

# Alcohol and Tobacco Use Prediagnosis and Postdiagnosis, and Survival in a Cohort of Patients with Early Stage Cancers of the Oral Cavity, Pharynx, and Larynx

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## Abstract

As more people begin to survive first cancers, there is an increased need for science-based recommendations to improve survivorship. For survivors of head and neck cancer, use of tobacco and alcohol before diagnosis predicts poorer survival; however, the role of continuing these behaviors after diagnosis on mortality is less clear, especially for more moderate alcohol consumption. Patients ( $n = 264$ ) who were recent survivors of early stage head and neck cancer were asked to retrospectively report their tobacco and alcohol histories (before diagnosis), with information prospectively updated annually thereafter. Patients were followed for an average of 4.2 years, with 62 deaths observed. Smoking history before diagnosis dose-dependently increased the risk of dying; risks reached 5.4 [95% confidence interval (95% CI), 0.7-40.1] among those with >60 pack-years of smoking.

Likewise, alcohol history before diagnosis dose-dependently increased mortality risk; risks reached 4.9 (95% CI, 1.5-16.3) for persons who drank >5 drinks/d, an effect explained by beer and liquor consumption. After adjusting for prediagnosis exposures, continued drinking (average of 2.3 drinks/d) postdiagnosis significantly increased risk (relative risk for continued drinking versus no drinking, 2.7; 95% CI, 1.2-6.1), whereas continued smoking was associated with nonsignificantly higher risk (relative risk for continued smoking versus no smoking, 1.8; 95% CI, 0.9-3.9). Continued drinking of alcoholic beverages after an initial diagnosis of head and neck cancer adversely affects survival; cessation efforts should be incorporated into survivorship care of these patients. (Cancer Epidemiol Biomarkers Prev 2009;18(12):3368-74)

## Introduction

Squamous cell carcinoma of the oral cavity, pharynx, and larynx, collectively referred to as head and neck cancer, is a major health problem in the United States and throughout the world. It is estimated that 47,560 new cases were identified and that 11,260 patients died of these cancers in the United States in 2008 (1). These cancers also assume a high relative importance because of the functional impairments and cosmetic deformity associated with the cancer and its treatment.

With advances in early detection, nearly half of the patients are diagnosed with early stage (stage I/II) disease. Although treatment given at this stage is relatively successful, failure remains common, due primarily to local recurrences and second primary cancers. The expected incidence of second primaries varies by head and neck site, but a reasonable estimate is that 4% of stage I/II patients will develop second primary cancers yearly (2-5). These second primary cancers are a consequence of field cancerization of the upper aerodigestive tract; field cancerization is thought to be a consequence of chronic exposure to tobacco and alcohol.

Consistent with this, recent studies have reported that predictors of second primary tumor development include both continued smoking and alcohol intake after the index diagnosis. In a large recent study of 1,181 patients enrolled in a chemoprevention trial, current smoking at registration and continued alcohol consumption postdiagnosis increased the risk of second primary tumor development 2.1-fold [95% confidence interval (95% CI), 1.3-3.6] and 1.3-fold (95% CI, 1.0-1.7), respectively (2). With the use of data from that same cohort, it was more recently reported that current smoking (which we interpret as baseline smoking; not specifically defined) also predicted poorer overall survival (current versus never smoking; hazard ratio, 2.51; 95% CI, 1.54-4.10; current versus former smoking; hazard ratio, 1.60; 95% CI, 1.23-2.07; ref. 6). The authors did not report on the effects of continued smoking postdiagnosis, with or without adjustment for prior smoking history, on the risk of all-cause mortality. The established effect of tobacco (at diagnosis) on risk of second primary tumors and mortality in this population, supported by the well-known positive association between tobacco use and all-cause mortality in the general population (7), indicates that these patients should aggressively pursue tobacco cessation interventions. In contrast, the relatively small and borderline significant effect of continuing alcohol consumption on second primary tumors, along with a well-known inverse association between moderate alcohol consumption and cardiovascular and all-cause mortality (8), results in a more ambiguous recommendation about the benefits of

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alcohol cessation postdiagnosis for this patient population with regard to all-cause mortality.

We previously conducted a single-nutrient supplementation trial in head and neck cancer patients aimed at prevention of second cancers (9). One of the aims of this trial was to identify risk factors for all-cause mortality to better inform the survivorship care of patients with these cancers. This analysis reports on the effects of prediagnosis use of tobacco and alcohol (total and by type of beverage), along with the effect of changes in these two exposures postdiagnosis, in predicting overall survival in this patient population.

## Subjects and Methods

**Patients and Study Design.** The participants in this study were part of a randomized, double-blind placebo-controlled trial to determine whether supplemental  $\beta$ -carotene reduces the incidence of second cancers in patients curatively treated for early stage cancers of the oral cavity, pharynx, or larynx. The efficacy results of the chemoprevention trial have been published, with full details of the trial methodology (9). The study methods will be briefly described here, with particular emphasis on the exposures (tobacco and alcohol) and outcomes (ascertainment of mortality) of interest for this analysis.

Subjects were recruited from two recruitment sites, one based at Yale University and recruiting from the state of Connecticut (population-based identification by the Rapid Case Ascertainment Shared Resource of the Yale Cancer Center, an agent of the Connecticut Tumor Registry), and the second based at the University of Miami and recruiting from 14 hospitals in South Florida. To be eligible, subjects had to have completed all treatment (e.g., surgery and/or radiation for stage I/II) and be free of disease after a diagnosis of stage I or stage II squamous cell carcinoma of one of the following sites: tongue, gum or mouth, oropharynx, hypopharynx, pharynx, or larynx. Patients with carcinoma *in situ* at the above sites were also eligible. Subjects also had to be between 20 and 79 y of age, be considered free of cancer at any site at entry into the trial, have no significant comorbidities, and not have taken supplements of retinol,  $\beta$ -carotene, vitamin E, or selenium within the past year (multivitamin use allowed). Most patients were enrolled within 1 y after diagnosis.

The following procedures were approved by the Connecticut Department of Public Health Human Investigation Committee and the Institutional Review Boards at all the hospitals from which subjects were recruited (a total of 49 hospitals). In the process of case ascertainment in Connecticut, certain data used in this study were obtained from the Connecticut Tumor Registry located at the Connecticut Department of Public Health. The authors assume full responsibility for the analyses and interpretation of these data. First, physician consent was obtained before contacting potential participants for consent purposes to confirm stage at diagnosis and to determine that patients had completed treatment with curative intent. Participants were approached for participation by letter and then by phone; those who agreed were subsequently visited in person by trained nurse or physician interviewers, who obtained signed consent before proceeding. Participants were interviewed in depth with the use of a structured questionnaire to obtain information about de-

mographics, use of tobacco and alcohol (see below for details), diet, and other possible risk factors, and those who agreed to participate in the trial underwent a placebo run-in period of 1 mo. Subjects who consumed >75% of the placebo capsules during the run-in were randomized to receive either supplemental  $\beta$ -carotene or placebo. The intervention consisted of a 50-mg dose of  $\beta$ -carotene/d, packaged into one capsule (Lurotin, BASF, Parsippany, NJ) or a corresponding placebo. Details of the randomization procedure and assessment of compliance are described elsewhere (9).

**Tobacco and Alcohol Exposure Assessment.** Subjects were visited in person at baseline after the 1-mo placebo run-in, and then at 3, 12, and 24 mo, and yearly thereafter for up to 60 mo. Full tobacco history was obtained at baseline, with subjects asked to report age started smoking, age stopped smoking, total number of years smoked, average number of cigarettes smoked per day, and smoking status before diagnosis of the index cancer. We also inquired about their use of other forms of tobacco, including cigars, pipes, chewing tobacco, and snuff. This information was updated annually, with detailed information elicited about changes in smoking habits over the prior year, including an assessment of current usage. Similarly, a detailed alcohol history was obtained at baseline. Subjects were asked about beer, wine, and liquor separately, with detailed questions on ever use, number of days per week used, number of drinks per day, and total number of years drinking that beverage type. At each annual visit, subjects reported if their drinking habits had changed over the past year, including current drinking habits for each beverage type.

**Follow-up of Cohort.** As described previously, in-person visits were made at 3 mo postrandomization, at 12 mo, and then annually thereafter for all active participants (those who continued taking supplements and did not experience a study end point). In-person contacts were supplemented with phone calls; active participants were contacted every 3 mo by phone (or visit). Inactive participants were contacted by phone every 6 mo, and were also asked to report tobacco and alcohol use during follow-up, although drinking by beverage type was not queried for inactive participants. Most deaths were reported to us by next of kin. Eleven subjects, all from South Florida, were lost to follow-up. Searches of the Florida Cancer Data System, which links with the Bureau of Vital Statistics of Florida, were done to ascertain vital status for these subjects. Death certificates were obtained for all deceased subjects and coded by a trained nosologist. The primary outcome of interest for this analysis was all-cause mortality.

**Statistical Analysis.** All of the analyses were done with SAS (SAS Institute, Cary, NC). For initial analyses, the population was stratified by vital status at the end of follow-up, and differences between the two groups in demographic characteristics, and tobacco and alcohol exposures were evaluated with the use of Student's *t*-test or  $\chi^2$  analyses as appropriate. Cox proportional hazards models were then used to estimate relative risks (RR) based on the exposures of interest, allowing for adjustment of other covariates.

A large number of potentially confounding variables were examined in the multivariate models. Final models

included age (continuous), gender, race, randomization group ( $\beta$ -carotene versus placebo), educational level, and body mass index (BMI). Models evaluating effects of smoking included adjustment for alcohol (beer, wine, and liquor intake), whereas models evaluating effects of alcohol included adjustment for smoking (pack-years, current versus former/never smoker). Tests for trend were conducted with the use of a Wald  $\chi^2$  statistic computed for continuous variables within adjusted models.

To evaluate the effects of continued smoking and drinking on mortality risk, we created a categorical variable for each exposure as follows: nonexposed (abstained throughout follow-up), transitionally exposed (exposed after diagnosis but not continuously), and continuously exposed (reported exposure at each annual follow-up interview). The transitional category was necessary because patients with head and neck cancers will commonly cease smoking and/or drinking at the time of diagnosis and abstain for some period of time after diagnosis, only to reinitiate some time later. All models for continued smoking and drinking were adjusted for smoking and drinking before diagnosis, and smoking during follow-up (for alcohol analyses) or drinking during follow-up (for smoking analyses) as appropriate. A *P*-value of 0.05 was considered statistically significant for all analyses.

Cigarette smoking was the predominant source of tobacco exposure in this population; however, a total of 11 persons reported current pipe smoking, 41 reported former pipe use, 14 reported current cigar smoking, and 40 reported former cigar smoking. The majority of these individuals reported using multiple tobacco products. To consider the confounding effects of these other tobacco sources on mortality, we added terms into the model for ever/never use of cigars and ever/never use of pipes, and

we also repeated the analyses excluding the 11 current pipe users and 14 current cigar users. The results were not materially altered, so the models shown are unadjusted for use of other tobacco products.

## Results

A total of 264 persons were randomized in the chemoprevention trial. Subjects were enrolled beginning in January 1991 and followed through until June 1998. The median follow-up in the study population was 51 months up to a maximum of 90 months.

A total of 62 deaths occurred during the follow-up period. This consisted of 35 deaths due to cancer, 18 deaths due to cardiovascular disease, and 9 deaths due to other causes. Subjects who died during the follow-up period were significantly older at enrollment (64.0 versus 61.0 years), had lower BMI (24.4 versus 25.8), and were more likely to have stage II disease (versus stage I or carcinoma *in situ*) compared with subjects who remained alive during the follow-up period, as shown in Table 1. Patients who had laryngeal cancers as their index cancer were somewhat less likely to die during the follow-up period compared with patients with oral or pharyngeal primary tumors (*P* for larynx versus other sites = 0.06). More highly educated patients (>12 years) were also less likely to die during the follow-up period, although this difference was not statistically significant.

Cigarette smoking habits at and before cancer diagnosis affected the risk of dying during the follow-up as expected. Current smokers at the time of diagnosis were 4.9-fold more likely to die during the follow-up (95% CI, 0.7-36.0) compared with never smokers (Table 2). We also

**Table 1. Baseline characteristics of early stage head and neck cancer patients according to survival status at the end of follow-up**

Characteristics	Patients who died, <i>n</i> = 62	Patients who survived, <i>n</i> = 202	<i>P</i>
Age (mean $\pm$ SD)	64.0 $\pm$ 7.5	61.0 $\pm$ 9.9	0.01
Sex			0.52
Male	52 (84%)	162 (80%)	
Female	10 (16%)	40 (20%)	
Race			0.85
White/non-Hispanic	54 (87%)	181 (90%)	
Hispanic/Puerto Rican	4 (6%)	11 (5%)	
Non-White	4 (6%)	10 (5%)	
Tumor site			0.15
Oral cavity	19 (31%)	46 (23%)	
Pharynx	7 (11%)	13 (6%)	
Larynx	36 (58%)	143 (71%)	
Treatment			0.33
Surgery	20 (32%)	61 (30%)	
Radiation	32 (52%)	111 (55%)	
Surgery and Radiation	9 (15%)	18 (9%)	
Unknown	1 (2%)	12 (6%)	
Stage*			0.002
Carcinoma <i>in situ</i>	4 (7%)	9 (4%)	
I	27 (44%)	138 (69%)	
II	30 (49%)	54 (27%)	
Recruitment site			0.23
Connecticut	52 (84%)	155 (77%)	
Florida	10 (16%)	47 (23%)	
Years of education*			0.82
<12	8 (13%)	23 (11%)	
12	29 (47%)	88 (44%)	
>12	25 (40%)	90 (45%)	
BMI (kg/m <sup>2</sup> )	24.4 $\pm$ 3.8	25.8 $\pm$ 3.8	0.01

\*Stage category missing for two patients and education for one.

**Table 2. Association between smoking status/smoking history at diagnosis and mortality during the follow-up period in a cohort of early stage head and neck cancer patients**

Smoking	Person-years	All-cause mortality	
		No. of deaths	RR* (95% CI)
Cigarette smoking			
Never smokers ( <i>n</i> = 17)	75	1	1.0
Former smokers ( <i>n</i> = 111)	460	18	2.14 (0.28, 16.47)
Current smokers ( <i>n</i> = 136)	568	43	4.91 (0.67, 35.98)
Smoking intensity, cigarettes/d <sup>†</sup>			
1-15 ( <i>n</i> = 49)	222	9	2.43 (0.30, 19.69)
16-30 ( <i>n</i> = 103)	423	22	3.59 (0.48, 27.04)
>30 ( <i>n</i> = 95)	382	30	5.33 (0.71, 40.00)
<i>P</i> -trend			0.17
Smoking duration, y <sup>†</sup>			
1-30 ( <i>n</i> = 78)	347	10	1.95 (0.24, 15.86)
31-40 ( <i>n</i> = 61)	256	15	3.59 (0.47, 27.54)
>40 ( <i>n</i> = 108)	423	36	5.15 (0.69, 38.47)
<i>P</i> -trend			0.004
Pack-years <sup>†</sup>			
Up to 40 ( <i>n</i> = 96)	407	15	2.49 (0.33, 19.11)
41-60 ( <i>n</i> = 67)	276	16	3.88 (0.50, 30.26)
>60 ( <i>n</i> = 84)	344	30	5.39 (0.73, 40.12)
<i>P</i> -trend			0.003

\*Adjusted for age, sex, educational level, BMI, race, randomization group, beer, wine, and liquor. *P*-trend refers to the test for a linear dose-response relationship for each measure of tobacco use (smoking intensity, duration, and pack-years separately).

<sup>†</sup>Among current and former smokers combined, relative to never smokers.

observed a dose-dependent increase in the risk of dying with smoking intensity, although the test for linear trend was not statistically significant ( $P = 0.17$ ). Longer smoking duration was associated with a dose-dependent increase in the risk of dying with a significant linear trend. Pack-years is a measure that integrates both intensity and duration; patients who had >60 pack-years of tobacco exposure at diagnosis (equivalent to smoking 1 pack/d for 60 years or 2 packs/d for 30 years) were 5.4 times more likely to die during the follow-up period (95% CI, 0.7-40.1) compared with never smokers ( $P$  for trend = 0.003).

Usual alcohol intake before diagnosis of the index cancer was associated with a dose-dependent increase in the risk of dying during the follow-up period (Table 3), with those who usually drank >35 drinks/wk 4.9 times more likely to die compared with those who did not drink (95% CI, 1.5-16.3;  $P$  for trend < 0.0001). This excess risk for alcohol history was observed for beer ( $P$  for trend = 0.04) and liquor ( $P$  for trend = 0.0001) but not for wine, even with daily consumption (compared with no wine consumption; RR, 0.75; 95% CI, 0.32-1.76;  $P$  trend = 0.27).

We then explored the effect of continued exposures postdiagnosis on the risk of dying. Transitional smokers (reported smoking at some point after diagnosis but not continuously) were not at increased risk of mortality, but continuous smokers (reported smoking at each follow-up interview) were at increased risk compared with persons who abstained from smoking throughout the follow-up. In models that only adjusted for age, continuous smoking was associated with a 3.3-fold increased risk (95% CI, 1.74-6.26). When we further adjusted for smoking history, continuous smokers remained at higher risk of dying during the follow-up period. For example, in a model that included age, smoking history, and continuous/transitional smoking, both smoking history and continuous smoking were significantly associated with mortality (RR for continuous smokers, 2.22; 95% CI, 1.10-4.48). With further adjustment for alcohol (historical use and continuing) and other covariates (Table 4), continued cigarette smoking

was positively but not significantly associated with mortality risk (RR, 1.83; 95% CI, 0.85-3.94). Of note, when the 11 current pipe users and 14 current cigar users were excluded from this RR calculation, the adverse effect of

**Table 3. Association between usual alcohol intake before diagnosis and mortality during the follow-up period, for total alcohol and by type of alcohol, in a cohort of early stage head and neck cancer patients**

Alcohol intake	Person-years	All-cause mortality	
		No. of deaths	RR* (95% CI)
Total (drinks/wk)			
0 ( <i>n</i> = 30)	145	3	1.0
1-7 ( <i>n</i> = 49)	197	6	1.46 (0.35, 6.14)
8-21 ( <i>n</i> = 60)	275	11	1.44 (0.39, 5.35)
22-35 ( <i>n</i> = 32)	133	7	2.36 (0.60, 9.31)
>35 ( <i>n</i> = 93)	352	35	4.87 (1.46, 16.27)
<i>P</i> -trend			<0.0001
Beer (drinks/wk)			
0 ( <i>n</i> = 82)	367	14	1.0
1-7 ( <i>n</i> = 76)	314	14	1.20 (0.53, 2.73)
8-21 ( <i>n</i> = 52)	201	13	2.37 (1.03, 5.44)
>21 ( <i>n</i> = 54)	219	21	2.86 (1.34, 6.12)
<i>P</i> -trend			0.04
Wine (drinks/wk)			
0 ( <i>n</i> = 160)	675	44	1.0
1-2 ( <i>n</i> = 43)	180	7	0.58 (0.25, 1.35)
3-7 ( <i>n</i> = 30)	121	4	0.44 (0.14, 1.35)
>7 ( <i>n</i> = 31)	125	7	0.75 (0.32, 1.76)
<i>P</i> -trend			0.27
Liquor (drinks/wk)			
0 ( <i>n</i> = 91)	405	16	1.0
1-7 ( <i>n</i> = 61)	244	12	1.27 (0.59, 2.75)
8-21 ( <i>n</i> = 48)	217	13	1.04 (0.47, 2.33)
>21 ( <i>n</i> = 64)	235	21	2.11 (1.04, 4.28)
<i>P</i> -trend			0.0001

\*Adjusted for age, sex, smoking history (pack-years, current versus former/never), educational level, BMI, race, randomization group, and other types of alcohol (where applicable). *P*-trend refers to the test for a linear dose-response relationship for each measure of alcohol use (total, beer, wine, and liquor separately).

**Table 4. Association between continued drinking and smoking habits postdiagnosis, and mortality during follow-up in a cohort of early stage head and neck cancer patients**

Habits during follow-up	Person-years	All-cause mortality		
		No. of deaths	RR* (95% CI)	RR† (95% CI)
<b>Drinking</b>				
Nondrinker ( <i>n</i> = 101)	451	13	1.0	1.0
Transitional drinker ( <i>n</i> = 64)	315	8	0.86 (0.36, 2.08)	0.73 (0.29, 1.86)
Continuous drinker ( <i>n</i> = 73)	305	20	2.48 (1.23, 5.02)	2.72 (1.20, 6.14)
<b>Cigarette smoking</b>				
Nonsmoker ( <i>n</i> = 163)	736	22	1.0	1.0
Transitional smoker ( <i>n</i> = 28)	133	3	0.86 (0.26, 2.90)	0.36 (0.10, 1.31)
Continuous smoker ( <i>n</i> = 50)	206	17	3.30 (1.74, 6.26)	1.83 (0.85, 3.94)

\*Adjusted for age.

†Adjusted for age, sex, smoking history, educational level, BMI, race, randomization group, history of beer, wine, and liquor consumption, and, as appropriate, smoking or drinking during follow-up.

continued cigarette smoking was more extreme and statistically significant (RR, 2.48; 95% CI, 1.06-5.82).

Likewise, transitional drinking (drinking at some point after diagnosis but not continuously) was not associated with an increased risk of dying during the follow-up, but continuous drinking postdiagnosis increased the risk of dying during the follow-up period compared with non-drinking during the follow-up. In unadjusted and adjusted models, continuous drinking was associated with a significant doubling or greater increase in mortality risk (Table 4). The mean overall consumption for the continuous drinkers (*n* = 73) during the follow-up period was 2.3 drinks/d. Because some of those who drank before diagnosis were no longer drinking during the follow-up period, and we did not have beverage-specific intake for inactive participants, we had insufficient power to examine the effects of continued drinking by type of beverage on overall mortality.

## Discussion

There has been considerable interest in the prevention of second primary tumors in patients with early stage head and neck cancers, and many large retinoid/carotenoid cancer prevention trials have been done to investigate the prevention of second primary tumors in this patient population (10-14). However, patients with early stage head and neck cancers are at considerable risk for other chronic conditions, such as coronary heart disease, given a history of substantial use of tobacco in the vast majority of these patients. This is shown by the fact that only 56% of the deaths that occurred in our cohort were deaths due to cancer (any type), with another 29% dying from coronary heart disease and the remaining 15% dying from other causes. This mortality breakdown is consistent with another large chemoprevention trial of head and neck cancer patients (2); in that cohort 51.1% died from causes other than local recurrences or second primary tumors, with a median of 3.7 years of follow-up. There is a paucity of studies focusing on prevention of all-cause mortality in this patient population, which is therefore the rationale for conducting this analysis.

Patients who died during the follow-up had a significantly lower BMI at baseline. To better understand this association, we examined BMI by smoking status at baseline. Current smokers, on average, had lower BMI than never/former smokers (24.95 versus 26.09; *P* = 0.02), suggesting that the univariate association between BMI and mortality was due, at least in part, to confounding by tobacco use.

Patients with older ages, with oral and pharyngeal primary tumors, and with stage II (versus stage I/carcinoma *in situ*) disease also had poorer survival in our cohort. These same patients have been observed to have a higher risk of second primary tumors of the head and neck (2), suggesting that our patient population is reasonably representative of other early stage head and neck cancer patient populations drawn from different geographic regions. Age, tumor site, and stage, however, are not modifiable risk factors, leading us to concentrate on modifiable risk factors, such as smoking and alcohol drinking, for improving survival.

Our results indicate that smoking prediagnosis and postdiagnosis increases the risk of dying during the follow-up period. This is in accord with studies examining smoking and second primary tumor prevention (2). In addition, smoking and drinking prediagnosis has previously been linked with poorer survival in patients with head and neck cancer, although that study had no follow-up information on alcohol consumption or smoking after cancer diagnosis (15). The concordance of results on smoking and prevention of second primary tumors, and smoking and prevention of total mortality emphasizes the critical role of tobacco cessation interventions in head and neck cancer patients. Clinicians routinely advise this patient population to quit smoking; however, these efforts are only partially successful. Gritz et al. (16) evaluated the efficacy of smoking cessation interventions in head and neck cancer patients. Among those patients who were smoking at the time of randomization, the abstinence rate at 1 year was 59%. In our own cohort, 21% (50 of 241) of patients smoked continuously after their cancer diagnosis. This occurred despite the fact that we supplemented the usual clinical recommendation for tobacco cessation with additional advisement to stop smoking at the time of randomization, with referrals to smoking cessation programs given as needed (minimal tobacco cessation intervention).

Likewise, alcohol use prediagnosis and postdiagnosis increased the risk of dying during the follow-up period, with the risk estimate for beer (prediagnosis) exceeding that of other types of alcoholic beverages. Notably, Day et al. (17) also observed that beer was the strongest predictor of risk for second primary tumors in patients with oral and pharyngeal cancers (all stages). Somewhat surprisingly, the point estimate for continued drinking exceeded that for continued smoking, despite the well-known inverse association between alcohol consumption and ischemic heart

disease in a general population of men, even at relatively high levels of intake (8). Many patients with head and neck cancers have a history of heavy alcohol consumption (18); in our cohort 35% of patients reported drinking  $\geq 5$  drinks/d before diagnosis. We advised participants who were heavy drinkers to abstain or reduce their alcohol use at the baseline visit, with referrals to alcohol control programs given as needed (minimal alcohol control intervention). As was the case with tobacco, many patients (31%, or 73 of 238) continued to drink alcohol postdiagnosis, with an average self-reported consumption of 2.3 drinks/d (continuous drinkers) and 1.3 drinks/d (transitional drinkers). Our results emphasize that these patients should be aggressively counseled to abstain from alcohol, given our findings of an increase in the risk of total mortality with continued drinking, along with the results of others indicating that continued drinking increases the risk of second primary tumors (2).

The strengths of our study include the prospective study design, with careful in-person collection of data on alcohol and tobacco exposures, which were updated annually. Despite this, a possible limitation of our study is that self-reported smoking status was not verified biochemically with cotinine or another marker, and there was no objective method available to validate self-reported alcohol exposures. Thus, subjects could have misreported their true exposure status (measurement error). Because all exposure data were obtained before the outcome of interest (mortality), and all deaths were confirmed by death certificate, this measurement error would most likely be nondifferential. Nondifferential measurement errors generally bias associations toward the null, suggesting that the true associations between continued tobacco and alcohol use and mortality are likely more extreme than was observed in this study.

Another limitation of our study is that we had a relatively small sample size, with 62 deaths occurring during the follow-up period. Whereas this sample size was sufficient for us to detect the main effects of alcohol and tobacco on total mortality, it was insufficient to examine interactions between these two exposures in determining mortality outcomes, and it also limited our ability to examine the effects of alcohol and tobacco on second primary tumors as a separate outcome. Also, as noted earlier, we were able to evaluate the effect of usual drinking before diagnosis by type of beverage consumed on overall mortality but had insufficient power to examine the effects of continued drinking by type of beverage on overall mortality. Consumption of wine before diagnosis did not increase the risk of dying postdiagnosis, whereas consumption of beer and liquor did. Wine is known to contain polyphenolic compounds, which have been suggested to have anticarcinogenic properties (19). Wine drinkers were also found to be at significantly lower risk for developing squamous cell carcinoma of the esophagus and adenocarcinoma of the esophagus (also upper aerodigestive tract sites) compared with non-wine drinkers (20). However, wine drinkers may differ from those who drink beer or liquor with regard to other health behaviors that might affect overall mortality. Also, wine drinking was associated with a nonsignificant 30% increase in the risk of second primary tumors in another large cohort study (2), suggesting a cautious interpretation to a null or protective effect of wine.

Another limitation of our study is that we did not know the human papilloma virus status of these patients;

human papilloma virus is known to be a causative factor in a subgroup of head and neck cancers (some oropharyngeal cancers), and has been shown to affect prognosis (21). However, even in patients with human papilloma virus-associated tonsillar carcinomas, tobacco use was the strongest prognostic indicator (22).

Patients with early stage head and neck cancer are routinely advised to stop smoking; our results from this prospective study indicate that survivorship care for early stage head and neck cancer patients should also include aggressive alcohol cessation efforts. Effective smoking and alcohol interventions will not only prevent second primary tumors but are also expected to improve overall survival in these patients.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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### References

1. American Cancer Society. Cancer Facts and Figures 2008. Atlanta: American Cancer Society; 2008.
2. Do KA, Johnson MM, Doherty DA, et al. Second primary tumors in patients with upper aerodigestive tract cancers: joint effects of smoking and alcohol (United States). *Cancer Causes Control* 2003;14:131–8.
3. Winn DM, Blot WJ. Second cancer following cancers of the buccal cavity and pharynx in Connecticut, 1935–1982. *J Natl Cancer Inst Monogr* 1985;68:25–48.
4. Sturgis EM, Miller RH. Second primary malignancies in the head and neck cancer patient. *Ann Otol Rhinol Laryngol* 1995;104:946–54.
5. Cooper JS, Pajak TF, Rubin P, 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.
6. Khuri FF, Lee JJ, Lippman S, et al. Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. *J Natl Cancer Inst* 2006;98:441–50.
7. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors [see comment]. *BMJ* 1994;309:901–11.
8. Doll R, Peto R, Hall E, Wheatley K, Gray R. Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors [see comment]. *BMJ* 1994;309:911–8.
9. Mayne ST, Cartmel B, Baum M, et al. Randomized trial of supplemental  $\beta$ -carotene to prevent second head and neck cancer. *Cancer Res* 2001;61:1457–63.
10. Hong WK, Lippman SM, Itri LM, 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.
11. Bolla M, Lefur R, Ton Van J, et al. Prevention of second primary tumors with etretinate in squamous cell carcinoma of the oral cavity and oropharynx. Results of a multicentric double-blind randomized study. *Eur J Cancer* 1994;30A:767–72.
12. van Zandwijk N, Dalesio O, Pastorino U, et al. For the European Organization for Research and Treatment of Cancer of the Head and Neck and Lung Cancer Cooperative Groups. EUROSCAN, a randomized trial of vitamin A and N-acetylcysteine in patients with head and neck cancer or lung cancer. *J Natl Cancer Inst* 2000;92:977–86.
13. Bairati J, Meyer F, Jobin E, et al. Antioxidant vitamins supplementation and mortality: a randomized trial in head and neck cancer patients. *Int J Cancer* 2006;119:2221–4.

14. Toma S, Bonelli L, Sartoris A, 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.
15. Deleyiannis FW-B, Thomas DB, Vaughan TL, Davis S. Alcoholism: independent predictor of survival in patients with head and neck cancer. *J Natl Cancer Inst* 1996;88:542-9.
16. 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.
17. Day GL, Blot WJ, Shore RE, et al. Second cancers following oral and pharyngeal cancers: role of tobacco and alcohol. *J Natl Cancer Inst* 1994;86:131-7.
18. Mayne ST, Morse DE, Winn DM. Cancers of the oral cavity and pharynx. In: Schottenfeld D, Fraumeni JF, Jr., editors. *Cancer Epidemiology and Prevention*. 3rd ed. New York: Oxford University Press; 2006, p. 674-96.
19. Soleas GJ, Grass L, Josephy PD, Goldberg DM, Diamandis EP. A comparison of the anticarcinogenic properties of four red wine polyphenols. *Clin Biochem* 2002;35:119-24.
20. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia: results from a multi-center, case-control study. *J Natl Cancer Inst* 1997;89:1277-84.
21. Curado MP, Hashibe M. Recent changes in the epidemiology of head and neck cancer. *Curr Opin Oncol* 2009;21:194-200.
22. Hafkamp HC, Manni JJ, Haesevoets A, et al. Marked differences in survival rate between smokers and nonsmokers with HPV 16-associated tonsillar carcinomas. *Int J Cancer* 2008;122:2656-64.

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