Cigarette use, comorbidities, and prognosis in a prospective head and neck squamous cell carcinoma population

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ABSTRACT: *Background.* To better understand the associations between a history of tobacco use and survival outcomes, cigarette use was prospectively surveyed in 687 previously untreated patients with cancer of the oral cavity ($n = 271$), oropharynx ($n = 257$), larynx ($n = 135$), or hypopharynx ($n = 24$).

Methods. Kaplan–Meier and Cox models explored the associations of tobacco use intensity (packs/day), duration (years of use), and timing before diagnosis with overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS).

Results. Cigarette use duration, timing, and intensity were significant predictors for all outcomes in univariate analysis. Never smoking and pack-years were not significantly associated with outcomes after adjustment for prognostic factors, such as stage, comorbidities, and human papillomavirus (HPV) status, which were strongly associated with clinical outcomes.

Conclusion. The findings confirm the association between smoking history and survival and the importance of clinical variables in evaluating smoking as a prognostic factor. Timing, intensity, and duration of cigarette use should be considered with other prognostic factors when considering risk stratification for treatment planning. © 2016 Wiley Periodicals, Inc. *Head Neck* **38:** 1810–1820, 2016

KEY WORDS: tobacco, epidemiology, head and neck cancer, survival, recurrence, comorbidities, intensity, duration

INTRODUCTION

Approximately 35% to 55% of patients with head and neck squamous cell carcinoma (HNSCC) experience locoregional recurrence or distant metastasis within 2 years of initial diagnosis[1,2] and are at high risk for developing a second primary.[3] There are many established factors associated with higher rates of recurrence, including tumor site, stage, human papillomavirus (HPV) status, and diet.[4] On average, patients with HPV-positive oropharyngeal cancer have better prognoses, which led to recommendations to deescalate aggressive treatment and limit toxicity for this group, particularly if they have a favorable smoking history.[5] Tobacco is a strong risk factor for the development of HNSCC via documented cellular, molecular, and epigenetic effects.[6–8] Previous studies have shown that all-cause mortality is worse among survivors who continue to smoke compared with never-smokers, but this same benefit is not seen when comparing patients who recently quit smoking with patients who continue to smoke after diagnosis.[9] However, analyzing smoking history is complex,[10–12] and studies in lung squamous cell carcinoma have indicated that duration of smoking as well as time since quitting is associated with incidence[13] and survival.[14–16]

It is essential to better define the association between tobacco use and HNSCC survival and oncologic outcomes. This is best derived from prospective, structured smoking assessments to properly understand the potential role of smoking in risk stratification treatment models that include other prognostic factors. Smoking is associated with lifestyle and health variables, such as alcohol use, body mass index (BMI), and comorbidities. All of these may also be associated with clinical outcomes of interest in patients with HNSCC. Thus, there is strong interest in examining the risk of tobacco use on long-term survival and recurrence rates in patients with HNSCC, particularly in combination with other established prognostic factors. These data will be instrumental in selecting the appropriate cohorts for potential treatment intensification or deescalation.

From an epidemiologic perspective, smoking status is frequently stratified into 3 groups of never, current, and former smokers. However, such a classification does not fully account for the intensity and duration of tobacco

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exposure. Intensity is usually defined in terms of cigarettes per day and duration in years of use. Because a long history of high-intensity tobacco use is associated with many adverse outcomes, and may contribute to carcinogenesis and treatment sensitivity, we hypothesize that separate consideration of recent and DSS time tobacco exposure groups may aid in better understanding the impact of tobacco use on oncologic and survival outcomes.

In this study, we assessed the effects of lifetime cigarette exposure in a prospectively collected, unselected population of previously untreated, incident patients with HNSCC. This cohort of 687 patients is actively followed as part of an epidemiologic study. The study protocol includes annual questionnaires and extensive quality control and completeness checks, and, thus, constitutes very high quality data on which to study questions regarding the potential importance of tobacco and other risk factors on survival and recurrence outcomes.

PATIENTS AND METHODS

Full details are provided in the Supplementary Materials, online only. Below is a brief description of the study design, the patients, and the methods.

Recruitment

From November 2008 through July 2013, every previously untreated, incident adult patient with HNSCC with primary disease evaluated in the Head and Neck Oncology Program of the University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, was prospectively screened for eligibility, and 92% signed a written informed consent and were enrolled in the study. This unselected study population represented 28% of incident HNSCC cases in the state of Michigan. The study was approved by a University of Michigan Institutional Review Board.

Variable definitions

The date of diagnosis was the date the patient was diagnosed with a biopsy confirmed squamous cell carcinoma at the University of Michigan. Comorbidity was assessed at diagnosis through medical chart review using the Adult Comorbidity Evaluation-27 (ACE-27),[17] a validated instrument to grade the severity of comorbidities in patients with cancer before HNSCC was defined as a previous primary tumor in the head and neck >5 years earlier. Self-reported smoking history was collected at the time of enrollment and included age of initiation, cessation, and smoking status, categorized into never, current (including patients who quit within 12 months of diagnosis), or former (quit over 12 months before diagnosis). Cigar, pipe, and smokeless tobaccos were frequently missing age of initiation and cessation. There were very few non-cigarette smokers in our cohort who only used pipe or cigar tobacco. Because it is known that the risk of HNSCC is not elevated among ever cigarette smoker who also uses cigar and pipe tobacco,[18] only cigarette data were further analyzed. The cumulative quantity of cigarettes smoked in the recent past (<10 years before diagnosis) and at DSS time times (earlier than 10 years before diagnosis) were considered. These cumulative amounts were calculated by multiplying the intensity of use (pack-years) by the duration of use during each period, as shown in Supplementary Figure S1, online only. Duration of use was determined by the cigarette initiation and cessation dates.

Follow-up

Patients were followed at National Comprehensive Cancer Network guideline intervals for routine cancer care and surveillance. Tumor status (recurrence, persistent disease, or second primary) was updated annually during a medical record review and annual surveys. Deaths were confirmed through the Social Security Death Master File, yearly surveys, family notification, and medical record reviews. Survival time was censored to February 1, 2014, or the last known contact date for subjects lost to follow-up. Tumor status was censored to the last date of each subject's annual medical record review[19]; the last data observation occurred in September 2014. Deaths because of other causes were censored at the date of death for disease-specific survival (DSS) time.

Study population

The study population of 687 subjects was comprised of patients mainly with oral cavity and oropharyngeal primary sites (39% and 37%, respectively) and stage IV (59%) disease (Table 1). The mean age at diagnosis was 61 years (SD = 12 years). Among all smokers, the mean age of initiation was 24 years (SD = 10 years); among former smokers, the mean age of cessation was 46 years (SD = 15 years). Treatment modalities included surgery alone (25%) or surgery with adjuvant radiotherapy or chemoradiotherapy (20%), chemoradiotherapy alone (40%), radiotherapy alone (7%), or palliative/unknown (8%) treatment. Ten percent of patients were never rendered disease-free after treatment. Recurrence patterns were local only (25%), regional ± locoregional (36%), and distant ± locoregional (39%). Median follow-up for overall survival (OS) was 30 months and the estimated 2-year OS rate was 78%. Median follow-up for recurrence-free survival (RFS) time was 24 months and the estimated 2-year RFS rate was 75%.

Human papillomavirus status

HPV status was determined from biopsy or surgical resection formalin-fixed, paraffin-embedded blocks for 362 subjects using previously reported and validated polymerase chain reaction methods.[20] HPV status was unable to be determined for 325 subjects. Subjects with equivocal or missing HPV status were included in the study and given an HPV status of "unknown." Among subjects with adequate DNA or tissue specimens, 84% of oropharyngeal cancers were HPV-positive, 12% of oral cavity, 13% of laryngeal, and 25% of hypopharyngeal.

Statistical analysis

Chi-square testing and analysis of variance assessed differences in clinical and epidemiological characteristics with tobacco use. The Kaplan–Meier method was used to estimate rates and graphically visualize OS, RFS, and

TABLE 1. Univariate Cox proportional hazards model for survival outcome.

		OS		RFS		DSS	
	No. of patients	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at diagnosis							
10 y	687	1.44 (1.26–1.64)	**< .0001**	1.26 (1.10–1.43)	**.0007**	1.21 (1.02–1.43)	.03
Sex*							
Male (ref)	504	(ref)		(ref)		(ref)	
Female	183	1.31 (0.94–1.83)	.11	1.13 (0.80–1.60)	.48	1.21 (0.78–1.86)	.39
Marital status							
Married	436	0.55 (0.40–0.74)	**.0001**	0.65 (0.48–0.89)	**.007**	0.66 (0.44–0.98)	.04
Not married‡	251	(ref)		(ref)		(ref)	
Prior cancer*	108	1.04 (0.69–1.57)	.86	0.86 (0.55–1.34)	.51	0.85 (0.48–1.50)	.58
Prior HNSCC†	31	2.83 (1.60–5.02)	**.0004**	3.10 (1.81–5.30)	**< .0001**	3.25 (1.63–6.49)	**.0008**
Cancer stage							
I/Cis (ref)	108	(ref)		(ref)		(ref)	
II	79	3.24 (1.32–7.95)	.01	1.47 (0.58–3.70)	.41	2.50 (0.60–10.47)	.21
III	97	4.14 (1.78–9.61)	**.0009**	3.04 (1.41–6.57)	**.005**	5.66 (1.63–19.69)	**.006**
IV	403	4.90 (2.28–10.50)	**< .0001**	3.98 (2.02–7.84)	**< .0001**	7.64 (2.41–24.21)	**.0005**
Disease site							
Oral cavity (ref)	271	(ref)		(ref)		(ref)	
Hypopharynx	24	1.60 (0.80–3.18)	.19	1.97 (1.01–3.82)	.05	1.91 (0.81–4.49)	.14
Larynx	135	0.69 (0.45–1.05)	.08	0.80 (0.52–1.22)	.30	0.90 (0.54–1.51)	.69
Oropharynx	257	0.58 (0.40–0.83)	**.003**	0.74 (0.51–1.06)	.10	0.64 (0.40–1.03)	.07
ACE comorbidity							
None (ref)	183	(ref)		(ref)		(ref)	
Mild	322	2.29 (1.44–3.63)	**.0005**	1.64 (1.07–2.52)	.02	1.71 (1.00–2.95)	.05
Moderate	125	2.66 (1.58–4.47)	**.0002**	1.96 (1.20–3.21)	**.007**	1.93 (1.03–3.63)	.04
Severe	57	3.99 (2.20–7.22)	**< .0001**	2.61 (1.46–4.65)	**.001**	3.13 (1.53–6.40)	**.002**
BMI							
1 unit increase	683	0.95 (0.92–0.98)	**.001**	0.97 (0.94–0.99)	.02	0.95 (0.92–0.99)	.01
HPV status							
HPV-negative (ref)	222	(ref)		(ref)		(ref)	
HPV-positive	140	0.39 (0.24–0.64)	**.0002**	0.48 (0.30–0.78)	**.003**	0.42 (0.23–0.77)	**.005**
Unknown	325	0.91 (0.65–1.26)	.56	0.89 (0.64–1.25)	.51	0.79 (0.52–1.22)	.29
Alcohol use							
Never (ref)	67	(ref)		(ref)		(ref)	
Current	450	0.75 (0.45–1.26)	.27	0.66 (0.40–1.07)	.09	0.72 (0.38–1.38)	.33
Former	170	1.11 (0.64–1.92)	.72	0.88 (0.52–1.51)	.65	1.01 (0.51–2.02)	.97
Cigarette use							
Never (ref)	184	(ref)		(ref)		(ref)	
Current	282	2.07 (1.32–3.25)	**.002**	1.31 (0.87–1.98)	.20	1.87 (1.05–3.31)	.03
Former	221	2.11 (1.33–3.36)	**.002**	1.51 (0.99–2.30)	.06	2.18 (1.22–3.90)	**.008**
Pack-years							
10 unit increase	687	1.10 (1.05–1.15)	**< .0001**	1.07 (1.02–1.12)	.007	1.09 (1.03–1.16)	**.005**
Years quit							
Never smoker	184	0.48 (0.31–0.76)	**.002**	0.77 (0.51–1.16)	.21	0.53 (0.30–0.94)	.03
Quit 10+ y	158	0.93 (0.64–1.37)	.73	1.09 (0.74–1.62)	.67	1.13 (0.70–1.82)	.61
Quit <10 y	59	1.26 (0.77–2.06)	.36	1.33 (0.79–2.23)	.29	1.20 (0.62–2.32)	.60
Current smoker	279	(ref)		(ref)		(ref)	
Remote pack-years							
10 unit increase	680	1.13 (1.07–1.19)	**< .0001**	1.09 (1.03–1.16)	**.004**	1.12 (1.04–1.20)	**.002**
Recent pack-years							
10 unit increase	680	1.20 (0.98–1.64)	.07	1.10 (0.89–1.36)	.40	1.12 (0.86–1.46)	.38

Abbreviations: OS, overall survival; RFS, recurrence-free survival; DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval; ref, reference; HNSCC, head and neck squamous cell cancer; Cis, in situ; ACE, Adult Comorbidity Evaluation-27 summary score; BMI, body mass index; HPV, human papillomavirus.

* Prior cancer is non-HNSCC and was diagnosed previous to the date of diagnosis of HNSCC malignancy.

† Prior HN cancer was diagnosed more than 5 years prior to current HN malignancy.

‡ Not married includes: Separated (12), Widowed (68), Divorced (110), Never married (38), Missing (1).

Figures in boldface indicate statistical significance.

DSS time. Time-to-event outcomes were defined from diagnosis to death of any cause (OS), time to disease recurrence (RFS), or time to death of HNSCC malignancy. For patients with persistent disease, time to recurrence was defined as 1 day.

Single variable and multivariable Cox proportional hazard models were used to test associations between clinical and epidemiological variables with OS, RFS, and DSS. Covariates included were age, sex, marital status, history of prior HNSCC or other cancer, stage, tumor site,

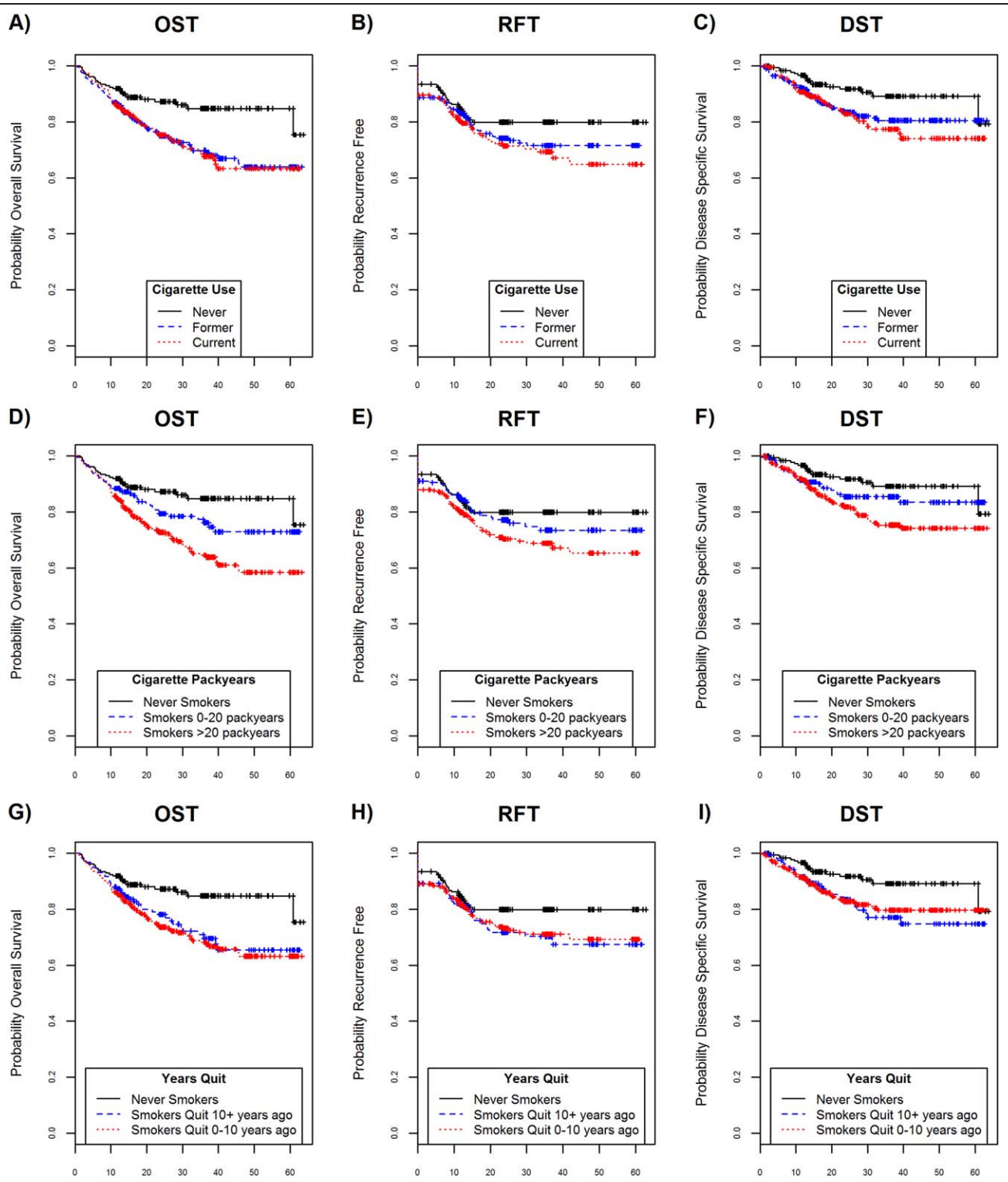

FIGURE 1. Survival benefits according to smoking status (A–C), pack-years (D–F), and years since quitting smoking (G–I). (A–C) Unadjusted overall survival (OS), recurrence-free survival (RFS), and disease-specific survival (DSS), respectively, by cigarette use (never, former, or current). Never smokers showed significantly better survival outcomes than smokers in univariable Cox models. Interestingly, there were no significant survival differences between former and current smokers. (D–F) Unadjusted OS, RFS, and DSS, respectively, by pack-years (never smoker, smokers 0 to 20 pack-years, and smokers >20 pack-years). Never smokers had significantly better survival outcomes than smokers (OS p value = .01 in univariable Cox model). There were apparent differences in each category of survival events with a 7% to 10% increase risk of outcome for every 10 pack-year increase in cigarette use (Cox proportional models for OS, RFS, and DSS; p = .01, .007, and .005, respectively). (G–I) Unadjusted OS, RFS, and DSS, respectively, by years since quitting (never smoker, smoker quit 10+ years ago, smoker quit 0–10 years ago). When grouped by year since quitting, there were no significant differences comparing DSS time smokers and quitters. [Color figure can be viewed at wileyonlinelibrary.com]

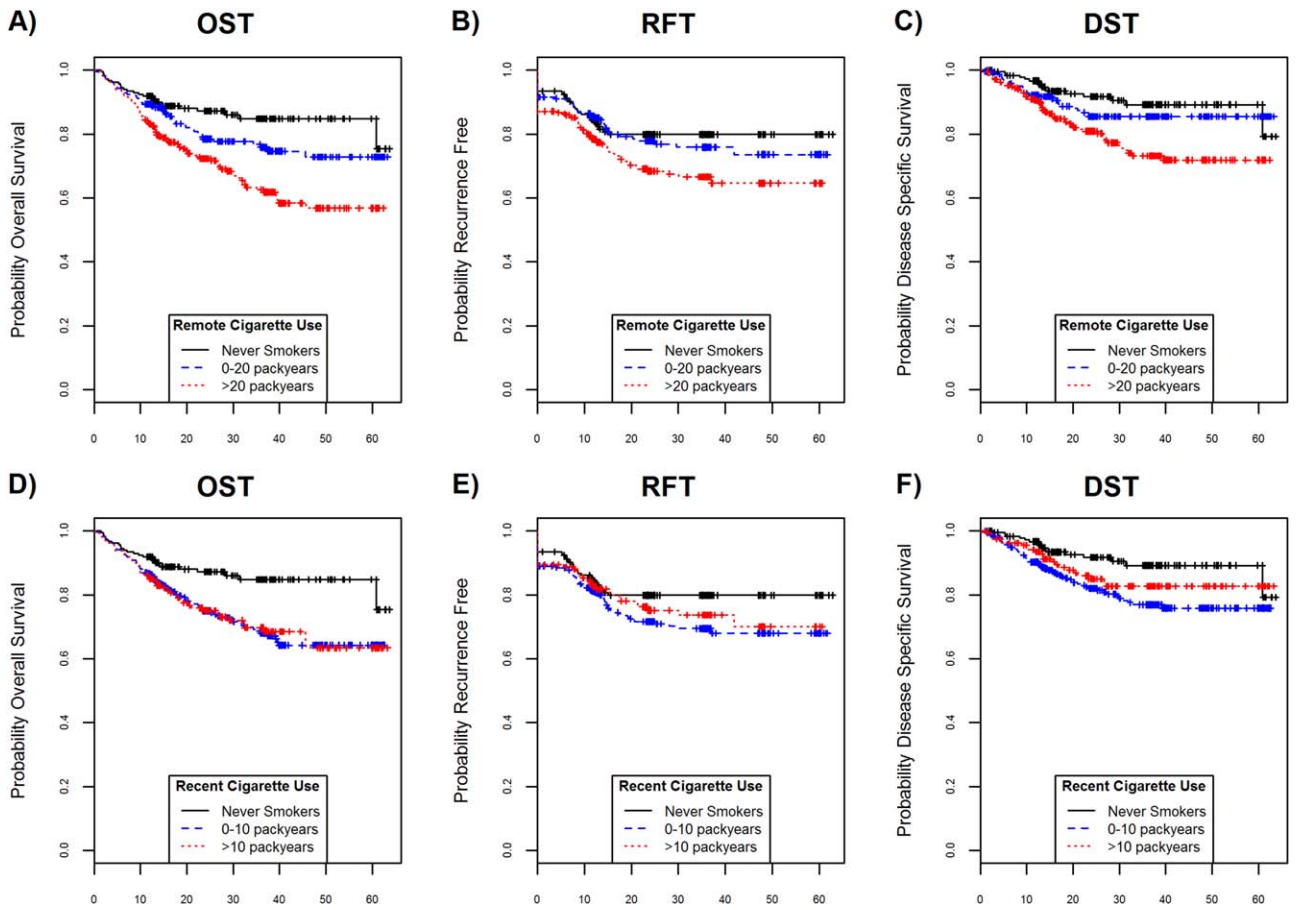

FIGURE 2. Association of DSS time smoking or recent pack-years with survival. (A–C) Unadjusted overall survival (OS), recurrence-free survival (RFS), and disease-specific survival (DSS), respectively, for pack-years comparing never smokers to 0 to 20 pack years and >20 pack years for DSS time use smokers. For DSS time use, significant differences in OS favored light pack-years compared to heavy pack-years, whereas RFS and DSS were more similar among light and never smokers. (D–F) Unadjusted OS, RFS, and DSS, respectively, for pack-years comparing never smokers to 0 to 20 pack-years and >20 pack-years for recent use smokers. For recent use, moderate differences in survival were only observed in RFS comparing light to heavy cigarette use. [Color figure can be viewed at wileyonlinelibrary.com]

comorbidity score, BMI, HPV status, alcohol, and tobacco use. Differences in outcome by planned treatment were explored, although ultimately eliminated from the final multivariable models because of the high collinearity observed between disease site and treatment plan. The multivariable analysis excluded 4 subjects missing BMI information, resulting in a total of 683 subjects for analysis. HPV status was defined in 3 groups; positive, negative, and unknown. To address potential bias introduced by creating a category for missing HPV status, sensitivity analyses were performed using multiple imputation and inverse probability weighting. The results from this are shown in the Supplementary Materials, online only section. A post-hoc subset analysis was also performed analyzing HPV-positive and HPV-negative cancers separately.

RESULTS

Univariate clinical and demographic effects on outcome

Clinical variables associated with worse OS, RFS, and DSS included increasing patient age, single marital status, history of prior HNSCC (>5 years previously), tumor stage, disease site, comorbidity score, lower BMI, and HPV-negative status (Table 1). We noted a 3% to 5% decrease in relative risk per year for every 1 unit increase in BMI. One of the strongest predictors of all measures of relapse and survival was comorbidity score, with a clear trend by extent of comorbidities. The effect of age and comorbidities were strongest for OS, whereas the effects of stage and prior HNSCC were strongest for DSS.

Univariate smoking effects on outcome

Cigarette use (never, current, and former) was significantly associated with an increased risk of death from all causes and disease-specific death. Never smoking was associated with improved OS (Figure 1A), RFS (Figure 1B), and DSS (Figure 1C). Significantly worse OS, RFS, DSS were associated with every 10-year increase in pack-years of use (hazard ratio [HR] = 1.10; 95% confidence interval = 1.05–1.15; HR = 1.07; 95% CI = 1.02–1.12; and HR = 1.09; 95% CI = 1.03–1.16; respectively; Table 1). As expected, smokers of over 20 pack-years had significantly worse outcomes compared with never smokers (Figures 1D–1F). When former smokers were categorized by year since quitting, there was little separation between

TABLE 2. Multivariable Cox proportional hazards model for survival outcomes.

		OS		RFS		DSS	
Variables	No. of patients	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, y			**.0005**		.05		.24
10 y unit	683	1.30 (1.12–1.51)		1.16 (1.00–1.35)		1.12 (0.93–1.36)	
Sex							
Male	500	(ref)		(ref)		(ref)	
Female	183	1.07 (0.74–1.54)	.73	0.95 (0.65–1.39)	.79	1.08 (0.68–1.73)	.74
Marital status							
Married	434	0.77 (0.55–1.09)	.14	0.78 (0.55–1.10)	.15	0.90 (0.58–1.39)	.63
Not married	249	(ref)		(ref)		(ref)	
Prior cancer	108	0.83 (0.53–1.30)	.41	0.73 (0.46–1.16)	.18	0.67 (0.37–1.23)	.20
Prior HNSCC	31	2.31 (1.25–4.26)	**.008**	2.73 (1.54–4.84)	**.0006**	2.77 (1.31–5.87)	**.008**
Cancer stage							
I/Cis	107	(ref)		(ref)		(ref)	
II	78	3.24 (1.31–8.02)	.01	1.40 (0.55–3.54)	.48	2.37 (0.56–9.97)	.24
III	97	5.02 (2.14–11.80)	**.0002**	3.34 (1.53–7.31)	**.003**	6.58 (1.87–23.19)	**.003**
IV	401	7.20 (3.29–15.73)	**< .0001**	5.03 (2.50–10.11)	**< .0001**	10.54 (3.26–34.05)	**< .0001**
Disease site							
Oral cavity	269	(ref)		(ref)		(ref)	
Hypopharynx	23	0.76 (0.35–1.66)	.50	1.11 (0.53–2.33)	.79	0.92 (0.37–2.31)	.86
Larynx	135	0.52 (0.33–0.82)	**.005**	0.66 (0.42–1.04)	.08	0.62 (0.35–1.08)	.09
Oropharynx	256	0.72 (0.47–1.11)	.14	0.81 (0.52–1.25)	.33	0.72 (0.41–1.26)	.25
ACE comorbidity							
None	182	(ref)		(ref)		(ref)	
Mild	320	1.63 (1.00–2.67)	.05	1.27 (0.81–2.01)	.30	1.35 (0.75–2.41)	.31
Moderate	125	2.66 (1.58–4.47)	**.003**	1.69 (1.00–2.87)	.05	1.81 (0.92–3.54)	.08
Severe	56	2.69 (1.38–5.25)	**.004**	1.95 (1.01–3.78)	.05	2.72 (1.21–6.12)	.02
BMI							
1 unit increase	683	0.96 (0.93–0.99)	.01	0.98 (0.95–1.00)	.09	0.97 (0.93–1.00)	.06
HPV status							
HPV-negative	221	(ref)		(ref)		(ref)	
HPV-positive	140	0.41 (0.22–0.73)	**.003**	0.48 (0.27–0.84)	.01	0.37 (0.17–0.77)	**.008**
Unknown	322	0.83 (0.58–1.20)	.32	0.79 (0.55–1.15)	.22	0.73 (0.46–1.17)	.20
Alcohol use							
Never	66	(ref)		(ref)		(ref)	
Current	448	1.21 (0.68–2.15)	.51	0.86 (0.50–1.49)	.60	0.96 (0.48–1.92)	.90
Former	169	1.16 (0.64–2.12)	.62	0.90 (0.51–1.61)	.72	0.99 (0.47–2.07)	.98
Cigarette use							
Never	183	0.76 (0.45–1.28)	.30	0.95 (0.59–1.53)	.83	0.81 (0.42–1.54)	.81
Pack-years							
10 unit increase	683	1.05 (0.99–1.11)	.13	1.05 (0.98–1.12)	.14	1.04 (0.96–1.13)	.33

Abbreviations: OS, overall survival; RFS, recurrence-free survival; DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval; ref, reference; HNSCC, head and neck squamous cell cancer; Cis, in situ; ACE, Adult Comorbidity Evaluation-27 summary score; BMI, body mass index; HPV, human papillomavirus.
Figures in boldface indicate statistical significance.

quitting within 10 years or quitting >10 years before diagnosis in OS, RFS, or DSS (Figures 1G–1I), although all outcomes were consistently worse in smokers compared with nonsmokers.

Recent tobacco use compared to DSS time use

To better understand the influence of cigarette smoking on outcome measures, smoking history was separated into recent and DSS time use derived from the patient's age at initiation, years of duration, and intensity. Graphically, we observed that the amount of DSS time cigarette use among smokers (accumulated up to 10 years before diagnosis) was associated with worse OS and RFS times (Figures 2A–2C). Although current cigarette use seemed associated with worse OS and RFS times when compared with never smokers, the amount of recent cigarette use (accumulated within 10 years of diagnosis) was not (Figures 2D–2F). Among smokers, differences in outcome (per 10 pack-years) by intensity of DSS time use were significant for worse OS, RFS, and for DSS (HR = 1.11; 95% CI = 1.04–1.18; HR = 1.09; 95% CI = 1.02–1.17; and HR = 1.11; 95% CI = 1.02–1.20; respectively). Among recent users, no evidence of meaningful differences in outcome by intensity of recent use were found, as evidenced in graphical representation and the fact that the HRs for each outcome were wide and contained 1.00 per 10 pack-years for OS, RFS, and DSS (HR = 0.94; 95% CI = 0.68–1.30; HR = 1.05; 95% CI = 0.75–1.46; and HR = 0.98; 95% CI = 0.64–1.49; respectively).

Multivariable clinical, demographic, and smoking effects on outcome

In multivariable analysis, history of prior HNSCC, tumor stage, comorbidity score, and HPV status remained significant prognostic factors for all outcome measures,

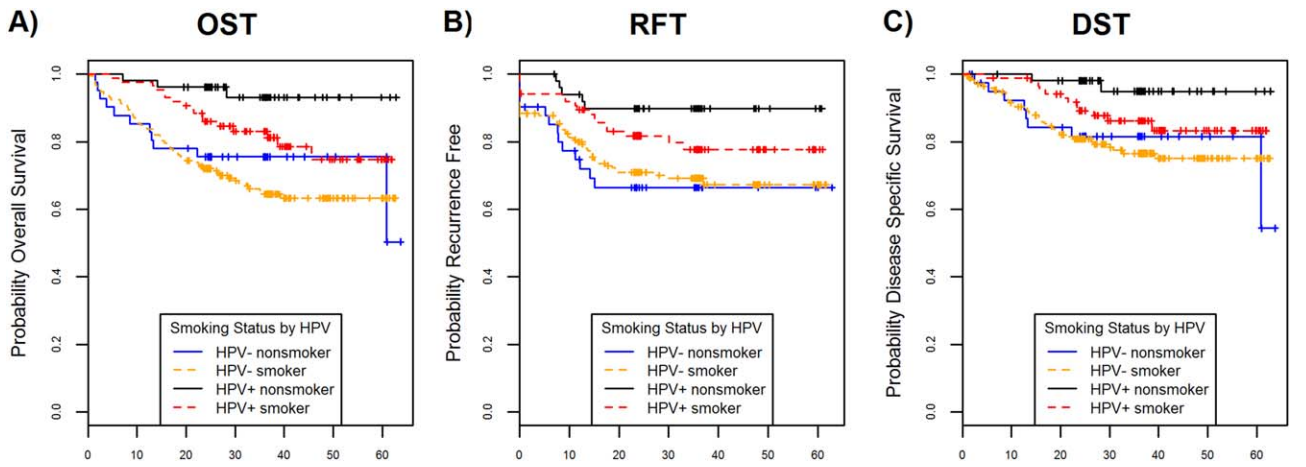

FIGURE 3. Survival benefits according to human papillomavirus (HPV) status by smoking history. (A–C) Unadjusted overall survival (OS), recurrence-free survival (RFS), and disease-specific survival (DSS), respectively, for HPV status by smoking history (HPV-negative nonsmoker [n = 44], HPV-negative smoker [n = 178], HPV-positive nonsmoker [n = 52], and HPV-positive smoker [n = 88]). Differences in outcomes for HPV-positive patients were evident in univariate analysis according to smoking history; however, outcomes for HPV-negative patients were similar comparing nonsmokers and ever smokers. [Color figure can be viewed at wileyonlinelibrary.com]

whereas smoking history was no longer statistically significant in the risk-adjusted models (Table 2). Age and BMI remained statistically significant for OS. Interestingly, pack-year of use among cigarette smokers was not significantly associated with the outcome measures after adjustment for confounding clinical factors. Sensitivity analyses did not suggest any changes to the conclusions reported after applying alternative strategies for missing HPV data (Supplementary Materials, online only; Table 1).

In multivariable analysis, DSS time (>10 years before diagnosis) cigarette use was not a significant prognostic variable after adjustment for other prognostic factors per 10 pack-years (HR = 1.03; 95% CI = 0.95–1.12; HR = 1.05; 95% CI = 0.97–1.15; and HR = 1.08; 95% CI = 0.97–1.20; respectively for OS, RFS, and DSS).

Tobacco use, human papillomavirus status, and outcome

In HPV-positive patients, for OS (Figure 3A), RFS (Figure 3B), and DSS (Figure 3C), nonsmokers showed marginal improvements in survival compared with smokers. Outcomes were better for HPV-positive patients compared with all HPV-negative patients, regardless of smoking history. In univariate analysis, HPV-positive nonsmokers had better outcomes compared with HPV-positive smokers, although only OS reached statistical significance (HR = 0.22; 95% CI = 0.05–0.94; HR = 0.36; 95% CI = 0.12–1.08; and HR = 0.16; 95% CI = 0.02–1.20; for OS, RFS, and DSS, respectively). In multivariable analysis, HPV-positive nonsmokers compared to HPV-positive smokers had improvements in outcome that did not achieve statistical significance (HR = 0.22; 95% CI = 0.05–1.04; HR = 0.34; 95% CI = 0.11–1.06; and HR = 0.15; 95% CI = 0.02–1.31 for OS, RFS, and DSS, respectively), after adjustment for confounding factors.

In HPV-negative patients, there was little survival difference between nonsmokers and smokers for OS (Figure 3A), RFS (Figure 3B), and DSS (Figure 3C). In univariate analysis, HPV-negative nonsmokers showed marginal improvements in OS compared with HPV-negative smokers (HR = 0.88; 95% CI = 0.48–1.59). For RFS and DSS in HPV-negative patients, never smoking status showed no significant improvements in survivorship compared with patients with a history of ever smoking (HR = 1.21; 95% CI = 0.68–2.14; and HR = 0.97; 95% CI = 0.47–2.00) for RFS and DSS, respectively. In multivariable analysis, among patients with HPV-negative disease, OS, RFS, and DSS were not significantly associated with never or ever smokers (HR = 1.45; 95% CI = 0.72–2.94; HR = 1.62; 95% CI = 0.82–3.19; and HR = 1.52; 95% CI = 0.65–3.55, respectively), after adjustment for confounding factors.

Association of tobacco use and clinical variables

Smoking status (never, current, and former) was strongly associated with comorbidity score, age, tumor site, BMI, and HPV status, all of which were significantly associated with outcomes (Table 3). Among subjects with a smoking history, cigarette pack-years, both recent and DSS time, were significantly associated with age and disease site (Table 4). Increased comorbidity score was significantly associated with pack-years among smokers (Table 4; $p < .001$) with a clear monotonic trend (Figure 4A). When taking into account duration and intensity of smoking, DSS time cigarette use (Figure 4B; $p < .0001$) was more strongly associated with severity of comorbidity score than recent cigarette use (Figure 4C; $p = .88$).

DISCUSSION

In this large, prospective cohort of patients with HNSCC, we have confirmed the simple association of cigarette use with OS.[21,22] When considering only smoking status, never smokers were consistently identified as a prognostically favorable patient group for OS, RFS, and DSS times. Similarly, pack-years showed a modest

TABLE 3. Association of smoking status with clinical and epidemiologic characteristics.

Variables	No. of patients	% of patients Never smokers	% of patients Current smokers	% of patients Former smokers	Chi-square *p* value
Age category, y					**< .001**
<60	345	30	50	21	
60–75	246	20	39	41	
>75	96	35	14	51	
Sex					.55
Male	504	26	41	33	
Female	183	28	43	29	
Marital status					**< .001**
Married	251	18	56	26	
Not married	436	32	33	36	
Prior cancer					.48
No	579	27	42	31	
Yes	108	26	37	37	
Prior HNSCC					**.07**
No	656	27	42	31	
Yes	31	29	23	48	
Stage					.37
I/Cis	108	28	42	31	
II	79	28	41	32	
III	97	16	48	35	
IV	403	29	39	32	
Disease site					**< .001**
Larynx	135	4	66	30	
Oral cavity	271	29	41	30	
Oropharynx	257	37	27	35	
Hypopharynx	24	17	46	38	
ACE comorbidity					**< .001**
None	183	40	36	24	
Mild	322	23	43	34	
Moderate	125	19	44	37	
Severe	57	19	42	39	
BMI category					**< .001**
Underweight, <18.5	33	3	76	21	
Normal weight, 18.5–24.9	233	19	54	27	
Overweight, 25–29.9	238	30	30	40	
Obese, 30+	179	37	33	30	
HPV					**.001**
HPV-negative	222	20	50	30	
HPV-positive	140	37	31	31	
Unknown	325	27	39	34	
Alcohol use					**< .001**
Never	67	48	31	21	
Current	450	29	42	29	
Former, quit >12 mo	170	13	43	44	

Abbreviations: %, proportion of patients within subgroup (row); HNSCC, head and neck squamous cell cancer; Cis, in situ; ACE, Adult Comorbidity Evaluation-27 summary score; BMI, body mass index; HPV, human papillomavirus.
Figures in boldface indicate statistical significance.

increased hazard of death for every 10 pack-years of use in univariate analysis. However, in multivariable analysis, we found that both smoking status and pack-years were not significant after adjustment for other clinical factors, including medical comorbidities, history of prior HNSCC, and BMI. When former smokers were grouped by year since quitting, there was not significant separation in OS, RFS, or DSS curves. This study demonstrates that a more refined consideration of cigarette use based upon timing and intensity may be useful when considering HNSCC outcomes. In particular, cigarette use at earlier times may be more clinically relevant than is more recent cigarette use.

Our data also demonstrate that comorbidities are highly related to pack-years, particularly with DSS time use, in bivariate analysis. The univariate effect of DSS time cigarette use diminishes in multivariate analyses, and comorbidities have a strong effect on outcome, particularly on OS. Because tobacco use is a likely contributing factor to these comorbidities, it is possible that some of the negative impact of smoking on outcomes in patients with HNSCC is mediated through comorbidities. These findings could have potential implications on the use of smoking history in risk stratification for patients with HNSCC.[5,23–25] It is likely that a more refined approach

TABLE 4. Associations of clinical and epidemiologic characteristics with cumulative pack-years remote time and recent among current and former smokers.

Variables	No. of patients	Mean (SD) total pack-years	*p* value	Mean (SD) DSS time pack-years	*p* value	Mean (SD) recent pack-years	*p* value
Age category, y			**< .001**		**< .001**		**< .001**
<60	243	30.2 (23.8)		21.5 (18.5)		9.1 (7.4)	
60–75	198	40.0 (27.6)		33.4 (23.4)		6.6 (6.8)	
>75	62	36.6 (34.4)		34.0 (31.1)		3.2 (5.5)	
Sex			.09		.10		.23
Male	372	36.1 (26.5)		28.8 (22.6)		7.6 (7.4)	
Female	131	31.4 (28.8)		24.9 (24.2)		6.7 (6.8)	
Marital status			**.03**		.14		**< .001**
Married	206	38.1 (27.1)		29.6 (23.4)		8.9 (7.1)	
Not married	297	32.6 (27.0)		26.5 (22.9)		6.3 (7.1)	
Prior cancer			.18		**.03**		.09
No	423	34.1 (27.2)		26.8 (22.7)		7.6 (7.4)	
Yes	80	38.6 (27.1)		32.9 (24.8)		6.1 (6.3)	
Prior head and neck cancer			.48		.12		**.01**
No	481	34.7 (27.3)		27.4 (23.0)		7.5 (7.3)	
Yes	22	38.9 (25.2)		35.3 (24.6)		3.6 (4.7)	
Stage			.47		.47		.55
I/Cis	78	35.9 (29.2)		28.0 (23.9)		7.9 (7.5)	
II	57	37.6 (25.6)		31.2 (21.1)		7.7 (6.5)	
III	81	37.7 (26.9)		29.6 (23.0)		8.1 (7.9)	
IV	287	33.3 (27.0)		26.5 (23.3)		7.0 (7.1)	
Disease site			**< .001**		**.002**		**< .001**
Larynx	129	42.3 (25.0)		32.9 (20.9)		9.7 (7.1)	
Oral cavity	193	36.1 (30.1)		28.6 (25.4)		7.7 (7.2)	
Oropharynx	161	27.5 (23.1)		22.6 (20.6)		5.1 (6.8)	
Hypopharynx	20	34.9 (27.4)		27.6 (24.7)		6.8 (6.8)	
Comorbidities			**< .001**		**< .001**		.88
None	109	26.3 (22.0)		19.9 (17.4)		7.0 (6.7)	
Mild	247	35.9 (28.1)		28.5 (23.8)		7.6 (7.4)	
Moderate	101	37.3 (27.4)		30.0 (22.9)		7.3 (7.5)	
Severe	46	43.9 (28.3)		37.0 (26.7)		7.0 (6.8)	
BMI category			.16		.34		**.01**
Underweight, <18.5	32	40.5 (31.1)		31.8 (25.7)		8.7 (6.9)	
Normal weight, 18.5–24.9	188	34.0 (25.0)		26.5 (20.7)		7.9 (7.0)	
Overweight, 25–29.9	167	32.2 (25.3)		26.6 (22.0)		5.9 (6.5)	
Obese, 30+	113	38.5 (31.8)		30.4 (27.5)		8.2 (8.3)	
HPV			**.03**		**.03**		.07
HPV-negative	175	38.2 (25.4)		30.2 (21.8)		8.4 (6.8)	
HPV-positive	86	28.7 (28.5)		22.1 (23.9)		6.7 (7.9)	
Unknown	235	34.6 (27.7)		28.0 (23.5)		6.8 (7.2)	
Alcohol use			.22		.07		.44
Never	35	37.6 (33.0)		29.3 (27.6)		8.3 (9.8)	
Current	320	33.3 (25.6)		26.0 (21.2)		7.5 (7.1)	
Former, quit >12 mo	148	37.7 (28.8)		31.3 (25.6)		6.8 (6.8)	
Cigarette use			**< .001**		.19		**< .001**
Never							
Current	282	40.4 (26.9)		29.0 (22.1)		11.6 (6.3)	
Former, quit >12 mo	221	27.7 (25.9)		26.2 (24.3)		1.9 (4.0)	

Abbreviations: Cis, in situ; BMI, body mass index; HPV, human papillomavirus.
Figures in boldface indicate statistical significance.

considering temporal smoking habits along with comorbidities would afford a more predictive model.

Remote cigarette use was significantly associated with outcomes, history of prior HNSCC, and comorbidities, whereas recent use was not. Greater pack-years were associated with an increasing monotonic trend with more severe comorbidity. We hypothesize that patients who initiated intense smoking for a long duration spanning their lifetime may accumulate more somatic mutations[7,26–28] than patients who smoked less or more recently, and the implications from a carcinogenesis standpoint merit further study. Lifetime smoking had a significant impact on OS, and this could be phenotypically associated with increased smoking-related comorbidities, such as cardiovascular and pulmonary disease, contributing to a poorer survival chance after cancer treatment. Comorbidities at diagnosis have been correlated with survival[29] and have been externally validated as an independent predictor of survival in a prognostic HNSCC model.[30] In another study, a model of comorbidities, clinical, and pathological

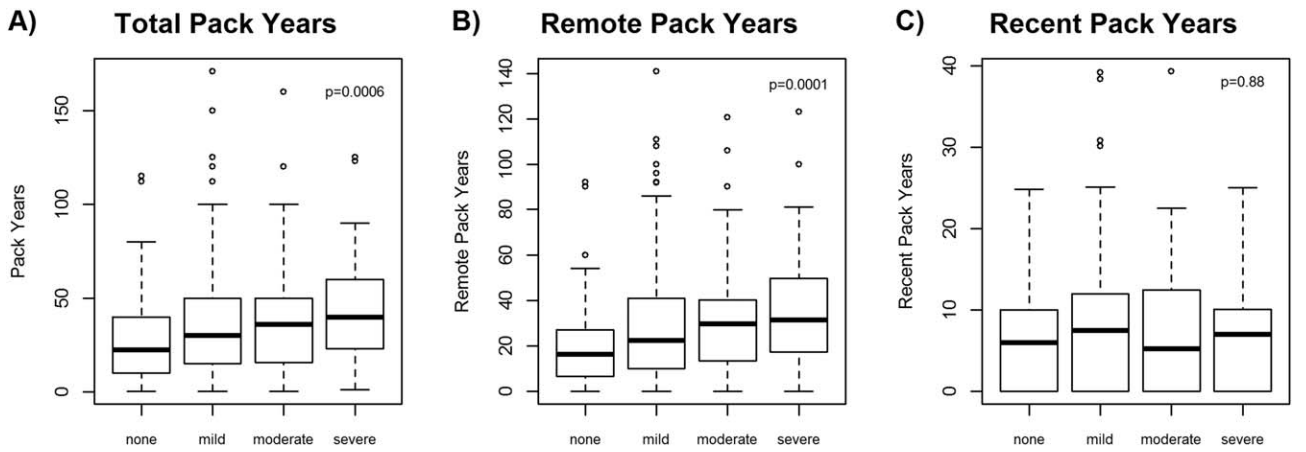

FIGURE 4. Pack-years and comorbidity score boxplots among ever smokers. (A) Overall pack-years differ by comorbidity score (none, mild, moderate, or severe) with an analysis of variance (ANOVA) test p value = .0006. (B) Remote use pack-years also differ by comorbidity (none, mild, moderate, or severe) with an ANOVA test p value = .0001. (C) Recent use pack-years did not differ significantly by comorbidity score (none, mild, moderate, or severe) with an ANOVA test p value = .88. Comorbidities were associated with pack-years in a monotonic trend when accounting for the intensity and duration of patient's smoking habits.

information predicted survival better than pathological TNM staging.[31] Management of comorbidities at diagnosis may be a key factor for improving survival rates in patients with HNSCC. Survivors who continue smoking compared with patients who never smoked are at higher risk of a recurrence or second primary.[32] Perhaps continued tobacco exposure exacerbates medical comorbidities in a manner that replicates the biology and medical condition of DSS time smokers. Further understanding of the biological and clinical impact of smoking during treatment is required.[33]

Our data did not demonstrate alcohol use as a prognostic factor, even in univariate analyses, in contrast to other studies that found alcohol use as a strong prognostic factor for patients with HNSCC.[34,35] In multivariable and bivariate analyses, increased BMI was associated with both longer survival and less tobacco use. Low BMI, as a measure of nutritional status, was prospectively associated with increased risk of HNSCC mortality among smokers,[36] increased risk of death during chemoradiation,[37] and a negative prognostic factor posttreatment.[38] Other studies found obesity to be adversely associated with DSS in patients with tongue cancer.[39] Smoking and BMI are likely related through the various metabolic effects of smoking on cell physiology, modification of dietary habits related to smoking,[40] hormonal effects mediated by nicotine,[41] and via other confounders.[42]

Subjects with HPV-positive disease had better OS than HPV-negative subjects, regardless of smoking history. In HPV-positive patients, smoking history was only marginally significant and was no longer significantly associated with survival outcomes after adjusting for other prognostic factors. In multivariable analysis, HPV-negative nonsmokers and ever smokers did not have significantly different OS, RFS, and DSS. It is an important and unique finding that HPV-negative nonsmokers did not fare noticeably better. For tumor recurrence, other factors, including stage, comorbidity score, and history of prior HNSCC, had stronger and more consistent associations. Although previous studies that reported a strong association among survival, extent of tobacco use, and HPV status,[5,23,43] these studies relied on highly selected clinical trial data, which have strong selection bias for patients with low comorbidity and may have incomplete smoking histories. In contrast, our detailed smoking history was obtained through self-reported surveys in an unselected prospectively collected cohort. Our contrasting results could also be partly because of the contemporary epidemiologic shift of HPV-related oropharyngeal cancer with increasing numbers of nonsmokers over the last 2 decades.[44–46]

This study analyzed the associations of cigarette use with oncologic and survival outcomes in head and neck cancer in a large, carefully studied prospective cohort. Smoking status was consistently correlated with worse oncologic and survival outcomes across our univariate analyses. In multivariable analyses, we identified high comorbidity score, history of prior HNSCC, negative HPV status, increasing cancer stage, and low BMI as highly significant characteristics that negatively affect OS, RFS, and DSS. However, in our patient population, smoking history was not an independent prognostic factor after adjusting for these other significant covariates. Our findings suggest that continued efforts at identifying and understanding the interactions of smoking and other health behaviors with other patient characteristics will be important in developing new patient risk profiles for use in personalized treatment strategies.

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