

A Randomized Trial of an Intervention to Increase Fruit and Vegetable Intake in Curatively Treated Patients with Early-Stage Head and Neck Cancer

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Abstract

The leading cause of death in patients who have had curatively treated early-stage head and neck cancer is a second primary cancer of the upper aerodigestive tract (lung, esophagus, larynx, pharynx, and oral cavity cancers). Low fruit and vegetable intake has been associated with increased risk of primary head and neck cancer and the available data suggest that increasing intake following diagnosis may reduce the risk of a second primary cancer. The goal of this study was to develop and test an easily administered intervention to increase fruit and vegetable intake in these patients following diagnosis and treatment. The 6-month intervention was based on the Stage of Change model. Seventy-five early-stage head and neck cancer patients were randomized to either the intervention group or to the "blinded" control group, with diet change data

available on 65 patients. Fruit and vegetable intake, assessed using a food frequency questionnaire, and plasma carotenoid concentrations were measured at baseline and at the end of the study period. The change in self-reported intake of fruit and vegetables (servings per day) over the study period was significantly greater ($P = 0.009$) in the intervention group ($n = 35$; +2.1) compared with the control group ($n = 30$; +0.5). Total plasma carotenoids, a biomarker of fruit and vegetable intake, increased by 70 nmol/L in the intervention group as compared with a reduction of 42 nmol/L in the control group, a relative difference of 12% (nonsignificant). An intervention that can be delivered in a physician's office resulted in a significant increase in intake of fruit and vegetables in early-stage head and neck cancer patients. (Cancer Epidemiol Biomarkers Prev 2005;14(12):2848–54)

Introduction

Head and neck cancer refers to cancers of the oral cavity, larynx, and pharynx. Collectively, these cancers account for 3% of all cancers diagnosed in the United States with a projected 39,250 new cases diagnosed in 2005 (1). Approximately 15,000 cases per year are diagnosed as localized, early-stage (stage I or II) disease.

Patients diagnosed with early-stage head and neck cancer, although treated with curative intent, experience a high rate of recurrences (20% in the first year) and second primary cancers (5% per year; refs. 2, 3). Second primary cancers typically occur in the upper aerodigestive tract, including lung cancer and esophageal cancer in addition to pharyngeal, laryngeal, and oral cancer second primaries (2). Unlike the recurrence rate, the second primary rate does not decline over time and second primary cancers are reported to be the leading cause of mortality in early-stage head and neck cancer patients who seem to be curatively treated (4). Therefore, reducing the rate of second primary cancers in this patient population is an important medical care goal. To date, no chemopreventive agent has been identified that consistently reduces the second primary cancer rate (5, 6). Tobacco and alcohol use are well-known risk factors for head and neck cancer and continued smoking following diagnosis has been associated with an increased risk of second primary cancers (7) and patients are

advised to modify these behaviors following diagnosis of head and neck cancer.

In a meta-analysis of case-control studies (8), low intake of fruit and vegetables was shown to be associated with an increased risk of cancers of the larynx, oral cavity, and pharynx as well as with cancers of the lung and esophagus, the predominant sites of the second primary cancers that survivors of early-stage head and neck cancer experience. The literature on the relationship between fruit and vegetable intake and numerous cancer sites was systematically reviewed by an IARC working group in 2003. Consistent with the meta-analysis, inverse associations were found between both fruit and vegetable intake and risk of cancers of the oral cavity, pharynx, and larynx (9).

Data about dietary risk factors for second primary head and neck cancers are more limited (10). In a follow-up study of patients with oral and pharyngeal cancer conducted by Day et al. (10), higher fruit and vegetable intake following diagnosis and treatment was associated with a significant decrease in risk of second primary cancer. Those with the highest quartile of intake (≥ 6.36 servings/d for men and ≥ 5.88 servings/d for women) had an odds ratio of 0.4 compared with those with the lowest quartile of intake (≤ 2.67 servings/d for men and ≤ 1.99 servings/d for women; ref. 10). Of interest, a recent study found that 6 to 60 months following successful treatment of early-stage oral cancer, intake of fruits and vegetables was significantly lower for these patients than for age- and sex-matched control subjects (11), indicating that the known relatively low intake of fruit and vegetables in these patients persists postdiagnosis.

The posttreatment period in patients diagnosed with early-stage head and neck cancer may offer a window of opportunity to affect a change in dietary behavior (12) although head and neck cancer patients may present a particular challenge with regard to behavior change as they

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often have a history of multiple poor health behaviors, such as tobacco smoking and excessive alcohol intake. However, high smoking cessation rates have been reported in patients following a diagnosis of head and neck cancer. In a smoking cessation study of 100 newly diagnosed head and neck cancer patients who were current smokers, Gritz et al. (13) reported that at the 12-month follow-up, 64.6% of subjects were continuous tobacco abstainers. It has been suggested that previously unreceptive patients may be highly motivated following a diagnosis of head and neck cancer (13). The regular medical follow-up care these patients receive also offers a convenient and potentially low-cost opportunity to intervene to change behavior, particularly if the intervention can be designed to be carried out by an office nurse or other nonphysician office personnel.

Several randomized trials have been conducted enrolling various high-risk populations in which the primary aim was to increase fruit and vegetable intake. Other trials have included fruit and vegetable increases as part of an overall change in dietary pattern. Trials that have employed high intensity interventions with several hours of contact time (14-16) as well as less intensive interventions (17, 18) have reported changing fruit and vegetable intake. We selected a less intensive model, with ~50 to 60 minutes of contact per participant over a 6-month period, to enable easier dissemination to clinical settings if the intervention was proved efficacious. The goal of the intervention was to get participants in the intervention group to consume ≥ 7 servings of fruits and vegetables per day.

The transtheoretical Stage of Change model (19) has been studied most extensively in relation to changing addictive behaviors, such as smoking cessation (20-22), but more recent research has also been conducted on the application of the model to other behaviors, including diet and specifically fruit and vegetable intake (23-25). Recently, Clark et al. (26) have used the model as the basis for developing an intervention to increase fruit and vegetable intake in older people. We used this model to design and tailor an intervention by assessing each participant's readiness to change and providing a stage-appropriate intervention to motivate dietary behaviors.

Materials and Methods

Patient Identification and Eligibility. All patients diagnosed with early-stage (*in situ*, stage I, or stage II) head and neck cancer from January 1, 1997 to February 28, 2001 who resided in the state of Connecticut were identified by the Rapid Case Ascertainment Shared Resource of the Yale Cancer Center. The Rapid Case Ascertainment Shared Resource acts as an agent of the Connecticut Tumor Registry.

The Connecticut Tumor Registry is a population-based registry that has been part of the National Cancer Institute Surveillance, Epidemiology and End Results Program since its inception in 1973.

Each patient's physician was contacted to confirm stage at diagnosis, that the patient was classified as curatively treated, and to obtain permission to contact the patient. Patients were not eligible to participate in the study if they were under 21, if they were non-English speakers, or if they reported taking >5 mg of supplemental β -carotene daily at the time of recruitment.

All procedures were approved by the Yale University School of Medicine Human Investigation Committee, the Connecticut Department of Public Health Human Investigation Committee, and the participating hospitals. In the process of case ascertainment through The Rapid Case Ascertainment Shared Resource, certain data used in this study were obtained from the Connecticut Tumor Registry located in the Connecticut Department of Public Health. The authors assume full responsibility for analyses and interpretation of these data.

Patient Recruitment. Patients were mailed a letter inviting them to participate in the study. Subsequently, the study interviewer called each patient to answer any questions and schedule a study visit. A food frequency questionnaire was mailed for completion by the patient before the visit; the reference period for completion of the food frequency questionnaire was the prior month. After obtaining signed consent at the visit, the interviewer conducted a baseline assessment, including assessment of stage of change for fruit and vegetable intake, along with demographic and risk factor information. Following the baseline assessment, each patient was randomized to the intervention arm or control arm. To ensure balance between the study arms, patients were stratified by gender (male, female) and time since diagnosis (<1 versus ≥ 1 year) then randomly assigned to intervention versus control using a random number table. A block size of four was used. All patients were blinded to the purpose of the study before randomization and the control group continued to be blinded until the end of the study. We achieved blinding by not including information about the specific purpose of the study in the patient letter or consent form. Patients were told that the study was about diet and head and neck cancer. The interviewer was blinded to the treatment assignment until completion of the assessment phase, at which time an envelope containing the intervention assignment (prepared by the biostatistician) was opened. When possible, both blood and urine samples were obtained during the visit. These were processed and stored within 4 hours of completion of the interview. Patients were asked not to eat any fruit, vegetables, or fruit juices or take any vitamin supplements for 6 hours before the visit.

The control group received usual care during the trial. At the end of the final visit, those in the control group were informed of the purpose of the study and given the information about increasing fruit and vegetable intake.

Intervention. The goal of the intervention was to increase participants' consumption of fruits and vegetables to ≥ 7 servings/d. Following randomization, an explanation of the purpose of the study and the potential health benefits of increasing fruit and vegetable intake was given to those randomized to the intervention group. The stage of change for fruit and vegetable intake was reassessed in these patients in order to deliver the appropriate intervention content. The intervention was delivered based on the reassessed stage of change and delivered during one 20- to 30-minute in-person session and subsequent contacts. Intervention patients were contacted by telephone at 6-week intervals to boost the intervention message and encourage adherence to the program. The telephone booster sessions lasted an average of 10 minutes. During the call, the interviewer discussed with the participant changes they had made in fruit and vegetable intake since the last contact, referring to specific goals that had been set at the in-person interview. At 12 weeks following randomization, tailored intervention material was mailed to each participant, consisting of a single page that contained information that reinforced material from the booklet and with supplementary information about the health benefits of eating fruits and vegetables. A trained nurse counselor delivered all the intervention activities. The food preparer in the family was encouraged to participate in the intervention session. As the intent was to develop an intervention that could be delivered in the setting of a busy physician's office by a nurse or other office personnel who would receive limited training, we included only two different sets of intervention content based on stage of change: one for those classified as in precontemplation or contemplation and one for those in preparation. Each group received a tailored intervention, which included personal interaction, and a booklet specifically designed for

the study. The booklet was used throughout the intervention session and was given to the patient for him or her to refer to during the study period.

Stage was defined as:

Precontemplation: eating ≤ 6 servings/d and *not* seriously thinking about eating more servings of fruits and vegetables starting sometime in the next 6 months.

Contemplation: eating ≤ 6 servings/d and seriously thinking about eating more servings of fruits and vegetables starting sometime in the next 6 months but *not* planning to eat more servings of fruits and vegetables during the next month.

Preparation: eating ≤ 6 servings/d and seriously thinking about eating more servings of fruits and vegetables starting sometime in the next 6 months and planning to eat more servings of fruits and vegetables during the next month.

For participants in the precontemplator/contemplator group, messages were provided about the usefulness of changing dietary behaviors to convince participants that changing behavior is a positive and potentially health-promoting idea. The interviewer discussed perceived pros and cons of changing behaviors with the patient; these pros and cons were also listed in the booklet provided. The interviewer also reviewed how one meal or snack could be changed to incorporate more fruits and vegetables; two or more meals or snacks were discussed with those in the preparation stage. The decisions made were recorded so they could be referred to in future contacts.

For participants in the preparation group, the intervention focused on the skills and strategies necessary to change behaviors. The goal of ≥ 7 servings of fruits and vegetables per day was discussed and methods for achieving this goal were identified as part of daily consumption. A checklist was reviewed with each patient to determine when fruits and vegetables were currently included in each meal or used as snacks.

Assessment of Fruit and Vegetable Intake. The food frequency questionnaire developed at the Fred Hutchinson Cancer Research Center (version 1992) contains 114 food line items and numerous questions on food preparation and purchasing in addition to several summary questions. The questionnaire contains the following fruit and vegetable items that are included in the total fruit and vegetable intake estimates used herein:

Apples and pears; bananas; peaches, nectarines, or plums (fresh or canned); cantaloupe, orange melon, muskmelon, mango, and papaya; watermelon and red melon; all other melon, such as honeydew; apricots (fresh, canned, or dried); other dried fruit, such as raisins and prunes; oranges, grapefruit, and tangerines (not juice); strawberries and kiwi; any other fruit.

Green or string beans; green or English peas; all other beans; avocado and guacamole; corn and hominy; tomatoes, fresh or juice; tomatoes, cooked, tomato sauce, salsa, and salsa picante; green peppers, green chilies, jalapenos, and green chili salsa; red peppers and red chilies; broccoli; cooked greens, spinach, mustard greens, turnip greens, and collards; carrots, including mixed dishes with carrots; summer squash, zucchini, and okra; winter squash, such as acorn, butternut, and pumpkin; coleslaw; cauliflower, cabbage, sauerkraut, and Brussel sprouts; onions and leeks, included in cooking; plantains, fried.

Intake estimates were adjusted by the use of a summary question asking the participants to report how often they ate a serving of vegetables, not counting potatoes, salad, or beans, and how often they ate a serving of fruit, not counting juices.

The use of this adjustment method has been found to slightly underestimate total fruit and vegetable intake as compared with the summation method which slightly overestimates intake compared with fruit and vegetable intake as assessed by food records; however, both methods have the same precision when compared with three criterion measures (27). Unadjusted fruit juice (orange juice, grapefruit juice, and other fruit juices such as apple and grape) and salad (lettuce and plain lettuce salad, mixed lettuce, spinach, and salad with vegetables) intakes are reported separately as they are not included in the adjusted fruit or vegetable estimates.

Outcome Assessment. Approximately 6 months following randomization, the final visit was conducted and dietary intake was again assessed using a self-administered food frequency questionnaire with the prior month as the reference period. At the final visit, blood and urine samples were collected, then processed and stored for analysis.

Carotenoid Analysis. Blood samples were collected by the phlebotomist/interviewer at baseline and at 6-month follow-up when possible. Blood was collected into two 10-mL heparinized (green top) vacutainer tubes and kept cold in the dark until the plasma could be separated. The samples were transported within 4 hours of collection to the processing laboratory where plasma was aliquotted and stored at -70°C , pending analysis. Plasma carotenoids were isolated and analyzed at the Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University. Plasma was prepared for extraction using 200 μL of sample and 0.5 mL of 0.9% saline. Echinone, in ethanol, was added as an internal standard. The mixture was extracted by using 2-mL $\text{CHCl}_3/\text{CH}_3\text{OH}$ (2:1, v/v), vortexed, then centrifuged at $800 \times g$ for 15 minutes at 4°C . The CHCl_3 layer was removed and evaporated to dryness under nitrogen. A second extraction was then done on the mixture using 3-mL hexane. The mixture was vortexed and centrifuged as above. The hexane layer was combined with the first extraction and evaporated to dryness under nitrogen. The residue was redissolved in 150 μL of ethanol, vortexed, and sonicated for 30 seconds. A 50- μL aliquot was used for the high-performance liquid chromatography analysis of each sample. Each of the high-performance liquid chromatography solvents was passed through a 0.45- μm membrane filter and degassed before use and all carotenoid standards were stored at -70°C .

The high-performance liquid chromatography system consisted of a 616 LC pump (Waters Corp., Milford, MA), Waters 717 plus autosampler (Waters), a C30 carotenoid column (3 μm , 150×4.6 mm, YMC, Wilmington, NC), and Waters 994 programmable photodiode array detector. The plasma data from this study were collected and analyzed using Millennium32 Software (version 3.05.01, Windows NT, Waters 1998). The high-performance liquid chromatography mobile phase was methanol/methyl-*tert*-butyl ether/water (83:15:2, v/v/v, with 1.5% ammonium acetate in H_2O ; solvent A) and methanol/methyl-*tert*-butyl ether/water (8:90:2, v/v/v, with 1% ammonium acetate in H_2O ; solvent B). The gradient procedure at a flow rate of 1 mL/min at 16°C was as follows: the procedure began at 100% solvent A before going to 93% solvent A and 7% solvent B over a 1-minute linear gradient. This was followed by a 3-minute hold at 93% solvent A, followed by a 17-minute linear gradient to 45% solvent A and a 1-minute hold at 45% solvent A, then an 11-minute linear gradient to 95% solvent B, a 4-minute hold at 95% solvent B, and finally a 2-minute gradient back to 100% solvent A. The system was held at 100% solvent A for 10 minutes for equilibration back to initial conditions. Using this method, lutein, zeaxanthin, β -cryptoxanthin, α -carotene, 13-*cis* β -carotene, all-*trans* β -carotene, and 9-*cis* β -carotene were adequately separated. In addition, four geometric isomers of

lycopene (15-*cis*, 13-*cis*, 9-*cis*, and all-*trans* lycopenes) were separated as well.

Carotenoids were quantified by determining peak areas in the high-performance liquid chromatography chromatograms calibrated against known amounts of standards. Concentrations were corrected for extraction and handling losses by monitoring the recovery of the internal standards. The lower limit of detection was 0.2 pmol.

Statistical Analysis. All analyses were done with SAS (SAS Institute, Cary, NC). The Student's *t* test and χ^2 analysis were used to evaluate the comparability of the baseline demographic factors, disease characteristics, and risk factors between the patient groups. The Wilcoxon rank-sum test and paired *t* test were used to compare changes over time in plasma carotenoids and food intake between the intervention and control groups. The median values for the plasma carotenoid concentrations are reported as the data were right skewed and the groups were relatively small.

Results

Physician consent was obtained to contact a total of 197 patients who were eligible for the study. Of these 75 (38%) were randomized, 79 (40%) declined to participate in the study, and 43 (22%) could not be contacted. The groups were comparable on gender, cancer site (oral versus larynx versus pharynx versus multiple sites), and stage at diagnosis (Table 1). A higher proportion of patients who could not be contacted were nonwhite ($n = 8$; 18.6%) as compared with those who were randomized ($n = 4$; 5.3%; $P < 0.005$) or those who declined ($n = 4$; 5.1%; $n < 0.01$). However, information on race was only available for 82% of the nonparticipants.

Of the 75 patients who were randomized, 70 (93%) completed the study, 4 patients died during the 6-month study (1 intervention and 3 control), and 1 withdrew (intervention) from the study due to increased difficulty eating due to prior cancer treatment. Of the 70 patients who completed the study, a total of 36 patients were randomized to the intervention arm and 34 to the control arm. The characteristics of the patients randomized are shown in Table 2. A total of 36 (51.4%) patients had laryngeal cancer, 28 (40%) had oral cancer, and 5 (7.1%) had pharyngeal cancer. One patient had more than one primary site. The majority of patients were diagnosed with stage I cancer. Most patients (75.7%) were former smokers, with few never (12.9%) or current (11.4%) smokers. The disease and personal

Table 1. A comparison of eligible patients by study participation

Characteristic	Randomized	Declined	Could not contact
Race			
White	71 (94.7)	64 (81.0)	24 (55.8)*
Black	4 (5.3)	3 (3.8)	5 (11.6)
Hispanic	0	1 (1.3)	3 (7.0)
Unknown	0	11 (13.9)	11 (25.6)
Gender			
Female	21 (28.0)	27 (34.2)	12 (27.9)
Male	54 (72.0)	52 (65.8)	31 (72.1)
Cancer site			
Oral	30 (40.0)	20 (25.3)	14 (32.6)
Larynx	38 (50.7)	52 (65.8)	23 (53.5)
Pharynx	6 (8.0)	7 (8.9)	6 (13.9)
Two sites	1 (1.3)	0	0
Stage			
<i>In situ</i>	7 (9.3)	4 (5.1)	4 (9.3)
I	48 (64.0)	56 (70.9)	20 (46.5)
II	20 (26.7)	19 (24.0)	19 (44.2)

**P* values from χ^2 estimate = 0.001.

Table 2. Characteristics of randomized patients

	No. patients (%)	
	Intervention arm (<i>n</i> = 36)	Control arm (<i>n</i> = 34)
Age at randomization*	63.6 ± 10.5	63.6 ± 12.5
Cancer site		
Larynx	19 (52.8)	17 (50)
Oral	15 (41.7)	13 (38.2)
Pharynx	1 (1.8)	4 (11.8)
More than one	1 (1.8)	0
Cancer stage		
<i>In situ</i>	5 (13.9)	2 (5.9)
Stage I	24 (66.7)	21 (61.8)
Stage II	7 (19.4)	11 (32.3)
Gender (males)	27 (75)	23 (67.5)
Race		
Black	1 (2.8)	3 (8.8)
White	35 (97.2)	31 (91.2)
Marital status		
Married	25 (69.4)	25 (73.7)
Not married	11 (30.6)	9 (26.3)
Income		
10,000-20,999	2 (5.6)	6 (17.6)
21,000-40,999	8 (22.2)	4 (11.8)
41,000-60,999	9 (25.0)	11 (32.4)
61,000-75,999	2 (5.6)	3 (8.8)
76,000-100,000	1 (2.8)	2 (5.9)
>100,000	6 (16.7)	4 (11.8)
Don't know or declined to answer	8 (22.2)	4 (11.8)
Smoking status		
Never	5 (13.9)	4 (11.8)
Former	26 (72.2)	27 (79.4)
Current	5 (13.9)	3 (8.8)
Age started smoking*	17.0 ± 5.7	15.9 ± 3.0
Packyears*	45.5 ± 31.6 (<i>n</i> = 31)	51.2 ± 27.1 (<i>n</i> = 30)
Supplemental vitamin intake (yes)	23 (63.9)	21 (61.8)
β-Carotene included in multivitamin (yes)	14 (38.9)	11 (32.4)

*Mean ± SD.

characteristics were well balanced between the study arms (Table 2).

Stage of change for fruit and vegetable intake was assessed at baseline during the evaluation phase of the interview (i.e., before randomization; Table 3). At this time, the majority (62.9%) of patients were in the precontemplation phase, 5.7% in the contemplation phase, and 31.4% in the preparation phase. There was an imbalance in stage of change for fruit and vegetable intake between the two arms with more patients in precontemplation phase in the intervention arm (75%) as compared with the control arm (50.0%); conversely, fewer patients randomized to the intervention arm were in the preparation phase (22.9%) as compared with those in the control arm (41.2%). However, the difference in distribution of stage by arm was not statistically significantly different ($\chi^2 = 4.86$, $P = 0.09$).

Following randomization, those in the intervention group were informed about the purpose of the study and the potential health benefits of increasing fruit and vegetable intake. Stage of change was then reassessed; 32 (88.9%) patients were in the preparation stage and 4 (11.1%) were in contemplation/precontemplation.

The self-reported intake of fruits, vegetables, fruit juices, and salad at baseline and the difference in intake between the baseline and 6-month assessment are shown in Table 4. Note that five patients were not included in the analysis as they did not complete both the baseline and 6-month food frequency questionnaire. There were statistically significantly greater increases in self-reported intake from baseline to the end of the 6-month study in the intervention group compared with the control group for fruit (0.92 servings; $P = 0.01$), vegetables

Table 3. Stage of change for fruit and vegetable intake and beliefs about fruit and vegetable intake required for good health in the two study groups

	No. patients (%)	
	Intervention arm	Control arm
Stage of change at baseline assessment		
Precontemplation	27 (75.0)	17 (50.0)
Contemplation	1 (2.9)	3 (8.8)
Preparation	8 (22.9)	14 (41.2)
How many servings of fruit and vegetables should a person eat for good health		
1	1 (2.9)	0*
2	11 (31.4)	2 (5.9)
3	14 (40.0)	14 (41.2)
4	6 (17.1)	10 (29.4)
5	3 (8.6)	4 (11.8)
6	0	4 (11.8)

**P* value from χ^2 estimate = 0.03.

(0.66 servings; *P* = 0.05), and fruit juices (0.45 servings; *P* < 0.01). At the follow-up visit, in the intervention group, 10 patients reported intake of ≥ 7 servings of fruits and vegetables a day, the goal of the study; in contrast, in the control group, one patient reported intake of ≥ 7 servings. The control group reported lower intake of both fruits and vegetables at baseline compared with the intervention group but these differences were not statistically significant.

The plasma carotenoid levels at baseline and the difference in plasma carotenoid levels between baseline and the 6-month assessment are shown in Table 5. Paired blood samples were available for 33 of the 36 patients in the intervention group and 24 of the 30 patients in the control group. This is a result of some patients having poor venous access. There was a greater change in the majority of serum carotenoids in the intervention group compared with the control group [difference in change from baseline to 6-month assessment: total carotenoids = 12.1% (*P* = 0.51); α -carotene = 12.8% (*P* = 0.33); lycopene = 13.4% (*P* = 0.35); cryptoxanthin = 11.7% (*P* = 0.53)]. However, there was no difference in change for β -carotene or lutein and a 6% decrease (*P* = 0.79) in zeaxanthin in the intervention group compared with the control group.

At baseline, fruit and vegetable intakes were significantly correlated with plasma cryptoxanthin (ρ = 0.31; *P* = 0.02 and 0.35 and *P* = 0.008, respectively). In addition, total carotenoids (ρ = 0.3; *P* = 0.02) and α -carotene (0.26; *P* = 0.05) were significantly correlated with vegetable intake, with β -carotene (0.5), lutein (0.25), and lycopene (0.23) having correlations of borderline significance.

Discussion

The results of this study show that patients who have been diagnosed with, and curatively treated for, early-stage head

and neck cancer increase fruit and vegetable intake in response to a relatively low-intensity intervention (50-60 minutes) designed to be conveniently implemented in a physician's office by a nurse (as in this study), a trained staff member, or a physician. Over the intervention period, patients in the intervention group reported a mean increase of 2.07 servings/d (1.07 servings of fruit and 1.0 serving of vegetables) compared with an increase of 0.49 serving in the control group. Likewise, the increase in plasma carotenoids over the study period was greater in the intervention group compared with the control group, supporting the self-reported differences in intake between the two groups, although the difference in plasma carotenoids between the groups did not reach statistical significance. The change in intake for fruits and vegetables in the intervention group reported in our study compares to a mean increase of 1.44 servings/d from a baseline of 3.60 servings/d reported for a low-income group of primary care patients who received a low-intensity behavioral intervention, which was similarly based on the Stage of Change model (17). To assess fruit and vegetable intake, participants in that study were asked how many pieces of fruit and how many portions of vegetables a day they ate on a typical day; potatoes were excluded and one serving of fruit juice was allowed. Other studies that used more intensive interventions reported larger self-reported increases in fruit and/or vegetables. Pierce et al. (15) reported vegetable and vegetable juice increases of 3.2 servings/d (82%) and fruit increase of 0.6 serving/d (18%) in an intervention group of women who were breast cancer survivors with no change in the comparison group. The study used telephone counseling, based on cognitive theory, as the primary method to promote dietary change in the intervention group, with monthly cooking classes and newsletters for those in the intervention group.

Rock et al. (14) reported on a randomized intervention study to increase fruit and vegetable intake in a group of 53 premenopausal women with cervical intraepithelial neoplasia. At the end of the 6-month intensive intervention period, those in the intervention group reported a median increase of 1.36 servings/d in fruits and vegetables (median baseline, 4.29 servings/d) compared with no change in the control group. In a randomized intervention designed to determine the efficacy of a low-fat, high-fiber diet in the prevention of recurrence of colorectal adenomas, those in the intervention arm in the first year of the intervention received individual weekly counseling sessions for the first 6 weeks, biweekly sessions for the next 6 weeks, and monthly sessions thereafter. A slightly less intensive intervention was implemented for the following 3 years of the study. Those in the intervention group reported an increase of 1.36 servings/d/1,000 kcal (equivalent to 2.5 servings/d) at the end of the intervention period compared with a baseline intake of 2.05 servings/d/1,000 kcal (equivalent to 3.9 servings/d) with little change reported in the control arm (18). A pilot study in head and neck cancer patients found that at least in the short term (3 months), a large increase in fruit and vegetable intake (from 4.2 to 9.5 servings/d) was

Table 4. Self-reported baseline intake (servings per day) and change in fruit and vegetable intake in the intervention and control arms

	Baseline		Change		Difference in change	<i>P</i>
	Intervention (35)	Control (30)	Intervention (35)	Control (30)		
Fruit and Vegetables	3.06 \pm 0.36	2.47 \pm 0.26	+2.07 \pm 0.50	+0.49 \pm 0.31	1.58	0.009
Fruit	1.30 \pm 0.21	1.19 \pm 0.19	+1.07 \pm 0.29	+0.15 \pm 0.20	0.92	0.01
Vegetables	1.75 \pm 0.20	1.28 \pm 0.14	+1.00 \pm 0.27	+0.34 \pm 0.18	0.66	0.05
Fruit juices, including orange juice	0.44 \pm 0.51	0.62 \pm 0.78	+0.34 \pm 0.66	-0.11 \pm 0.52	0.45	0.004
Salad*	0.62 \pm 0.69	0.37 \pm 0.43	+0.22 \pm 0.79	+0.08 \pm 0.24	0.14	0.36
Calories	1619 \pm 132.7	1662 \pm 105.1	+90.4 \pm 100.8	+22.3 \pm 123.9	68.1	0.67

NOTE: Data given are mean \pm SE.

*Lettuce and plain lettuce salad, mixed lettuce, spinach, and salad with vegetables.

Table 5. Median baseline and change in plasma carotenoids in the intervention and control arms

	Baseline (nmol/L)		Change (nmol/L)		Difference in change*
	Intervention (33)	Control (24)	Intervention (33)	Control (24)	
Total carotenoids	951 (626:1,502)	896 (583:1,233)	+70 (-177:260)	-42 (-07:63)	112 (12.1%)
β-Carotene	249 (113:482)	208 (123:336)	+12 (-22:81)	+12 (-51:51)	0 (0%)
α-Carotene	46 (30:90)	52 (28:98)	+6 (-12:28)	0 (-19:10)	6 (12.8%)
Lycopene	304 (191:477)	302 (158:447)	+36 (0:121)	-5 (-68:59)	41 (13.4%)
Lutein	161 (128:215)	164 (107:222)	-9 (-39:42)	-10 (-38:13)	-1 (0%)
Cryptoxanthin	79 (54:145)	55 (43:158)	+5 (-25:26)	-3 (-16:25)	8 (11.7%)
Zeaxanthin	49 (37:70)	47 (31:62)	-3 (-14:98)	0 (-14:13)	-3 (-6%)

NOTE: 25th and 75th percentile shown in parentheses. None of the difference in change in plasma carotenoids concentrations are statistically significantly different. *Percent change is calculated using the mean of the two medians (control, intervention) at baseline.

achieved (16) by intensive dietary counseling, which consisted of two home visits within the first 4 days of participation followed by intermittent visits and telephone calls from the study dietitians.

Changes in plasma or serum carotenoid concentrations have been used in many studies to validate self-reported changes in fruit and vegetable intake. We observed a 12.6% increase in median total plasma carotenoid concentration in the intervention compared with the control group, with the greatest percentage change seen for α-carotene, lycopene, and cryptoxanthin. In a controlled feeding study, where fruit and vegetable intake was more than doubled (2 servings of fruit and vegetables a day for 2 weeks followed by 5 servings for 2 weeks), the greatest changes in blood carotenoid concentrations were seen for α-carotene, β-carotene, lutein, and lycopene; collectively, a 29% increase in these four carotenoids was observed between the two diets (28). In contrast, in an observational study involving 561 Dutch men and women, plasma β-cryptoxanthin was found to be the best predictor of fruit intake and similarly lutein for vegetable intake (29). However, change in blood carotenoid concentration is highly dependent on the carotenoid composition of the fruit and vegetables introduced into the diet to achieve the increase in intake.

The correlations between plasma carotenoid concentrations and fruit and vegetable intake observed in this study are of similar magnitude to those reported in other studies (29), supporting the validity of the self-reported intake of fruit and vegetable intake. Between the baseline and end of study visits, a nonsignificant reduction in plasma total carotenoid concentration was seen in the control group despite controls self-reporting a small increase in servings of fruits and vegetables over the same time period. This may indicate underreporting of fruit and vegetables at baseline in controls, overreporting of fruit and vegetables at the end-of-study visit in the controls, or may simply reflect increased consumption of low-carotenoid fruits and vegetables.

The change in plasma carotenoids seen in our study is lower than that seen in some studies that report similar changes in self-reported fruit and vegetable intake (14-17). This could be due to differences in the way fruit and vegetable intake is assessed and/or reported or to differences in the statistical presentation of blood carotenoid concentrations. Carotenoid distributions tend to be right skewed; thus, reporting mean values versus the median values or geometric means may inflate the average change in carotenoids, especially in small studies. Additionally, study populations may differentially overreport fruit and vegetable intake in response to an intervention to please the study staff or study populations may differ in their serum/plasma response to increasing intake of carotenoid-rich fruit and vegetables (30). Lastly, as previously mentioned, total plasma carotenoid concentration is not so perfect a biomarker for fruit and vegetable intake, as participants could increase intake of low-carotenoid fruits and vegetables. Pierce et al.

(15) encouraged consumption of juice from carotenoid-rich vegetables and saw a correspondingly large increase in blood carotenoid concentrations; however, interventions that do not focus on increasing intake of carotenoid-rich fruits and vegetables or their juices will not observe such a large increase in blood carotenoid for a comparable increase in fruit and vegetable intake.

Of note, plasma carotenoid concentrations at enrollment were relatively low in this group of head and neck cancer patients compared with the concentrations reported in the general population of a similar age as assessed in The National Health and Nutrition Examination Survey III. Our population median plasma β-carotene concentration was 209 nmol/L (11.2 μg/dL) for males and 231 nmol (12.4 μg/dL) for females, compared with median concentrations of 285 nmol/L (15.3 μg/dL) in 51- to 70-year-old men and 384 nmol/L (20.6 μg/dL) in 51- to 70-year-old women who participated in The National Health and Nutrition Examination Survey III (31). Similarly, plasma lycopene concentrations were lower than the median for 51- to 70-year-old participants: 302 nmol/L (16.21 μg/dL) in our male participants and 341 nmol/L (18.33 μg/dL) in our female participants compared with 385 nmol/L (20.7 μg/dL) and 363 nmol/L (19.5 μg/dL), respectively, in The National Health and Nutrition Examination Survey III. Such levels are consistent with those previously reported by us for a similar group of curatively treated early-stage head and neck cancer patients (32) and likely reflect the relatively poor nutritional habits in this population.

At enrollment to the study, the majority of patients (63%) were precontemplators on stage of change for fruit and vegetable intake. Resnicow et al. (33) measured stage of change for fruit and vegetable intake in 861 volunteer members of Black churches who attended Church run health fairs and found the majority (62.7%) to be in the preparation stage. In our study, following an explanation of the purpose of our study given to those assigned to the intervention group before the intervention, the majority of precontemplators rapidly transitioned to the preparation stage. We therefore had a limited ability to assess any difference in response to the intervention based on stage of change. The rapid transition through the stages of change for fruit and vegetable intake indicates that these patients are lacking in knowledge that they should be eating more fruits and vegetables and indicates that the postdiagnosis period represents an intervention opportunity for these early-stage head and neck cancer patients.

The strengths of this study are the randomized design in which the control group was blinded to the purpose of the study and the inclusion of an objective biomarker to assess response to the intervention. In addition, although this study was conducted in a challenging patient population, a reasonable change in intake was achieved with a minimal intervention. However, the study experienced a lower than ideal participation rate. Although not affecting the internal validity, the results may not be generalizable to all early-stage head and

neck cancer patients. In addition, the inability to obtain blood samples from all participants further limited our power to detect differences in change in plasma carotenoid concentrations over time. An additional limitation is that as the intervention group could not be blinded, the patients in the intervention group may have reported higher dietary intake of fruits and vegetables in response to being advised that they should increase their intake but without doing so. This possibility cannot be ruled out as changes in plasma carotenoids over the study period were not significantly different between the intervention and control groups. Alternately, those in the intervention group may have increased fruit and vegetable intake due to simply receiving dietary information and, therefore, any change may not be attributed to receiving stage-based information. Future research could pit a stage-based intervention against an informational one, with no stage-based content to test this possibility.

In summary, this study indicates that patients with head and neck cancer, most of whom have or have had a history of unhealthy lifestyle habits including smoking and/or excessive alcohol drinking, respond to a relatively low-intensity intervention that could be incorporated into their routine medical follow-up care by significantly increasing their fruit and vegetable intake. As these patients have heightened risk for several common chronic diseases (e.g., heart disease), which might be reduced by increasing fruit and vegetable intake, introducing an intervention such as this into their follow-up care may provide several health benefits.

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References

- Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin* 2005;55:10–30.
- Khuri FR, Kim ES, Lee JJ, et al. The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the head and neck retinoid chemoprevention trial. *Cancer Epidemiol Biomarkers Prev* 2001;10:823–9.
- Lippman SM, Hong WK. Second malignant tumors in head and neck squamous cell carcinoma: the overshadowing threat for patients with early-stage disease. *Int J Radiat Oncol Biol Phys* 1989;17:691–4.
- Vikram B. Changing patterns of failure in advanced head and neck cancer. *Arch Otolaryngol* 1984;110:564–5.
- Mayne ST, Cartmel B, Baum M, et al. Randomized trial of supplemental β -carotene to prevent second head and neck cancer. *Cancer Res* 2001;61:1457–63.
- Mayne ST, Cartmel B, Morse DE. Chemoprevention of oral premalignant lesions. In: Ensley J, Gutkind J, Jacobs J, Lippman SM, editors. *Head and neck cancer*. San Diego (CA): Academic Press; 2003.
- Do K-A, Johnson MM, Lee JJ, et al. Longitudinal study of smoking patterns in relation to the development of smoking-related secondary primary tumors in patients with upper aerodigestive tract malignancies. *Cancer* 2004;101:2837–42.
- Riboli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr* 2003;78:559–69S.
- IARC. Fruits and vegetables. IARC handbooks of cancer prevention. Vol. 8. Lyon: IARC; 2003.
- Day GL, Shore RE, Blot WJ, et al. Dietary factors and second primary cancers: A follow-up of oral and pharyngeal cancer patients. *Nutr Cancer* 1994;21:223–32.
- Steward DL, Wiener F, Gleich LL, Falciglia G. Dietary antioxidant intake in patients at risk for second primary cancer. *Laryngoscope* 2003;113:1487–93.
- Robison LL. Cancer Survivorship: Unique opportunities for research. *Cancer Epidemiol Biomarkers Prev* 2004;13:1093.
- Gritz ER, Carr CR, Rapkin D, et al. Predictors of long-term smoking cessation in head and neck cancer patients. *Cancer Epidemiol Biomarkers Prev* 1993;2:261–70.
- Rock CL, Moskowitz A, Huizar B, et al. High vegetable and fruit diet intervention in premenopausal women with cervical intraepithelial neoplasia. *J Am Diet Assoc* 2001;100:1167–74.
- Pierce JP, Newman VA, Flatt SW, et al. Telephone counseling intervention increases intakes of micronutrient- and phytochemical-rich vegetables, fruit and fiber in breast cancer survivors. *J Nutr* 2003;134:452–8.
- Le Marchand L, Hankin JH, Carter FS, et al. A pilot study on the use of plasma carotenoids and ascorbic acid as markers of compliance to a high fruit and vegetable dietary intervention. *Cancer Epidemiol Biomarkers Prev* 1994;3:245–51.
- Steptoe A, Perkins-Porras L, McKay C, Rink E, Hilton S, Cappuccio FP. Behavioral counselling to increase consumption of fruit and vegetables in low income adults: randomised trial. *BMJ* 2003;326:855–60.
- Lanza E, Schatzkin A, Daston C, et al. Implementation of a 4-y, high-fiber, high-fruit-and-vegetable, low-fat dietary intervention: results of dietary changes in the Polyp Prevention Trial. *Am J Clin Nutr* 2001;74:387–401.
- Prochaska JO, DiClemente CC. Transtheoretical therapy: toward a more integrative model of change. *Psychother: Theory Res Pract* 1982;19:276–88.
- Plummer W, Velicer W, Redding C, et al. Stage of change, decisional balance, and temptations for smoking: measurement and validation in a large, school-based population of adolescents. *Addict Behav* 2001;26:551–71.
- Velicer W, Prochaska J. An expert system intervention for smoking cessation. *Patient Educ Couns* 1999;36:119–29.
- Pallonen U, Prochaska J, Velicer W, Prokhorov A, Smith N. Stages of acquisition and cessation for adolescent smoking: an empirical integration. *Add Behav* 1998;23:303–24.
- Hargreaves M, Schlundt D, Buchowski M, Hardy R, Rossi S, Rossi J. Stages of change and the intake of dietary fat in African-American women: improving stage assignment using the Eating Styles Questionnaire. *J Am Diet Assoc* 1999;99:1392–9.
- Havas S, Anliker J, Damron D, Feldman R, Langenberg P. Uses of process evaluation in the Maryland WIC 5-a-day promotion program. *Health Educ Behav* 2000;27:254–63.
- Ma J, Betts N, Horacek T, Georgiou C, White A, Nitzke S. The importance of decisional balance and self-efficacy in relation to stages of change for fruit and vegetable intakes by young adults. *Am J Health Promot* 2002;16:157–66.
- Clark PG, Nigg CR, Greene G, Riebe D, Saunders SD. The Study of Exercise and Nutrition in Older Rhode Islanders (SENIOR): translating theory into research. *Health Educ Res* 2002;17:552–61.
- Kristal AR, Vizenor NC, Patterson RE, Neuhouser ML, Shattuck AL, McLerran D. Precision and bias of food frequency-based measures of fruit and vegetable intakes. *Cancer Epidemiol Biomarkers Prev* 2000;9:939–44.
- Brevik A, Andersen L, Karlsen A, Trygg K, Blomhoff R, Drevon C. Six carotenoids in plasma used to assess recommended intake of fruits and vegetables in a controlled feeding study. *Eur J Clin Nutr* 2004;58:1166–73.
- Jansen M, Van Kappel A, Ocke M, et al. Plasma carotenoid levels in Dutch men and women, and the relation with vegetable and fruit consumption. *Eur J Clin Nutr* 2004;58:1396–5.
- Brown E, Micozzi M, Craft N, et al. Plasma carotenoids in normal men after a single ingestion of vegetables or purified β -carotene. *Am J Clin Nutr* 1989;49:1258–65.
- Panel on Dietary Antioxidants and Related Compounds, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids*. Washington: National Academy Press; 2000.
- Mayne ST, Cartmel B, Silva F, et al. Effect of supplemental β -carotene on plasma concentrations of carotenoids, retinol and α -tocopherol in humans. *Am J Clin Nutr* 1998;68:642–7.
- Resnicow K, McCarty F, Baranowski T. Are precontemplators less likely to change their dietary behavior? A prospective analysis. *Health Educ Res* 2003;18:693–705.