placebo arm[f]	1.61	0.72–3.64	1.15	0.51–2.57	1.11	0.59–2.09
Supplementation arm¶	1.84	0.77–4.42	1.84	0.73–4.64	1.39	0.71–2.75

a: ORs after adjustment for intervention arm and dietary energy intake. There was no interaction between intervention arm and dietary beta carotene ($P = 0.56$) or alpha tocopherol ($P = 0.67$).
b: ORs after adjustment for dietary energy intake.
c: ORs after adjustment for intervention arm. There was no interaction between intervention arm and plasma beta carotene ($P = 0.79$).
d: Crude ORs.
e: ORs after adjustment for intervention arm and plasma cholesterol. There was no interaction between intervention arm and plasma alpha tocopherol ($P = 0.86$).
f: ORs after adjustment for plasma cholesterol.

3.07) as well as among those who received alpha tocopherol supplement alone (HR = 1.29, 95% CI = 0.89–2.08). The randomized trial and this prospective study suggest that alpha tocopherol, either from diet or from supplements, cannot protect against radiation therapy severe acute adverse effects and does not reduce cancer recurrence. On the other hand, there is evidence that beta carotene, either from diet or from supplements, is able to reduce the frequency of severe acute adverse effects of radiation therapy. There is a striking contrast, however, between dietary and supplemental beta carotene concerning the risk of local recurrence: evidence of a protective effect of usual dietary intake (as reflected by plasma level) and suggestion of an increased risk from supplementation.

Although the tests for interaction between the trial intervention arm and all 4 diet and plasma alpha tocopherol and beta carotene variables were not statistically significant, we presented arm-specific measures of association in addition to those based on the entire trial population. These results could suggest the hypothesis that dietary and plasma beta carotene are associated with cancer recurrence only in the intervention arm. Because the supplementation in the trial tended to increase cancer recurrence, dietary or plasma beta carotene could have reduced the adverse effects from the supplementation. However, these considerations are speculative because there could be no true difference between intervention arms. Antioxidant vitamins, including beta carotene, can modify the effects of irradiation on normal and cancer cells (26). In our study, both dietary beta carotene and high-dose supplementation with beta carotene were associated with a reduction in the frequency and severity of severe adverse effects of radiation therapy. This reflects the capacity of beta carotene over a large range of doses to protect normal tissues against radiation damage. It was speculated that antioxidant vitamins at high doses would be cytotoxic for tumor cells but not for normal cells (26). In our trial, the increased local cancer recurrence among patients in the supplementation arm suggests that, contrary to expectations, the antioxidant supplementation may have reduced the efficacy of radiation therapy presumably by protecting the tumor cells from radiation damage. No such undesirable effect was seen for dietary or plasma beta carotene.

The risk of cancer recurrence associated with dietary or supplemental antioxidant vitamins has been rarely studied. Randomized trials have examined the influence of antioxidant vitamins on colorectal adenoma recurrence (27,28). In the Antioxidant Polyp Prevention Study, supplementation with beta carotene (25 mg per day) did not affect adenoma recurrence overall (27). In the Polyp Prevention Trial, a dietary intervention aiming at increasing fiber, fruit, and vegetable

Table 3. Baseline Characteristics of Patients According to Local Recurrence of Head and Neck Cancer

Characteristic	Local Recurrence $N = 103$	No Local Recurrence $N = 437$	P Value
Supplementation arm of trial No. of patients (%)	59 (57)	214 (49)	0.13
Laryngeal cancer No. of patients (%)	74 (72)	376 (86)	0.0005
Stage II No. of patients (%)	61 (59)	147 (34)	<0.0001
Total dose of radiation therapy, gy Mean (SD)	62.8 (7.3)	61.2 (7.6)	0.06
No of radiation therapy fractions Mean (SD)	29.7 (5.9)	28.9 (5.9)	0.20
Age (yr) Mean (SD)	59.5 (10.2)	63.2 (9.5)	0.0007
Female sex No. of patients (%)	24 (23)	90 (21)	0.54
Smokers in preceding yr No. of patients (%)	74 (72)	269 (62)	0.05
Smokers at time of randomization No. of patients (%)	29 (28)	104 (24)	0.36
Body mass index, kg/m^2 Mean (SD)	25.9 (4.4)	26.1 (4.8)	0.62
Dietary beta carotene intake, mg/day Median	4.69	4.94	0.26
Dietary alpha tocopherol intake, mg/day Median	5.60	5.43	0.71
Dietary energy intake, kcal/day Median	1,852	1,885	0.98
Plasma beta carotene, μmol/l Median	0.15	0.18	0.11
Plasma alpha tocopherol, μmol/l Median	31.3	31.4	0.85
Plasma cholesterol, mmol/l Median	5.36	5.65	0.69

Table 4. Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Local Recurrence of Head and Neck Cancer Associated With Baseline Dietary and Plasma Beta Carotene and Alpha Tocopherol Among All Patients and by Intervention Arm

	Local Recurrence of Head and Neck Cancer	
	HR	95% CI
Dietary beta carotene intake		
All patients[a]	0.93	0.63–1.38
Placebo arm[b]	1.37	0.74–2.52
Supplementation arm[b]	0.70	0.41–1.18
Dietary alpha tocopherol intake		
All patients[a]	1.10	0.68–1.78
Placebo arm[b]	1.56	0.75–3.26
Supplementation arm[b]	0.86	0.45–1.64
Plasma beta carotene		
All patients[c]	0.67	0.45–0.99
Placebo arm[d]	0.90	0.50–1.64
Supplementation arm[d]	0.54	0.32–0.91
Plasma alpha tocopherol		
All patients[e]	0.81	0.52–1.26
Placebo arm[f]	0.75	0.39–1.47
Supplementation arm¶	0.84	0.47–1.50

a: HRs after adjustment for intervention arm and dietary energy intake. There was no interaction between intervention arm and dietary beta carotene ($P = 0.12$) or alpha tocopherol ($P = 0.44$).
b: HRs after adjustment for dietary energy intake.
c: HRs after adjustment for intervention arm. There was no interaction between intervention arm and plasma beta carotene ($P = 0.20$).
d: Crude HRs.
e: HRs after adjustment for intervention arm and plasma cholesterol. There was no interaction between intervention arm and plasma alpha tocopherol ($P = 0.88$).
f: HRs after adjustment for plasma cholesterol.

intakes and at reducing fat consumption was not associated with a reduction in the recurrence of adenomatous polyps (28). It is interesting to note that a prospective cohort study conducted in the Polyp Prevention Trial population reported a lower polyp recurrence among subjects with higher serum levels of beta carotene and alpha carotene and with higher dietary intakes of carotenoids (29).

In recent years, supplementation trials have failed to corroborate experimentally the protective effect of antioxidant vitamins observed in epidemiological prospective studies looking at usual dietary intakes. Many reasons have been evoked to explain the discrepancy including differences in timing, doses, and associated compounds and the possibility that beta carotene may not be the real agent but only surrogate of it, a marker of fruit and vegetable intake. A high consumption of fruits and vegetables has been advocated for many years for cancer control. Dietary modifications following this recommendation increase beta carotene intake and its plasma level. Our study suggests that subjects with dietary intakes in accordance with these recommendations have, when they develop HNC, a more favorable response to radiation therapy.

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References

1. Ladas EJ, Jacobson JS, Kennedy DD, Teel K, Fleishauer, et al.: Antioxidants and cancer therapy: a systematic review. *J Clin Oncol* **22,** 517–528, 2004.
2. Weiger WA, Smith M, Boon H, Richardson MA, Kaptchuk TJ, et al.: Advising patients who seek complementary and alternative medical therapies for cancer. *Ann Intern Med* **137,** 889–903, 2002.
3. Brown J, Byers T, Thompson K, Eldridge B, Doyle C, et al.: Nutrition during and after cancer treatment: a guide for informed choices by cancer survivors. *CA Cancer J Clin* **51,** 153–187, 2001.
4. Camphausen K, Citrin D, Krishna MC, and Mitchell JB: Implications for tumor control during protection of normal tissues with antioxidants. *J Clin Oncol* **23,** 5455–5457, 2005.
5. Seifreid HE, McDonald SS, Anderson DE, Greenwald P, Milner JA, et al.: The antioxidant conundrum in cancer. *Cancer Res* **63,** 4295–4298, 2003.
6. Prasad KN, Cole WC, Kumar B, and Prasad KC: Pros and cons of antioxidant use during radiation therapy. *Cancer Treat Rev* **28,** 79–91, 2002.
7. Lamson DW and Brignall MS: Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. *Altern Med Rev* **5,** 304–329, 1999.
8. Bairati I, Meyer F, Gélinas M, Fortin A, Nabid A, et al.: Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. *J Clin Oncol* **23,** 5805–5813, 2005.
9. Marshall JR: β-Carotene: a miss for epidemiology. *J Natl Cancer Inst* **91,** 2068–2069, 1999.
10. World Cancer Research Fund: *Food, Nutrition and The Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research, 1997, pp. 136–142.
11. Alpha-tocopherol, beta-carotene prevention study group: the effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* **330,** 1029–1035, 1994.
12. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, et al.: Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* **334,** 1150–1155, 1996.
13. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, et al.: Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* **334,** 1145–1149, 1996.
14. Lee IM, Cook NR, Manson JE, Buring JE, and Hennekens CH: β-Carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst* **91,** 2102–2106, 1999.
15. Bairati I, Meyer F, Gélinas M, Fortin A, Nabid A, et al.: A randomized trial of antioxidant vitamins to prevent second primary cancers in head and neck cancer patients. *J Natl Cancer Inst* **97,** 481–488, 2005.
16. Karnofsky DA and Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer. In *Evaluation of Chemotherapeutic Agents,* MacLeod CM (ed.). New York, NY: Columbia Press, 1949, pp. 191–205.
17. Labbé J: *Validation d'un questionnaire de fréquence alimentaire semi-quantitatif chez des patients québécois atteints d'un cancer de la tête et du cou*. Mémoire de maîtrise, Université Laval, Quebec, Canada, 1996.
18. Health Canada. Canadian Nutrient File. Ottáwa. http://www.hc-sc.gc.ca/fnan/nutrition/fiche-nutri-data/index_e.html. Accessed August 13th, 2007.
19. Miller KW, Lorr NAS, and Yang CS: Simultaneous determination of plasma retinol, alpha-tocopherol, lycopene, alpha-carotene, and beta-carotene by high-performance liquid chromatography. *Anal Biochem* **138,** 340–345, 1984.
20. Catignani GL and Bieri JG: Simultaneous determination of retinol and α-tocopherol in serum or plasma by liquid chromatography. *Clin Chem* **29,** 708–712, 1983.
21. Cox JD, Stetz J, and Pajak TF: Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiation Oncol Biol Phys* **31,** 1341–1346, 1995.
22. Lemeshow S and Hosmer DW: *Applied Logistic Regression*. New York, NY: John Wiley & Sons, 1989.
23. Collett D: Modelling Survival Data in Medical Research, 2nd ed. Boca Raton, FL: Chapman & Hall, CRC press, 2003.
24. McEligot AJ, Rock CL, Flatt SW, Newman V, Faerber S, et al.: Plasma carotenoids are biomarkers of long-term vegetable intake in women with breast cancer. *J Nutr* **129,** 2258–2263, 1999.
25. Willett WC: *Nutritional Epidemiology.* New York, NY: Oxford University Press, 1990.
26. Prasad KN: *Handbook of Radiobiology,* 2nd ed. Boca Raton, FL: CRC Press,1995.
27. Greenberg ER, Baron JE, Tosteson TD, Freeman DH Jr., Beck GJ, et al.: A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group. *N Engl J Med* **331,** 141–147, 1994.
28. Schatzkin A, Lanza E, Corle D, Lance P, Iber F, et al.: Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas: Polyp Prevention Trial Study Group. *N Engl J Med* **342,** 1149–1155, 2000.
29. Steck-Scott S, Forman MR, Sowell A, Borkowf CB, Albert PS, et al.: Carotenoids, vitamin A and risk of adenomatous polyp recurrence in the Polyp Prevention Trial. *Int J Cancer* **112,** 295–305, 2004.