

A Randomized Trial of Antioxidant Vitamins to Prevent Second Primary Cancers in Head and Neck Cancer Patients

Isabelle Bairati, François Meyer, Michel Gélinas, André Fortin, Abdenour Nabid, François Brochet, Jean-Philippe Mercier, Bernard Têtu, François Harel, Benoît Mâsse, Eric Vigneault, Sylvie Vass, Pierre del Vecchio, Jean Roy†

Background: Although low dietary intakes of antioxidant vitamins and minerals have been associated with higher risks of cancer, results of trials testing antioxidant supplementation for cancer chemoprevention have been equivocal. We assessed whether supplementation with antioxidant vitamins could reduce the incidence of second primary cancers among patients with head and neck cancer. **Methods:** We conducted a multicenter, double-blind, placebo-controlled, randomized chemoprevention trial among 540 patients with stage I or II head and neck cancer treated by radiation therapy between October 1, 1994, and June 6, 2000. Supplementation with α -tocopherol (400 IU/day) and β -carotene (30 mg/day) or placebo began on the first day of radiation therapy and continued for 3 years after the end of radiation therapy. In the course of the trial, β -carotene supplementation was discontinued after 156 patients had enrolled because of ethical concerns. The remaining patients received α -tocopherol or placebo only. Survival was evaluated by Kaplan-Meier analysis. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical tests were two-sided. **Results:** After a median follow-up of 52 months, second primary cancers and recurrences of the first tumor were diagnosed in 113 and 119 participants, respectively. The effect of supplementation on the incidence of second primary cancers varied over time. Compared with patients receiving placebo, patients receiving α -tocopherol supplements had a higher rate of second primary cancers during the supplementation period (HR = 2.88, 95% CI = 1.56 to 5.31) but a lower rate after supplementation was discontinued (HR = 0.41, 95% CI = 0.16 to 1.03). Similarly, the rate of having a recurrence or second primary cancer was higher during (HR = 1.86, 95% CI = 1.27 to 2.72) but lower after (HR = 0.71, 95% CI = 0.33 to 1.53) supplementation with α -tocopherol. The proportion of participants free of second primary cancer overall after 8 years of follow-up was similar in both arms. **Conclusions:** α -Tocopherol supplementation produced unexpected adverse effects on the occurrence of second primary cancers and on cancer-free survival. [J Natl Cancer Inst 2005;97:481-8]

Epidemiologic studies suggest that low dietary intake and low plasma concentrations of antioxidant vitamins and minerals are associated with increased risks of cancer, especially for epidermoid tumors (1,2). However, large randomized controlled trials that evaluated the relationship between antioxidant vitamin and mineral supplements and cancer incidence have been conducted in the general population (3-5) and in smokers (6,7), with varying results. Since the 1980s, α -tocopherol and β -carotene have been the most studied vitamins in cancer chemoprevention trials because of their antioxidant properties (8).

Squamous cell carcinomas of the oral cavity, pharynx, and larynx, referred to as head and neck cancers, account for 3% to 4% of all newly diagnosed cancers in Canada (9). Between 40% and 50% of head and neck cancers are diagnosed at stage I or II. These patients have a good prognosis, with a 5-year relative survival of 60% to 90%, depending on the site of the tumor (10). However, the benefit of treatment is often compromised by the occurrence of second primary cancers, which develop in 15% to 20% of patients during the first 5 years after diagnosis (10-12). Thus, it is important to determine whether interventions such as supplementation with antioxidant vitamins could reduce the risk of second primary cancers in this patient population (8,13-15).

In 1994, we initiated a randomized trial among patients with head and neck cancer treated by radiation therapy to determine whether supplementation combining the two most promising antioxidant vitamins, α -tocopherol and β -carotene, could reduce the incidence of second primary cancers and improve cancer-free survival (13). Here, we report the results of the trial for these two outcomes.

Affiliations of authors: Centre de Recherche en Cancérologie de L'Université Laval (IB, FM, BT, FH) and the Centre Hospitalier Universitaire de Québec (AF, EV, JR), Québec City, Québec, Canada; the Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada (MG, PDV); the Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec, Canada (AN); the Complexe Hospitalier de la Sagamie, Saguenay, Québec, Canada (FB, SV); the Hôpital Maisonneuve-Rosemont, Montréal, Québec, Canada (J-PM); the Fred Hutchinson Cancer Research Center, Seattle, WA (BM).

Correspondence to: François Meyer, MD, DSc, Centre de Recherche en Cancérologie, Université Laval, 11 côte du Palais, Québec, Québec G1R 2J6, Canada (e-mail: francois.meyer@chuq.qc.ca).

†Deceased.

See "Notes" following "References."

DOI: 10.1093/jnci/dji095

Journal of the National Cancer Institute, Vol. 97, No. 7, © Oxford University Press 2005, all rights reserved.

SUBJECTS AND METHODS

Study Design

We conducted a multicenter, double-blind, placebo-controlled, randomized chemoprevention trial among patients treated by radiation therapy for stage I or II head and neck cancer. The primary objective of the trial was to assess whether the intervention would reduce the incidence of second primary cancers; the second objective was to assess whether the intervention would reduce the adverse effects of radiation therapy without compromising treatment efficacy; the third objective was to assess whether the intervention would improve cancer-free survival. The institutional review board of each participating center approved the study protocol. All patients gave written informed consent prior to randomization. An independent ethical and safety monitoring committee was established to provide guidance to the investigators.

Study Population

Eligible patients were aged 18 years or older; had received a first diagnosis of stage I or II, histologically documented, squamous cell carcinoma of the tongue, gum, mouth, oropharynx, hypopharynx, pharynx, or larynx; and were scheduled to be treated by radiation therapy between October 1, 1994, and June 6, 2000, in one of five radiation therapy centers in the province of Quebec, Canada. Patients with any of the following conditions were ineligible for the study: a Karnofsky performance score (16) of less than 60; multiple primary head and neck cancers or a history of cancer; severe cardiovascular disease; inadequate renal, hepatic, or hematologic function; anticoagulant therapy; pregnancy; or average daily supplement intake of β -carotene or vitamin E in the preceding year greater than 6.0 mg and 50 IU, respectively.

Intervention

A computer-generated randomization list was prepared in advance for each collaborating center by using an allocation ratio of 1:1 (supplementation to placebo) and random-permuted blocks. For each eligible patient, the randomization number was obtained from the coordinating center through a telephone call. Patients were randomly assigned to receive a daily supplementation consisting of α -tocopherol (one capsule of 400 IU dl- α -tocopherol) and β -carotene (one capsule of 30 mg) or placebos during radiation therapy and for 3 years after radiation therapy ended. The intervention began on the first day of radiation treatment so that we could assess whether the supplementation could reduce the adverse effects of radiation therapy without compromising treatment efficacy, which was the trial's second objective (13,17). All capsules were supplied by Roche Vitamins Inc. (Parsippany, NJ). Bottles containing the capsules were prepared centrally at St-Sacrement Hospital in Quebec City by a single pharmacist according to the randomization lists and were identified by the randomization number. Throughout the trial, the patients, the treating physicians, the study personnel, and the investigators were kept blind to the patients' intervention arm assignment.

Discontinuation of Beta Carotene

Patients were already enrolled in the trial when the results of two large trials using β -carotene supplements were released in January 1996 (National Cancer Institute Press Conference of

January 18, 1996). One study showed an increase in lung cancer incidence associated with a supplementation comprising β -carotene (7), whereas the other showed no association of β -carotene supplementation with cancer incidence (4). Subsequently, the ethical and safety monitoring committee for this trial recommended halting the use of β -carotene but continuing the trial with α -tocopherol alone. The ethical and safety monitoring committee also recommended that the potential effects of the combination of β -carotene and α -tocopherol supplements on study outcomes be examined at the end of the study for the first 156 patients enrolled before β -carotene supplementation was halted. The committee requested that the main analyses be conducted in two ways: 1) among all participants and 2) by excluding the first 156 patients. The trial investigators followed all the committee recommendations.

Data Collection and Follow-Up

Baseline data collection was completed before patients were randomly assigned. The study nurses administered several questionnaires on patients' characteristics, including socioeconomic data, height and weight, alcohol consumption, smoking, and diet. Medical history was recorded. The radiation oncologists provided detailed information on the primary tumor: precise site, dimensions, and clinical stage according to the fourth tumor-node-metastasis (TNM) classification (18). Follow-up information was obtained by the radiation oncologists and the study nurses at predetermined times: immediately and 1 month after radiation therapy ended, every 6 months during the 3 years following the end of radiation therapy, and then once a year until the end of the study (June 30, 2003). Patients were asked to report all potential side effects, which were coded according to the National Cancer Institute of Canada Clinical Trial Group expanded common toxicity criteria (19). At each follow-up visit during the supplementation period, the study nurse assessed compliance separately for each supplement or placebo by dividing the total number of unreturned capsules by the number of days between visits. A 10-mL blood specimen was collected at baseline, at the end of radiation therapy, and at 6, 12, 24, and 36 months after the end of radiation therapy. Plasma α -tocopherol and β -carotene were analyzed by reverse-phase high-performance liquid chromatography according to established methods (20,21). During each visit, the radiation oncologists assessed the recurrence of the initial tumor and the occurrence of any second primary cancer. Medical notes and hospital records were requested for all important health events and hospitalizations during follow-up. Copies of pathology reports were obtained from the appropriate medical centers. Death certificates were obtained either from the hospital where the patient had died or from the Institut de la statistique du Québec. As per protocol, follow-up was continued beyond the supplementation period because a prolonged residual effect of antioxidant supplementation was anticipated (22). Follow-up ended when the last patient enrolled had completed the supplementation period on June 30, 2003.

Outcome

The diagnosis of a second primary cancer was made according to one of the following four criteria (23–25): 1) if the second primary cancer is of the same histologic type as the first cancer, then there must be at least 2 cm of normal epithelium between the first cancer and the second; 2) any new cancer of a different histologic type qualifies as a second primary cancer without the

2-cm separation requirement; 3) if the second primary cancer is a lung cancer of the same histologic type as the first cancer, then it must be a solitary nodule without evidence of metastasis in the anterior cervical lymph nodes; and 4) any new lung cancer of a different histologic type qualifies as a second primary cancer without these restrictions. Cancer-free survival was defined as survival without a second primary cancer and recurrence (local, nodal, or distant) of the initial cancer.

Statistical Analysis

The accrual goal was set before the beginning of the trial at 555 randomized patients based on the following criteria: enrollment period of 42 months, total study duration of 87 months, overall second primary cancer rate of 2.6% per year, censoring rate of 3.0% per year because of death or loss of follow-up, statistical power of 80% to detect a 50% reduction of the rate of second primary cancers in the supplement arm compared with the placebo arm by using a proportional hazards regression model with a two-sided $\alpha = 0.05$ (26).

In accordance with the study protocol and the decision of the ethical and safety monitoring committee, no interim analysis was conducted. For the analysis of the main outcome (i.e., the incidence of second primary cancer), follow-up time was calculated from the time of randomization until the first occurrence of a second primary cancer, death, or date of last visit. For the analysis of cancer-free survival, follow-up continued until the first event among the following: recurrence of the initial cancer, occurrence of a second primary cancer, death, or date of last visit. Distribution of time until failure in the two treatment arms was described using Kaplan-Meier survival curves. The primary analysis, performed under the intention-to-treat principle, was designed to compare the rates of second primary cancers in the two study arms in Cox proportional hazards models (27). For each hazard ratio (HR), the 95% confidence interval (CI) was calculated. The Cox models were used to adjust for covariates and to take participating treatment centers into account. However, none of the observed effects was confounded by patient baseline characteristics. Analyses stratified by center yielded the same results as the crude analyses (data not shown). We assessed whether smoking (current versus past or never smokers) modified the association between supplementation and the two main outcomes, second primary cancer incidence and cancer-free survival.

The proportionality assumption of the models was assessed 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 (27,28). Because the proportionality assumption was not satisfied for the main outcome over the entire follow-up period, the analyses were performed by partitioning the time: 1) from entry until 3.5 years after randomization, and 2) beyond 3.5 years after randomization. The cutoff at 3.5 years after randomization coincided with the loss of parallelism on the log-log plots. The period of entry to 3.5 years after randomization corresponded to the duration of the supplementation plus a few months.

The initial trial power calculation was revisited with the actual data: 540 patients were randomly assigned over a 69-month period, with a total study duration of 106 months, an overall second primary cancer rate of 3.9% per year, and a censoring rate of 5.4% per year because of death or loss of follow-up. Thus, the study had 90.6% power to detect the set hazard ratio of 0.50.

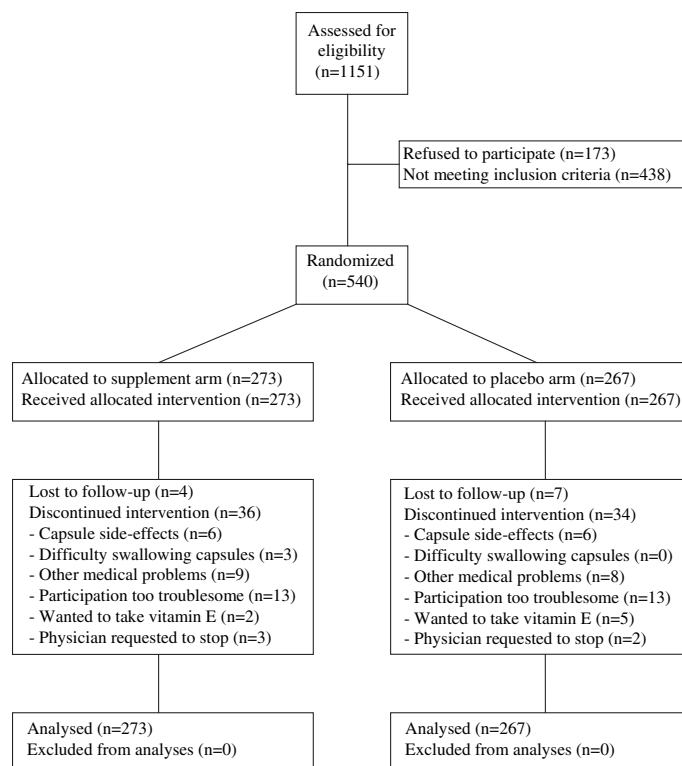


Fig. 1. Flow diagram of subjects' progress through the trial.

Because the first 156 patients enrolled in the trial had received β -carotene in addition to α -tocopherol or their placebos, the analyses were also conducted separately for the first 156 participants and for the 384 patients subsequently enrolled. After excluding the first 156 patients, the trial power was 75.5%. All analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). All statistical tests were two-sided.

RESULTS

Participants

During the recruitment period, 1151 new patients with stage I or II squamous cell carcinoma of the head and neck were treated in the participating radiation oncology centers. Of these 1151, 15% refused to participate and 38% were ineligible. The remaining 47% ($n = 540$) were eligible and consented to be enrolled (Fig. 1). The baseline characteristics of the 273 and 267 patients randomly assigned to the supplement and placebo arms, respectively, were similar between the two groups (Table 1). Four patients (one in the

Table 1. Baseline characteristics of the 540 patients with head and neck cancer randomly assigned to the supplement or placebo arm of the trial

Characteristic	Supplement arm (N = 273)	Placebo arm (N = 267)
Mean age (SD), y	62.9 (10.0)	62.3 (9.5)
No. of men (%)	223 (82)	203 (76)
No. with stage T2 disease (%)	101 (37)	107 (40)
No. with laryngeal cancer (%)	225 (82)	225 (84)
No. who smoked in preceding year (%)	178 (65)	165 (62)
Mean plasma β -carotene (SD), $\mu\text{mol/L}$	0.23 (0.18)	0.23 (0.24)
Mean plasma α -tocopherol (SD), $\mu\text{mol/L}$	32.6 (10.4)	33.8 (14.2)

*SD = standard deviation.

Table 2. Number of side effects of any grade attributed to the supplementation in each arm of the trial according to the National Cancer Institute of Canada Clinical Trial Group expanded common toxicity criteria categories

Side effect	Supplement arm (N = 273)	Placebo arm (N = 267)
Cardiovascular	1	0
Endocrine	1	0
Flu-like symptoms	3	0
Gastrointestinal	31	23
Genitourinary	1	1
Neurologic	3	2
Skin	3	6
Yellowing of the skin	19	0
Total	62	32

supplement arm and three in the placebo arm) did not complete their radiation therapy as planned but were included in the analyses.

Compliance

During the supplementation period, 36 participants in the supplement arm and 34 in the placebo arm stopped taking the capsules for the reasons mentioned in Fig. 1. Compliance, as assessed by capsule count, was similar in the two arms. In the supplement arm, compliance was 90% during radiation therapy and 88%, 84%, and 80% during the first, second, and third years after the end of radiation therapy, respectively. In the placebo arm, these figures were 89%, 86%, 83%, and 80%, respectively. Compliance was also assessed by measuring levels of α -tocopherol and β -carotene in plasma during the supplementation period. For patients who received β -carotene supplements, the mean plasma β -carotene level increased from 0.23 $\mu\text{mol/L}$ at baseline to 2.7 $\mu\text{mol/L}$ at the end of radiation therapy; the corresponding figures were 0.23 $\mu\text{mol/L}$ and 0.22 $\mu\text{mol/L}$ for patients in the placebo arm. Once β -carotene supplementation was discontinued, plasma β -carotene levels of patients in the supplement arm returned to baseline levels. Three years after the end of radiation therapy, the mean plasma β -carotene levels were 0.29 $\mu\text{mol/L}$ and 0.23 $\mu\text{mol/L}$ in the supplement arm and in the placebo arm of the trial respectively. For patients in the supplement arm, the average plasma α -tocopherol level increased from 32.6 $\mu\text{mol/L}$ at baseline to 60.9 $\mu\text{mol/L}$ at the end of radiation therapy; the corresponding figures were 33.8 $\mu\text{mol/L}$ and 30.2 $\mu\text{mol/L}$ in the placebo arm. In the supplement arm, the average plasma α -tocopherol level remained high, between 60.9 $\mu\text{mol/L}$ and 70.2 $\mu\text{mol/L}$, during the 3 years following the end of radiation therapy,

Table 3. Number of second primary cancers by site in each arm of the trial

Second primary cancer site	Supplement arm (N = 273)	Placebo arm (N = 267)
Lung or trachea	27	26
Head and neck	7	5
Prostate	7	5
Colon or rectum	5	4
Basal-cell carcinoma of the skin	7	3
Squamous-cell carcinoma of the skin	2	1
Kidney	2	1
Breast	1	2
Bladder	2	0
Oesophagus	1	1
Others	2	2
Smoking-related second primary cancers	39	33
Total	63	50

whereas the mean plasma α -tocopherol level in the placebo arm ranged from 30.2 $\mu\text{mol/L}$ to 33.3 $\mu\text{mol/L}$ during these 3 years.

Supplementation Side Effects

Side effects of any severity grade were attributed to the supplementation by 42% of the participants who received both α -tocopherol and β -carotene supplements (mostly yellowing of the

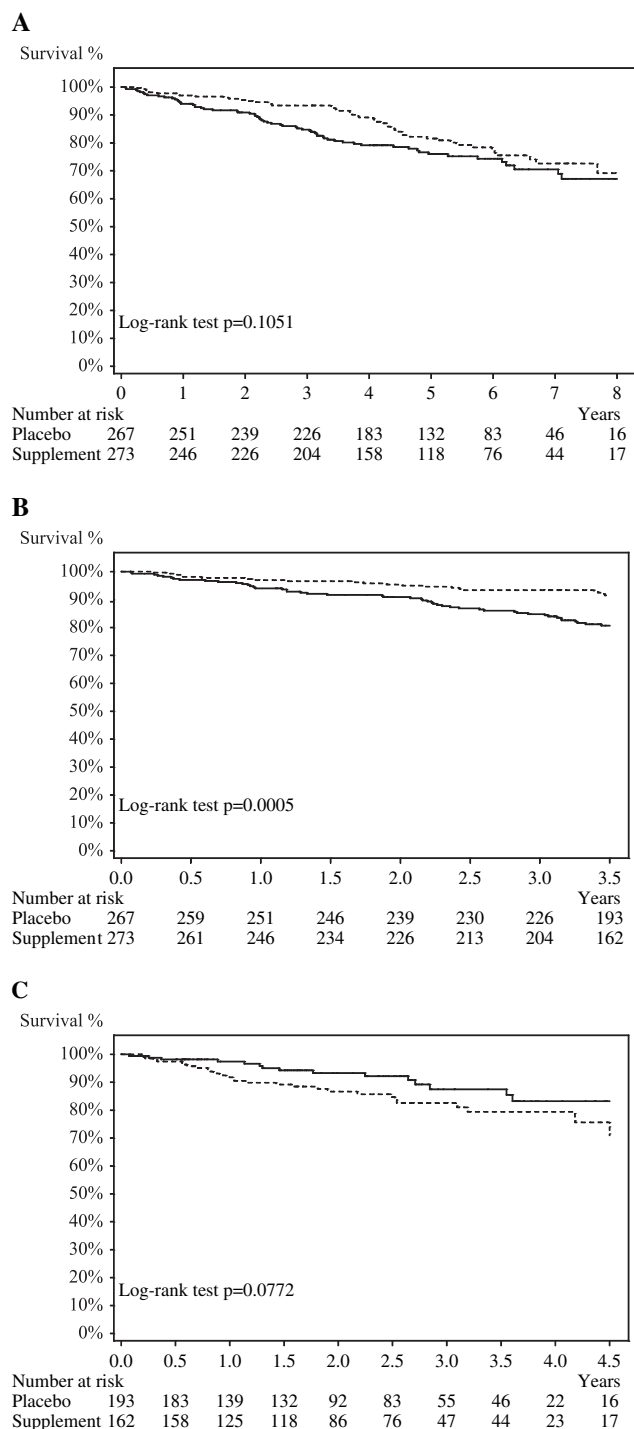


Fig. 2. Kaplan-Meier curves of survival until occurrence of a second primary cancer among participants randomly assigned to the supplement arm (solid line) or to the placebo arm (dotted line) for the entire follow-up period (A), during the first 3.5 years after randomization (B), and beyond 3.5 years after randomization (C). Data are shown only up to 8 years of follow-up because of the small numbers of participants beyond that time.

skin) and by 16% of those who received both placebos. When α -tocopherol alone was used, side effects of any severity grade were reported by 6% and 8% of participants in the supplement and placebo arms, respectively. During the entire trial, there was no life-threatening side effect (grade 4) and only one severe (grade 3) side effect (abdominal pain), which occurred in a patient in the placebo arm. Overall, patients in the supplement arm reported 62 side effects of any grade attributed to the supplementation, whereas those in the placebo arm reported 32 such side effects. A list of the side effects, categorized according to the National Cancer Institute of Canada (NCIC) Clinical Trial Group, is presented in Table 2 (19).

Second Primary Cancers

After a median follow-up of 52 months, second primary cancers were diagnosed in 113 patients. The main sites of second primary cancers were the lung and trachea (53 patients), the prostate (12 patients), and the head and neck (12 patients). The complete list of second primary cancers is presented in Table 3. Only 11 participants (four in the supplement arm and seven in the placebo arm) who were still alive on June 30, 2003, had had their last visit more than 1 year before this date and were considered lost to follow-up. The distribution of survival time until the occurrence of a second primary cancer is presented for the two treatment arms over the entire study period (Fig. 2A), during the first 3.5 years (Fig. 2B), and beyond 3.5 years after randomization (Fig. 2C).

Table 4 presents the crude hazard ratios associated with supplementation in the two consecutive follow-up periods. During the first 3.5 years of follow-up, the rate of second primary cancers was statistically significantly higher among patients in the supplement arm (60 per 1000 person-years) than among patients in the placebo arm (25 per 1000 person-years), HR = 2.42 (95% CI = 1.45 to 4.04), especially when α -tocopherol was the only supplement (HR = 2.88, 95% CI = 1.56 to 5.31). After supplementation was discontinued, former supplement users had a lower rate of second primary cancers (39 per 1000 person-years) than former placebo users (69 per 1000 person-years): HR = 0.57 (95% CI = 0.31 to 1.07). The inverse association was stronger when α -tocopherol was the only supplement (HR = 0.41, 95% CI = 0.16 to 1.03). Smoking did not modify the association between supplementation use and rate of second primary cancers in either of the two time periods. During the first 3.5 years of follow-up, the hazard ratio of second primary cancers associated with supplementation was 2.37 (95% CI = 1.27 to 4.42) among smokers and 2.48 (95% CI = 1.01 to 6.08) among nonsmokers.

Cancer-Free Survival

We determined cancer-free survival for the two treatment arms over the entire study period (Fig. 3A), during the first 3.5 years (Fig. 3B), and beyond 3.5 years (Fig. 3C). There were 215 events: 92 local recurrences, 14 lymph node recurrences, 8 distant metastases of the first cancer, and 101 second primary cancers (12 patients had a recurrence of the first cancer before a second primary cancer). Table 5 shows that, during the first 3.5 years of follow-up, the rate of having either a recurrence or second primary cancer was statistically significantly higher among patients in the supplement arm (141 per 1000 person-years) than among patients in the placebo arm (85 per 1000 person-years): HR = 1.65 (95% CI = 1.21 to 2.25), especially when α -tocopherol was the only supplement (HR = 1.86, 95% CI = 1.27 to 2.72). After supplementation was discontinued, former supplement users had lower rates of either recurrence or second primary cancer (65 per 1000 person-years) than patients who received placebo (76 per 1000 person-years): HR = 0.85 (95% CI = 0.48 to 1.50), especially when α -tocopherol was the only supplement (HR = 0.71, 95% CI = 0.33 to 1.53). Smoking did not modify the association between supplementation use and cancer-free survival in either of the two time periods. During the first 3.5 years of follow-up, the hazard ratio of either a recurrence or second primary cancer associated with the supplementation was 1.64 (95% CI = 1.13 to 2.38) among smokers and 1.62 (95% CI = 0.92 to 2.83) among nonsmokers.

Because approximately 50% of the events in the cancer-free survival analysis were recurrences of the initial tumor, we also examined the effect of supplementation use on cancer recurrence. More than 90% of all 119 recurrences (five of these 119 patients had a second primary cancer before a recurrence of the first cancer) occurred during the first 3.5 years after randomization. Because the proportionality assumption of the Cox model was satisfied for this outcome, only hazard ratios over the entire follow-up period are presented: 1.41 (95% CI = 0.98 to 2.02) for any supplement, 1.36 (95% CI = 0.74 to 2.51) for α -tocopherol and β -carotene, and 1.44 (95% CI = 0.91 to 2.26) for α -tocopherol alone.

DISCUSSION

In this chemoprevention trial, α -tocopherol and β -carotene supplements were given to patients at high risk of second primary cancers with the primary aim of determining whether supplementation would reduce their incidence of second primary

Table 4. Number of second primary cancers and rate of second primary cancers (per 1000 person-years) by treatment arm, crude hazard ratios, and 95% confidence intervals associated with supplementation in two consecutive follow-up periods according to the type of supplementation*

Parameter	Supplement arm		Placebo arm		HR (95% CI)
	No. of SPC/ no. at risk	Rate of SPC (/1000 py)	No. of SPC/ no. at risk	Rate of SPC (/1000 py)	
<i>From entry until 3.5 years after randomization</i>					
Any supplementation	48/273	60.07	21/267	25.05	2.42 (1.45 to 4.04)
α -Tocopherol and β -carotene	10/79	42.28	7/77	28.07	1.51 (0.58 to 3.98)
α -Tocopherol only	38/194	67.55	14/190	23.77	2.88 (1.56 to 5.31)
<i>Beyond 3.5 years after randomization</i>					
Any supplementation	15/162	39.43	29/193	68.75	0.57 (0.31 to 1.07)
α -Tocopherol and β -carotene	9/57	43.35	12/64	54.35	0.80 (0.34 to 1.90)
α -Tocopherol only	6/105	34.72	17/129	84.57	0.41 (0.16 to 1.03)

*SPC = second primary cancers; py = person-years; HR = hazard ratio; CI = confidence interval.

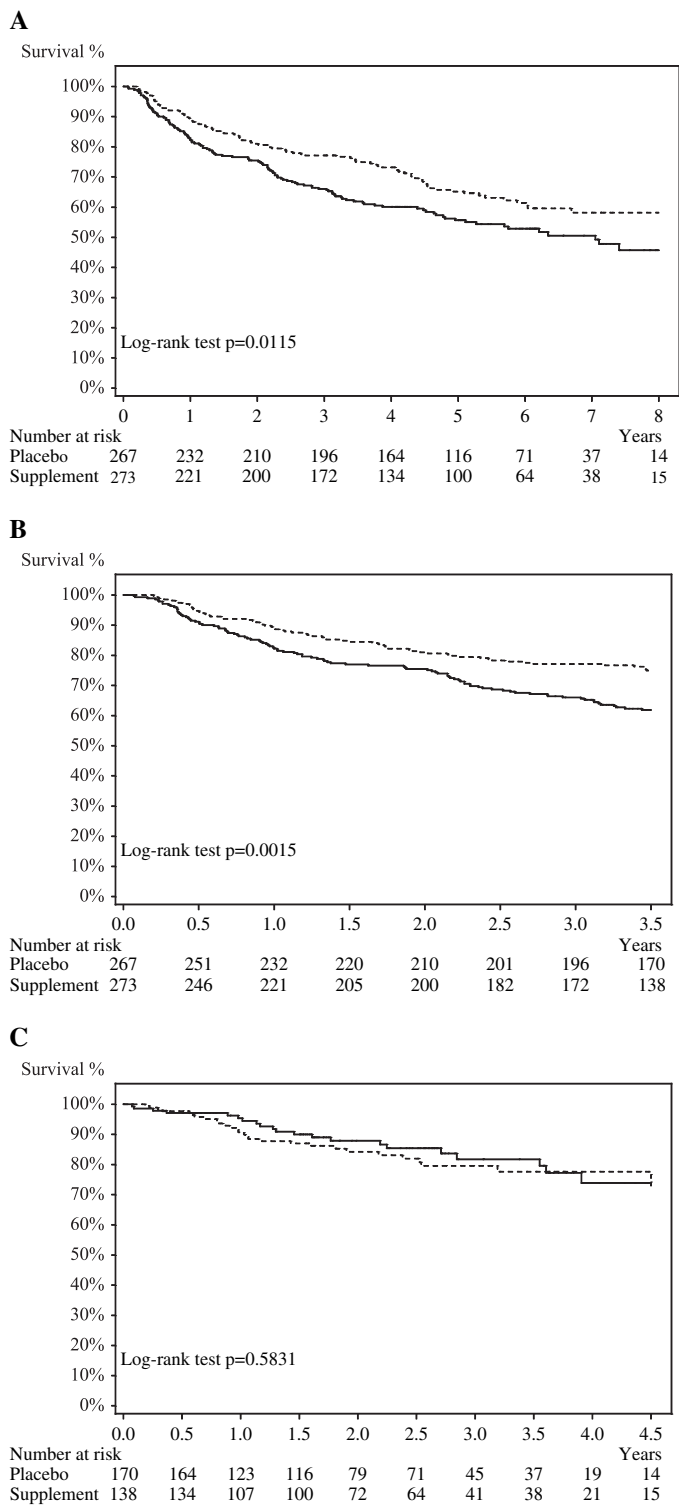


Fig. 3. Kaplan-Meier curves of cancer-free survival (no recurrence of the first tumor and no second primary cancer) among participants randomly assigned to the supplement arm (solid line) or to the placebo arm (dotted line) for the entire follow-up period (A), during the first 3.5 years after randomization (B), and beyond 3.5 years after randomization (C). Data are shown only up to 8 years of follow-up because of the small numbers of participants beyond that time.

cancers. Some patients received both α -tocopherol and β -carotene supplements and some received α -tocopherol alone because the study protocol was revised after the study began after concerns about the adverse effects of β -carotene surfaced. Given this situation, the most straightforward interpretation of the study results

can be made for the supplementation with α -tocopherol alone. Contrary to the scientific rationale that led to the trial, α -tocopherol supplementation statistically significantly increased the risk of second primary cancers during the first 3.5 years of follow-up, a period that corresponded to the supplementation period plus a few months during which tissue levels of α -tocopherol were likely to return to baseline levels (29). However, during the period after supplementation was discontinued, the risk of second primary cancers was lower among the participants who had taken α -tocopherol than among those who had taken placebo. Overall, the proportions of participants who were free of second primary cancers after 8 years of follow-up were identical in both arms of the trial. The rate of second primary cancers in the placebo arm of the trial was not constant over the first 5 years of follow-up as is often assumed but actually increased with time. Based on the rates observed in the placebo arm of the trial, the proportion of patients with a second primary cancer occurring during the first 5 years would be 18%, a figure in agreement with those in the literature: 15% to 20% (10–12).

Our results should be compared with those of the three cancer chemoprevention trials in which α -tocopherol supplements have been used (3,5,6). In the Alpha-Tocopherol, Beta-Carotene (ATBC) Lung Cancer Prevention Study (6,30), the beneficial effect of α -tocopherol supplements (50 mg/day) on prostate cancer and the adverse effect of β -carotene supplements (20 mg/day) on lung cancer observed during the supplementation period disappeared during follow-up after the intervention. Our results, which support those of the ATBC study (6,30), might suggest that antioxidant vitamin supplementation accelerates the progression of cancers and leads to earlier clinical diagnosis of more advanced latent tumors. Two population-based chemoprevention trials were conducted with combinations of antioxidant vitamins and minerals, including α -tocopherol (30 mg/day) (3,5). In China, cancer incidence was reduced by 13% among those receiving a combination of β -carotene, α -tocopherol, and selenium compared with those not receiving this combination (3). Compared with placebo, supplementation with five antioxidant minerals and vitamins at nutrition-like dosages in the SU.VI.MAX trial (5) was associated with a lower incidence of cancer in men (HR = 0.69, 95% CI = 0.53 to 0.91) but not in women (HR = 1.04, 95% CI = 0.85 to 1.29).

We observed stronger associations between supplementation use and cancer incidence than other cancer prevention trials with antioxidant vitamins (3–7), possibly because of the high risk of second primary cancers in our study population and, therefore, possibly to the high prevalence of latent cancers at the beginning of the intervention. In addition, participants in our study received a much higher dose of α -tocopherol than those in the three preceding trials (3,5,6). This could have contributed to the increased risk of cancer observed during the supplementation period. Three large cancer prevention trials (31–33) are underway in the United States with high doses of α -tocopherol supplements. The results of these trials are being awaited to clearly determine the effects of α -tocopherol at pharmacologic doses in cancer prevention.

Our results should also be compared with those of two cancer chemoprevention trials in patients with head and neck cancer that tested the chemopreventive effects of β -carotene supplementation (14,15). In both trials, no statistically significant association was observed between supplement use and cancer-free survival or recurrence of the initial head and neck cancer. In these studies (14,15), supplementation was started after successful completion

Table 5. Number of events (recurrence of the first tumor or occurrence of a second primary cancer) and rate of event (per 1000 person-years) by treatment arm, crude hazard ratios and 95% confidence intervals associated with supplementation in two consecutive follow-up periods according to the type of supplementation*

Parameter	Supplement arm		Placebo arm		HR (95% CI)
	No. of events/ no. at risk	Rate of event (/1000 py)	No. of events/ no. at risk	Rate of event (/1000 py)	
<i>From entry until 3.5 years after randomization</i>					
Any supplementation	101/273	141.4	65/267	85.08	1.65 (1.21 to 2.25)
α-Tocopherol and β-carotene	28/79	133.0	23/77	105.3	1.27 (0.73 to 2.21)
α-Tocopherol only	73/194	145.0	42/190	76.97	1.86 (1.27 to 2.72)
<i>Beyond 3.5 years after randomization</i>					
Any supplementation	21/138	64.91	28/170	76.14	0.85 (0.48 to 1.50)
α-Tocopherol and β-carotene	11/49	61.22	10/51	55.39	1.11 (0.47 to 2.61)
α-Tocopherol only	10/89	69.52	18/119	96.15	0.71 (0.33 to 1.53)

*py = person-years; HR = hazard ratio; CI = confidence interval.

of the initial treatment. In our trial, supplementation began on the first day of radiation therapy as an adjuvant intervention aimed at preventing the adverse effects of radiation therapy, which was the second objective of the trial (13) without compromising treatment efficacy (17). Although supplementation with α-tocopherol in our trial resulted in a 44% increase of the risk of tumor recurrence, this increase was of borderline statistical significance. In recent years, there has been much debate regarding the use of antioxidants during cancer therapy. Although some suggest that antioxidants can reduce the toxic side effects of therapy without compromising treatment efficacy (34), others argue that they interfere with treatment (35). Our results support this latter view.

Our trial has several strengths, including the good compliance of participants with the intervention and the almost complete follow-up. A major protocol change occurred in the course of the trial with the cessation of the supplementation with β-carotene. This could be viewed as a limitation. The effect of a supplementation combining α-tocopherol and β-carotene could not be examined with adequate statistical power. On the other hand, this change enabled us to observe effects attributable to supplementation with α-tocopherol alone. This cancer chemoprevention trial was conducted in a population of patients at high risk of second primary cancers. There is some concern about the generalization of the study results to individuals in the general population who are at low risk of a first primary cancer. Nevertheless, our results suggest that caution should be advised regarding the use of high-dose α-tocopherol supplements for cancer prevention.

REFERENCES

- (1) Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. I. Epidemiology. *Cancer Causes Control* 1991;2:325–57.
- (2) American Institute for Cancer Research/World Cancer Research Fund. Food, nutrition and the prevention of cancer: a global perspective. Washington (DC): American Institute for Cancer Research; 1997.
- (3) Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993;85:1483–92.
- (4) Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, 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* 1996;334:1145–9.
- (5) Herceberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, et al. The SU.VI.MAX study: a randomized, placebo-controlled trial of the health effect of antioxidant vitamins and minerals. *Arch Intern Med* 2004;164:2335–42.
- (6) The Alpha-Tocopherol, Beta-Carotene Cancer 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* 1994;330:1029–35.
- (7) Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334:1150–5.
- (8) Lippman SM, Benner SE, Hong WK. Cancer chemoprevention. *J Clin Oncol* 1994;12:851–73.
- (9) National Cancer Institute of Canada. Canadian cancer statistics 2004. Toronto, Canada, 2004.
- (10) Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: DeVita VT, Hellman S, Rosenberg SA, editors. *Cancer, principles & practice of oncology*. Philadelphia (PA): JB Lippincott Company; 1989. p. 488–590.
- (11) Cooper JS, Pajak TF, Rubin P, Tupchong L, Brady LW, Leibel SA, et al. Second malignancies in patients who have head and neck cancer: incidence, effect on survival and implications based on the RTOG experience. *Int J Radiat Oncol Biol Phys* 1989;17:449–56.
- (12) McDonald S, Haie C, Rubin P, Nelson D, Divers LD. Second malignant tumors in patients with laryngeal carcinoma: diagnosis, treatment, and prevention. *Int J Radiat Oncol Biol Phys* 1989;17:457–65.
- (13) Bairati I, Brochet F, Roy J, Gélinas M, Nabid A, Tetu B, et al. Prévention des seconds cancers par supplémentation vitaminique chez les patients traités pour un premier cancer ORL. *Bull Cancer Radiother* 1996;83:12–6.
- (14) Mayne ST, Cartmel B, Baum M, Shor-Posner G, Fallon BG, Briskin K, et al. Randomized trial of supplemental beta-carotene to prevent second head and neck cancer. *Cancer Res* 2001;61:1457–63.
- (15) Toma S, Bonelli L, Sartoris A, Mira E, Antonelli A, Beatrice F, et al. Beta-carotene supplementation in patients radically treated for stage I-II head and neck cancer: results of a randomized trial. *Oncol Rep* 2003;10:1895–901.
- (16) Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, editor. *Evaluation of chemotherapeutic agents*. New York (NY): Columbia Press; 1949. p. 191–205.
- (17) Prasad KN, Kumar A, Kochupillai V, Cole WC. High doses of multiple antioxidant vitamins: essential ingredients in improving the efficacy of standard cancer therapy. *J Am Coll Nutr* 1999;18:13–25.
- (18) American Joint Committee on Cancer. *Manual for staging of cancer*. 4th ed. Philadelphia (PA): J.B. Lippincott Company; 1993.
- (19) National Cancer Institute of Canada Clinical Trial Group. NCIC common toxicity criteria (CTC) grading system. In: Cassidy J, Bissett D, Spence R, editors. *Oxford handbook of oncology*. Appendix 1. London (United Kingdom): Oxford University Press; 2002.
- (20) Miller KW, Lorr NAS, Yang CS. Simultaneous determination of plasma retinol, alpha-tocopherol, lycopene, alpha-carotene, and beta-carotene by high-performance liquid chromatography. *Anal Biochem* 1984;138:340–5.
- (21) Catignani GL, Bieri JG. Simultaneous determination of retinol and α-tocopherol in serum or plasma by liquid chromatography. *Clin Chem* 1983;29:708–12.
- (22) Gridley G, McLaughlin JK, Block G, Blot WJ, Gluch M, Fraumeni JF Jr. Vitamin supplement use and reduced risk of oral and pharyngeal cancer. *Am J Epidemiol* 1992;135:1083–92.

- (23) Warren S, Gates O. Multiple primary malignant tumors: A survey of the literature and a statistical study. *Am J Cancer* 1932;16:1358–414.
- (24) Lefor AT, Bredenberg CE, Kellman RM, Aust JC. Multiple malignancies of the lung and head and neck. Second primary tumor or metastasis? *Arch Surg* 1986;121:265–70.
- (25) Hong WK, Lippman SM, Itriss LM, Karp DD, Lee JS, Byers RM, et al. Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. *N Engl J Med* 1990;323:795–801.
- (26) EGRET SIZ. A program for sample size and power estimation. Reference manual. Seattle (WA): Statistics and Epidemiology Research Corporation; 1993.
- (27) Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York (NY): Springer-Verlag; 2000.
- (28) Collett D. Modelling survival data in medical research. Boca Raton (FL): CRC Press; 2003.
- (29) Machlin LJ, Gabriel E. Kinetics of tissue alpha-tocopherol uptake and depletion following administration of high levels of vitamin E. *Ann N Y Acad Sci* 1982;393:48–60.
- (30) Virtamo J, Pietinen P, Huttunen JK, Korhonen P, Malila N, Virtanen MJ, Albanes D, Taylor PR, Albert P, the ATBC Study Group. Incidence of cancer and mortality following α -tocopherol and β -carotene supplementation: a postintervention follow-up. *JAMA* 2003;290:476–85.
- (31) Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II—a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of the results of completed trials. *Ann Epidemiol* 2000;10:125–34.
- (32) Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. β -carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst* 1999;91:2102–6.
- (33) Hoque A, Albanes D, Lippman SM, Spitz MR, Taylor PR, Klein EA, et al. Molecular epidemiologic studies within the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Cancer Causes Control* 2001;12:627–33.
- (34) Prasad KN, Cole WC, Kumar B, Prasad KC. Pros and cons of antioxidant use during radiation therapy. *Cancer Treat Rev* 2002;28:79–91.
- (35) Seifried HE, McDonald SS, Anderson DE, Greenwald P, Milner JA. The antioxidant conundrum in cancer. *Cancer Res* 2003;63:4295–8.

NOTES

This study was supported by grants 4738, 8176, and 13211 from the NCIC with funds from the Canadian Cancer Society. I. Bairati is the recipient of a senior scientist award from the Fonds de Recherche en Santé du Québec.

We are grateful to the following persons who participated in the Ethical and Safety Monitoring Committee: J. F. Boivin (chair), D. Roy, and M. Archer. We also thank L. Nadeau, who determined levels of α -tocopherol and β -carotene in plasma. Finally, we are grateful to the study participants, the hospital pharmacists, and the research staff.

Manuscript received September 24, 2004; revised January 25, 2005; accepted February 16, 2005.