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Pretreatment Health Behaviors Predict Survival Among Patients With Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Purpose
Our prior work has shown that the health behaviors of head and neck cancer patients are interrelated and are associated with quality of life; however, other than smoking, the relationship between health behaviors and survival is unclear.

Patients and Methods
A prospective cohort study was conducted to determine the relationship between five pretreatment health behaviors (smoking, alcohol, diet, physical activity, and sleep) and all-cause survival among 504 head and neck cancer patients.

Results
Smoking status was the strongest predictor of survival, with both current smokers (hazard ratio [HR] = 2.4; 95% CI, 1.3 to 4.4) and former smokers (HR = 2.0; 95% CI, 1.2 to 3.5) showing significant associations with poor survival. Problem drinking was associated with survival in the univariate analysis (HR = 1.4; 95% CI, 1.0 to 2.0) but lost significance when controlling for other factors. Low fruit intake was negatively associated with survival in the univariate analysis only (HR = 1.6; 95% CI, 1.1 to 2.1), whereas vegetable intake was not significant in either univariate or multivariate analyses. Although physical activity was associated with survival in the univariate analysis (HR = 0.95; 95% CI, 0.93 to 0.97), it was not significant in the multivariate model. Sleep was not significantly associated with survival in either univariate or multivariate analysis. Control variables that were also independently associated with survival in the multivariate analysis were age, education, tumor site, cancer stage, and surgical treatment.

Conclusion
Variation in selected pretreatment health behaviors (eg, smoking, fruit intake, and physical activity) in this population is associated with variation in survival.

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INTRODUCTION

Five-year survival rates for head and neck cancer have not changed in several decades and remain at approximately 60% depending on tumor site.[1,2] Although new surgical, radiation, and chemotherapy regimens hold promise, healthy lifestyle behaviors may be instrumental in improving survival among head and neck cancer patients. A clearer understanding of the pretreatment health behaviors that are associated with improved survival may provide insight into the types of behavioral interventions needed among head and neck cancer patients.

Tobacco and alcohol use are well-known primary risk factors for developing head and neck cancer and have been shown to be associated with decreased quality-of-life scores[3,4] and decreased survival.[5] Diets high in fruits and vegetables are protective against most cancers of the head and neck,[6] can affect the occurrence of second primary cancers,[7] and are associated with reduced cancer mortality.[5] Malnutrition,[8] cachexia,[9] and weight loss[10] are poor prognostic indicators for head and neck cancer patients. There is also evidence that a sedentary lifestyle may promote certain types of cancer, such as colon or breast[11]; however, the association with physical activity and head and neck cancer is less clear. Sleep disturbances are common in head and neck cancer patients, and although there is no evidence of causality, associations have been drawn between amount of sleep and mortality.[12]

In prior research, our team profiled the health behaviors of newly identified head and neck cancer patients at baseline and during the first year after diagnosis, but inadequate follow-up was available at that time to assess the associations between health behaviors and survival. Now, with longer follow-up, the present study was undertaken to determine

whether five pretreatment health factors (including smoking, alcohol use, diet, exercise, and sleep) predict survival among head and neck cancer patients.

PATIENTS AND METHODS

This was a prospective cohort study of patients enrolled onto the University of Michigan Head and Neck Cancer Specialized Program of Research Excellence. The independent variables were five health factors (smoking, alcohol use, diet, exercise, and sleep). Control variables were age, sex, race, education, marital status, cancer site and stage, treatment, and comorbidities. The dependent (outcome) variable was all-cause survival.

Study Population

Research assistants approached 1,084 newly diagnosed patients with head and neck squamous cell carcinoma to participate. Exclusion criteria were as follows: age less than 18 years; pregnant; non-English speaking; psychologically or mentally unstable (eg, suicidal ideation, acute psychosis, or dementia); and non–upper aerodigestive tract cancer (eg, thyroid or skin cancer). Exclusions included 65 patients who were ineligible, 240 patients who refused, 45 patients with second primary tumors, and 110 patients who did not complete a baseline survey, which left a sample size of 625 patients. The data set was further limited for the Cox proportional hazard models analyses to 504 patients with no missing data. Similar to other studies, comparisons of those with missing data versus those without missing data are consistent with serious health problems (higher comorbidities)[13] and race[14] as being responsible for nonparticipation.

Human patient approval was received from the following three study sites: University of Michigan Medical Center, Ann Arbor Veterans Affairs (VA) Healthcare System, and Henry Ford Health System. Recruitment began in January 2003. Patients were censored as being dead or alive as of August 1, 2008.

Procedure

Research assistants recruited patients to the study in the waiting rooms of otolaryngology clinics by obtaining signed informed consent and providing a written survey that had questions on demographics and health behaviors. A medical record audit was also conducted. Patients were resurveyed every 3 months for 2 years and then every year thereafter.

Measures

Health behavior variables. Patients were asked to self-characterize themselves as a current smoker, former smoker (quit 1 month to > 1 year ago), or never smoker (including cigarettes, cigars, and pipe tobacco). The previously validated 10-item instrument, Alcohol Use Disorders Identification Test,[15] was used to measure alcohol use; the score ranges from 0 to 40, with a score of 8 or more indicating problem drinking.[16] The validated Willett food frequency questionnaire[17] was used to measure average servings of fruits and vegetables in the past year and average calories per day.[18] Body mass index (BMI; weight in kilograms divided by the square of height in meters) was also used to measure nutritional/physical activity status; the 1999 to 2002 population mean was 28.4 kg/m^2 for adults older than 40 years in the United States.[19] The validated Physical Activity Scale for the Elderly[20] was used to measure activity; the population mean score for people age 65 to 100 years was 103. Given that many of our head and neck cancer patients are elderly and all of them are chronically ill, we felt that the Physical Activity Scale for the Elderly was appropriate to use because it focuses on activities of daily living versus rigorous exercise regimens, and the mean score for a population with end-stage renal disease was 90.3.[21] Sleep was assessed using validated questions from the Medical Outcomes Study; scores range from 0 to 100, with a mean of 72 for adults visiting a medical clinic.[22]

Control variables. Standard questions included age, sex, race (white *v* nonwhite), educational level (high school or less *v* some college or more), and marital status (married *v* not married). Because there were few sinus (n = 12) and nasopharynx (n = 5) cancers, tumor sites were classified into the following three groups based on proximity: larynx; oropharynx, hypopharynx, nasopharynx, or unknown primary; and oral cavity or sinus. Tumor stage (0 to IV) was classified using the American Joint Committee on Cancer staging classification system.[23] Comorbidities were measured using the Adult Comorbidity Evaluation-27[24] as no, mild, moderate, or severe comorbidities. Type of curative treatment received (surgery, radiation, and/or chemotherapy) was recorded by yearly chart audit or patient self-report when treated at an outside facility. By including three separate yes or no treatment variables, all possible treatment combinations are controlled for in the multivariate analysis.

Outcome variable: Survival. By contacting patients every 3 months, patient vital status (dead or alive) was determined. For those patients who were lost to follow-up, the Social Security Administration Death Master File was used to determine whether and when the patients had died. Patients lost to follow-up and not found on the Death Master File were assumed to be alive as of August 1, 2008.

Statistical Analysis

Means and frequency distributions were examined for all variables. To assess collinearity between health behaviors and control variables, Pearson's correlation coefficients were calculated, and variance inflation factors were evaluated. To avoid confounding, hospital site was not included as a control variable because it was highly correlated with race and sex, with more males coming from the VA and more blacks coming from the VA and Henry Ford Hospital. Kaplan-Meier plots and the log-rank test were used to compare the health behavior variables with survival. Univariate and multivariate Cox proportional hazards models were used to study the relationship between health behaviors, control variables, and survival.

RESULTS

Descriptive Statistics

Descriptive characteristics of the sample are listed in Table 1. At the time of diagnosis, more than one quarter of patients were current smokers, whereas more than half were former smokers. More than one quarter of the patients screened positive for problem drinking. Approximately one third of patients ate fewer than four servings of fruit per month, and more than two-thirds ate less than one vegetable per day. The mean calorie intake was 2,351 calories per day, and the mean BMI was 26.7 kg/m^2. The mean physical activity score was 115, and the mean sleep score was 67. The 2-year death rate was 24.2% (SE = 1.99%). The median follow-up time was 999 days (range, 19 to 2,010 days).

Univariate and Multivariate Analyses

Univariate analyses showed that four of the five health behaviors (smoking status, alcohol problem, fruit intake, and physical activity, but not vegetable intake) were significantly associated with survival (Fig 1). Because there was no association between calories and BMI with survival in the univariate analyses, fruits and vegetables were chosen as the nutrition markers for the final multivariate analysis. In addition, several control variables (age, marital status, education, cancer stage, and comorbidities) were also associated with survival in the univariate analyses. The results of the univariate and multivariate Cox proportional hazards regression models are listed in Table 2.

All control variables were included in the multivariate analyses, regardless of the univariate results. Several of the control variables were associated with each other; however, the variance inflation factor was less than 2.5 for all variables in the multivariate regression, indicating that the multicollinearity was not severe. Hence, no variables were omitted from the multivariate model as a result of concerns about collinearity.

Table 1. Pretreatment Patient Characteristics of Newly Diagnosed Head and Neck Cancer Patients

Characteristic	No. of Patients (N = 504)	%
Follow-up time, days		
Median	999	
Range	19-2,010	
Age, years		
Mean	58.8	
SD	10.8	
Range	25-92	
Body mass index, kg/m^2 (population mean ≈ 28-29 kg/m^2)		
Mean	26.7	
SD	5.8	
Range	15.2-64.6	
Daily calorie intake, kcal (RDA = 2,000 kcal)		
Mean	2,351	
SD	954	
Range	519-5,752	
PASE physical activity score (population mean = 102)		
Mean	115.0	
SD	81.5	
Range	0-472.8	
MOS sleep score (population mean = 72)		
Mean	67.1	
SD	21.1	
Range	0-100	
Smoking status*		
Current	133	26.4
Former	278	55.2
Never	93	18.4
Alcohol problem (AUDIT ≥ 8)		
Yes	132	26.2
No	372	73.8
Average fruit intake servings (prior year)		
None to 1-3 per month	161	31.9
1 per week to 2-4 per week	189	37.5
5-6 per week or more	154	30.6
Average vegetable intake servings (prior year)		
None to 1 per week	99	19.6
2-4 per week	151	30.0
5-6 per week	102	20.2
1 per day or more	152	30.2
Sex		
Male	394	78.2
Female	110	21.8
Race		
Non-Hispanic white	448	88.9
Nonwhite/Hispanic	56	11.1
Marital status		
Married	301	59.7
Not married	203	40.3
Educational level		
High school or less	242	48.0
Some college or more	262	52.0
Hospital site		
University of Michigan	377	74.8
Ann Arbor Veterans Affairs Medical Center	58	11.5
Henry Ford Hospital	69	13.7
Tumor site		
Larynx	120	23.8
Pharynx (oro-, hypo-, or nasopharynx, or unknown primary)	274	54.4
Oral cavity/sinus	110	21.8
Tumor stage		
0	9	1.8
I	50	9.9
II	45	8.9
III	75	14.9
IV	325	64.5
ACE-27 comorbidity score		
None	146	29.0
Mild	194	38.5
Moderate	109	21.6
Severe	55	10.9
Treatment		
Radiation	425	84.3
Chemotherapy	324	64.3
Surgery	253	50.2

Abbreviations: SD, standard deviation; RDA, Recommended Dietary Allowance; PASE, Physical Activity Scale for the Elderly; MOS, Medical Outcomes Study; AUDIT, Alcohol Use Disorders Identification Test; ACE-27, Adult Comorbidity Evaluation-27.
*Includes cigarettes, cigars, and pipe tobacco.

Of the health behaviors, pretreatment smoking status was the strongest predictor of survival, with both current smokers (hazard ratio [HR] = 2.4; 95% CI, 1.3 to 4.4) and former smokers (HR = 2.0; 95% CI, 1.2 to 3.5) showing significant associations with poor survival. Pretreatment problem drinking was associated with survival in the univariate analysis but not in the multivariate model. Low fruit intake was negatively associated with survival in only the univariate analysis, whereas vegetable intake was not significant in either the univariate or multivariate analysis. Physical activity was associated with survival in univariate analysis and was approaching significance in the multivariate model (HR = 0.98; 95% CI, 0.95 to 1.00). However, sleep was not associated with survival in either the univariate or multivariate analyses. Control variables that were also independently associated with poor survival in the multivariate analysis were higher age, lower education, cancer site (oral cavity), and cancer stage. Those treated with surgery had improved survival. Sex, race, marital status, comorbidity score, and treatment with radiation or chemotherapy were not independently associated with survival in the multivariate analysis.

DISCUSSION

Because smoking is a major causative factor for head and neck cancer, it was not surprising that more than one quarter of patients smoked at diagnosis or that current smoking at diagnosis was the strongest predictor of survival among head and neck cancer patients in this population, as well as in previously reported studies.[25,26] Approximately one in four head and neck cancer patients were smoking at the time of their diagnosis, and our prior work has shown that approximately half quit after diagnosis.[27] Continued smoking may increase the risk of

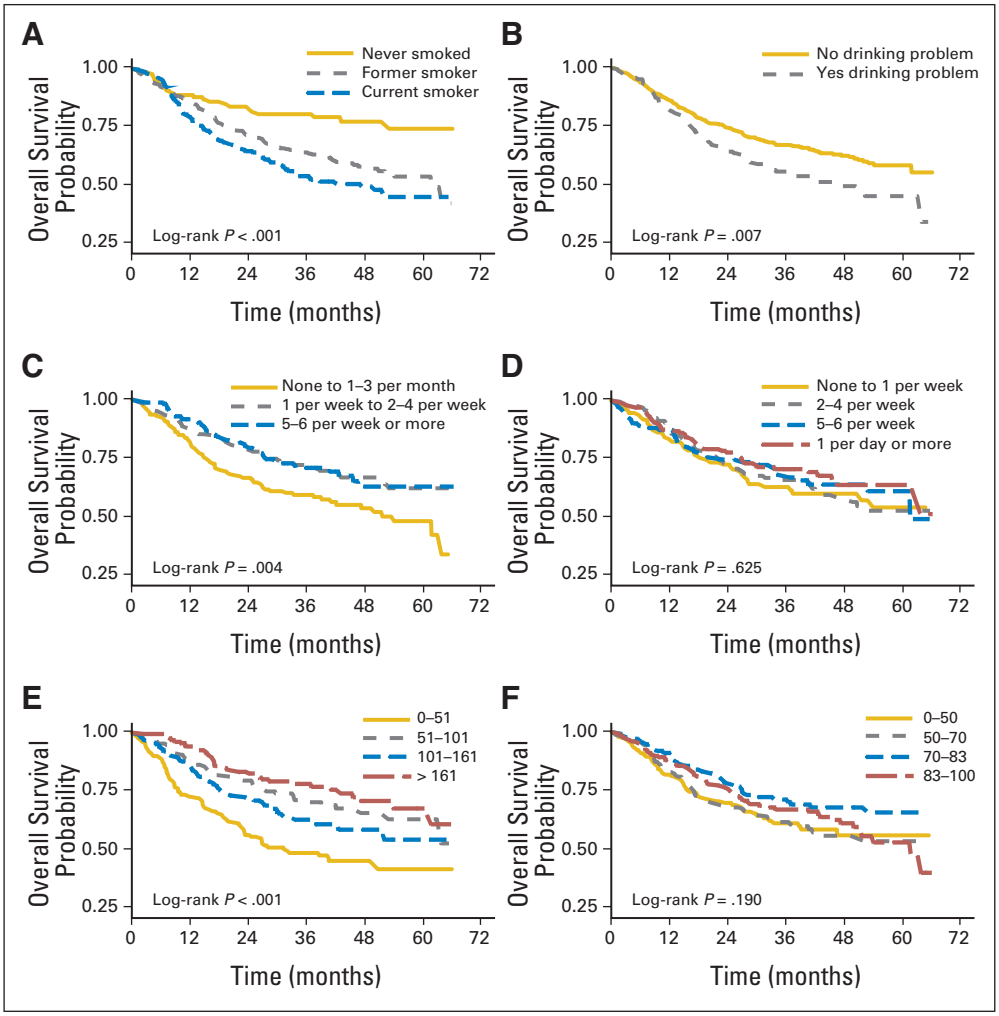

Fig 1. Kaplan-Meier plots of survival for health behaviors of head and neck cancer patients. (A) Smoking status (n = 712; 260 events and 452 patients censored). (B) Alcohol problem (Alcohol Use Disorders Identification Test ≥ 8; n = 689; 248 events and 441 patients censored). (C) Average prediagnosis fruit intake (n = 520; 175 events and 345 patients censored). (D) Average prediagnosis vegetable intake (n = 544; 184 events and 360 patients censored). (E) Physical Activity Scale for the Elderly score by quartile (n = 625; 223 events and 402 patients censored). (F) Medical Outcomes Study sleep scale by quartile (n = 621; 220 events and 401 patients censored).

second primary cancers among head and neck cancer patients and decrease survival.[28] Although it may be difficult to comprehend why a head and neck cancer patient would continue to smoke, nicotine dependence is an addiction, which is defined as "persistent compulsive use of a substance known by the user to be harmful."[29] Fortunately, efficacious cessation interventions, including medications (nicotine replacement therapy, bupropion, and varenicline), are available for head and neck cancer patients.[30,31] Behavioral interventions, such as brief physician advice, nurse counseling, and 1-800-QUIT NOW telephone counseling, have been shown to increase quit rates.[32]

Alcohol use, in conjunction with smoking, has been found to be a causative factor for head and neck cancer,[33] and continued drinking is associated with second primary tumors.[28] Although approximately one quarter of patients were problem drinkers at diagnosis, unlike other studies,[34,35] pretreatment alcohol problem was not a predictor of survival in the multivariate analyses in this study. Similarly, our prior work has shown that continued drinking among this population is not associated with quality of life.[36] It is important to note that smoking and alcohol use are highly interrelated,[27] and problem drinkers may have a harder time quitting smoking.[37] Moreover, alcohol use may complicate or interfere with adherence to treatment regimens.[38] For some, treatment for alcohol use must first take place before smoking cessation or other interventions can be accomplished. Unfortunately, for those who are highly alcohol dependent, inpatient detoxification programs may be needed. For others, referrals to outpatient and community-based programs such as Alcoholics Anonymous are effective strategies.

Surprisingly, before treatment, less than one third of patients reported eating more than five servings of fruit per week, whereas approximately one third reported eating less than four servings of fruit per month compared with an average of 1.5 servings per day for healthy adults.[39] Similarly, less than one third of patients ate at least one vegetable per day, whereas one in five patients ate less than two servings of vegetables per week compared with an average of 3.7 servings per day for healthy adults.[39] This is substantially less than the recommended nine servings of fruits and vegetables per day.[18] Fruit intake predicted survival in the univariate analysis but did not predict survival in the multivariate analysis, whereas vegetable intake did not predict survival in either analysis. Longer follow-up may show a survival advantage for fruit and vegetable intake as shown in other studies.[7,40,41]

Although fruit and vegetable intake after diagnosis was not assessed in this analysis, it is possible that patients may potentially have even worse dietary intake after treatment. For example, radiation can lead to xerostomia (dry mouth), which can make it more difficult to

Table 2. Univariate and Multivariate Cox Proportional Hazards Models for Survival

Variable	Univariate Model			Multivariate Model		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Smoking status (*v* never smoker)						
Current smoker	2.43	1.41 to 4.20	.001*	2.36	1.28 to 4.37	.006*
Former smoker	1.95	1.16 to 3.27	.011*	2.02	1.16 to 3.51	.013*
Alcohol problem	1.41	1.02 to 1.96	.038*	1.32	0.91 to 1.93	.146
PASE physical activity score (per 10 points)	0.95	0.93 to 0.97	< .001*	0.98	0.95 to 1.00	.085
MOS sleep scale (per 10 points)	0.94	0.88 to 1.02	.118	0.96	0.89 to 1.04	.350
Low fruit intake (none to 1-3 per month)	1.55	1.14 to 2.12	.006*	1.26	0.88 to 1.81	.208
Low vegetable intake (none to 2-4 per week)	1.09	0.81 to 1.48	.565	0.82	0.59 to 1.15	.242
Age (in decades)	1.40	1.22 to 1.62	< .001*	1.50	1.25 to 1.79	< .001*
Female	0.72	0.48 to 1.07	.101	0.74	0.47 to 1.16	.183
Nonwhite	1.25	0.80 to 1.96	.326	1.09	0.68 to 1.77	.715
Married	0.70	0.51 to 0.95	.020*	0.87	0.63 to 1.21	.413
High school education or less	1.70	1.25 to 2.32	< .001*	1.43	1.03 to 1.99	.032*
Cancer site (*v* oral cavity/sinus)						
Larynx cancer site	0.65	0.42 to 1.02	.062	0.41	0.24 to 0.69	< .001*
Pharynx cancer site	0.81	0.56 to 1.17	.264	0.61	0.39 to 0.94	.026*
Stage	1.38	1.16 to 1.64	< .001*	1.52	1.25 to 1.85	< .001*
ACE-27 comorbidity score	1.39	1.18 to 1.63	< .001*	1.15	0.96 to 1.37	.125
Radiation	1.11	0.71 to 1.72	.656	0.75	0.42 to 1.32	.318
Chemotherapy	1.04	0.76 to 1.43	.801	0.96	0.62 to 1.47	.835
Surgery	0.81	0.60 to 1.10	.186	0.69	0.49 to 0.99	.043*

NOTE. Of 504 patients, there were 166 events and 338 patients were censored.
Abbreviations: PASE, Physical Activity Scale for the Elderly; MOS, Medical Outcomes Study; ACE-27, Adult Comorbidity Evaluation-27.
*Significant at $P < .05$.

eat particulate (rather than liquid) food items. Given poor pretreatment dietary intake, post-treatment difficulties with eating, and the potential prognostic value of fruits and vegetables, there may be a considerable and underemphasized need for nutrition counseling among head and neck cancer patients. Tailored, low-intensity nutrition interventions have been shown to increase fruit and vegetable consumption among head and neck cancer patients.[42]

Although pretreatment mean calorie intake was similar to the recommended levels, BMI was lower than population means, perhaps because many patients smoke and drink at problematic levels, which are both associated with lower BMI.[43,44] Similar to other studies,[45] neither pretreatment calorie intake nor BMI was associated with survival. Although numerous studies have shown that malnutrition, cachexia, and weight loss are poor prognostic indicators for head and neck cancer patients and are associated with higher complication rates, these conditions are likely to occur after treatment in response to radiation, chemotherapy, and surgical procedures or disease progression, all of which alter nutritional intake.

In this study, pretreatment physical activity was higher than population norms. Similar to other studies of breast,[46] colorectal,[47] and prostate cancer,[48] physical activity predicted survival in the univariate analysis and was marginally associated with survival in the multivariate analysis. However, from these analyses, it is difficult to determine whether higher levels of pretreatment physical activity actually improved survival or whether those patients who did not survive simply displayed lower levels of physical activity as the beginning of the normal dying trajectory. While some head and neck cancer patients may be encouraged to conserve their energy, which may result in decreased muscle mass and strength, physical activity in head and neck cancer patients has been shown to be correlated with quality of life,[49] fewer side effects,[50] and survival.[51] Yet, our prior work[27] has shown that, while physical activity declines during the first 6 months after diagnosis, probably in relation to the rigors of treatment, for those who survive, physical activity levels return to pretreatment levels one year after diagnosis, even without intervention. Hence, randomized control trials are needed to determine if head and neck cancer patients should conserve energy or push themselves to engage in physical activity during the often grueling treatment period.

Similar to other studies of cancer patients,[52] the sleep scores of this sample of head and neck cancer patients were lower than population means at clinically relevant levels but were not associated with poor survival. The etiology of sleep problems among cancer patients is not easy to determine and are likely to be multifactorial and, at the very least, related to pain, fatigue, and psychological distress.[53] Head and neck cancer patients may also have sleep problems related to difficulty with oral secretions, dysphagia, cough, aspiration, xerostomia, pain, and sleep apnea.[54] Our prior work has shown that poor sleep is correlated with nicotine use and low physical activity, which may confound the analyses. Behavioral and pharmaceutical interventions may help head and neck cancer patients improve their sleep; however, the underlying causes of insomnia should first be assessed and treated.[55]

Although the focus of this study was the relationship between health behaviors and survival among head and neck cancer patients, several control variables were also associated with survival. In prior studies, the impact of age has been variable[56,57]; however, in this study, older patients were less likely to survive than younger patients. As

shown in other studies,[58,59] educational level (a marker for socioeconomic status) also predicted survival. Similar to other studies,[60] oral cancer patients had poorer survival than did patients with pharyngeal or laryngeal cancers. Although human papillomavirus–positive tumors have been shown to be associated with improved survival,[61] unfortunately, human papillomavirus status was not available for these analyses. As shown in multiple studies,[60,62,63] those with higher cancer stage had poorer survival than those with lower cancer stage. Our work[64] and that of others[62,63] has shown that those with increased comorbidities had poorer survival; however, in this study, comorbidity scores were significantly associated with survival only in the univariate analysis. Similar to other studies that found an association between marital status (a marker for social support) and survival,[65,66] being married in the present study was significantly associated with improved survival in the univariate analysis but was not an independent predictor in the multivariate model. Surgery was the only treatment variable associated with survival in the multivariate analysis, perhaps because, in many cases, those patients who receive surgery are the ones with the best prognosis (lower cancer stage and more localized disease). The lack of effects from radiation and chemotherapy is likely a result of the fact that there was little variability in treatment in that all patients were from tertiary care centers that provided standard of care treatment for their particular cancer site and stage. Interestingly, sex and race, which have been shown to predict survival in selected other studies of cancer patients,[58,67] did not predict survival in this study.

To our knowledge, this study is the first to comprehensively assess the association of five pretreatment health behaviors and conventional prognostic factors with survival among head and neck cancer patients. Pretreatment health behaviors can identify those at risk for poor survival. Multicomponent behavioral interventions can be efficacious among head and neck cancer patients,[30] and future research is needed to determine whether changes in the health behaviors after diagnosis can improve survival rates.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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