Cigarette Use, Comorbidities and Prognosis in a Prospective Head and Neck Squamous Cell Carcinoma Population

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Financial disclosures: None.

Keywords: tobacco, epidemiology, head and neck cancer, survival, recurrence, comorbidities, intensity,

duration

ABSTRACT

INTRODUCTION:

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

METHODS:

Kaplan-Meier and Cox models explored associations of tobacco use intensity (packs/day), duration (years of use) and timing prior to diagnosis with overall and disease specific survival and recurrence free time .

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 HPV status which were strongly associated with clinical outcomes.

CONCLUSIONS:

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.

INTRODUCTION

Approximately 35- 55% of patients with head and neck squamous cell carcinoma (HNSCC) experience locoregional recurrence or distant metastasis within two 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 status, and diet(4). Patients with Human Papillomavirus positive (HPV(+)) oropharyngeal cancer on average have better prognoses, which led to recommendations to de-escalate 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 to never smokers, but this same benefit is not seen when comparing patients who recently quit smoking to 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, BMI and comorbidities. All of these may also be associated with clinical outcomes of interest in HNSCC patients. Thus, there is strong interest in examining the risk of tobacco use on long term survival and recurrence rates in HNSCC, particularly in combination with other established prognostic factors. These data will be instrumental in selecting the appropriate cohorts for potential treatment intensification or de-escalation.

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

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duration of tobacco exposure. Intensity is usually defined in terms of cigarettes per day and duration in years of use. Since 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 remote tobacco exposure groups may aid in better understanding the impact of tobacco use on oncologic and survival outcomes.

In this paper we assessed the effects of lifetime cigarette exposure in a prospectively collected, unselected population of previously untreated, incident HNSCC patients. This cohort of 687 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 online supplementary materials, 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 HNSCC patient with primary disease evaluated in the Head and Neck Oncology Program of the University of Michigan (UM; Ann Arbor, MI) Comprehensive Cancer Center was prospectively screened for eligibility and 92% signed a written informed consent and were enrolled. 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 UM. 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. Prior HNSCC was defined as a previous primary tumor in the head and neck more than five 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

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12 months prior to 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 smokers who also us cigar and pipe tobaccos (18),

only cigarette data were further analyzed. The cumulative quantity of cigarettes smoked in the recent past (less than 10

years before diagnosis) and at remote 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 1. Duration of use was determined by the cigarette initiation and cessation dates.

Follow-up. Patients were followed at NCCN guideline intervals for routine cancer care and surveillance. Tumor status

(recurrence, persistent disease, 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 2/1/14 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 due to other causes were censored at date of death for disease

specific survival time (DST). *Study Population.* The study population of 687 subjects was comprised of patients mainly

with oral cavity and oropharynx 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 radiation or chemoradiation (20%), chemoradiation alone (40%), radiation

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 was 30 months and the estimated two year overall survival rate was 78%. Median

follow-up for recurrence-free time was 24 months and the estimated two year recurrence- free rate was 75%.

   HPV Status. HPV status was determined from biopsy or surgical resection formalin-fixed, paraffin-embedded

blocks for 362 subjects using previously reported and validated PCR methods (20). HPV status was unable to be

determined for 325 subjects. Subjects with equivocal or missing HPV status were included in study and given an HPV

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status of "unknown". Among subjects with adequate DNA or tissue specimens, 84% of oropharynx cancers were HPV(+),

12% of oral cavity, 13% of larynx, and 25% of hypopharynx.

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 overall survival (OST), recurrence-free (RFT), and disease specific survival (DST) time. Time-to-event outcomes

were defined from diagnosis to death any cause (OST), time to disease recurrence (RFT), or time to death from HNSCC

malignancy. forFor patients with persistent disease, time to recurrence was defined as one day.

Single variable and multivariable Cox proportional hazard models were used to test associations between clinical

and epidemiological variables with OST, RFT, and DST. Covariates included were age, gender, marital status, history of

prior HNSCC or other cancer, stage, tumor site, comorbidity score, BMI, HPV status, alcohol, and tobacco use.

Differences in outcome by planned treatment were explored, though 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

three 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 online supplementary materials section. A post-hoc subset analysis was also

performed analyzing HPV(+) and HPV(-) cancers separately.

RESULTS

Univariate Clinical and Demographic Effects on Outcome: Clinical variables associated with worse

OST, RFT, and DST 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 3-5% decrease in relative risk per year for every one 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

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comorbidities. The effect of age and comorbidities were strongest for OST, whereas the effects of stage and prior HNSCC were strongest for DST.

Univariate Smoking Effects on Outcome: Cigarette use (never, current, former) was significantly associated with an increased risk of death from all causes and disease-specific death. Never smoking was associated with improved overall (Figure 1A), relapse-free (Figure 1B), and disease-specific survival (Figure 1C). Significantly worse OST, RFT, DST were associated with every 10 year increase in pack years of use (HR (95% CI): 1.10 (1.05, 1.15), 1.07 (1.02, 1.12), 1.09 (1.03, 1.16), respectively, Table 1). As expected, smokers of over 20 pack years had significantly worse outcomes compared to never smokers (Figures 1D – 1F). When former smokers were categorized by year since quitting, there was little separation between quitting within 10 years or quitting more than 10 years before diagnosis in OST, RFT, or DST (Figures 1G – 1I), although all outcomes were consistently worse in smokers compared to nonsmokers.

Recent Tobacco Use Compared to Remote Use: To better understand the influence of cigarette smoking on outcome measures, smoking history was separated into recent and remote use, derived from the patient's age at initiation, years of duration, and intensity. Graphically, we observed that the amount of remote cigarette use among smokers (accumulated up to 10 years prior to diagnosis) was associated with worse survival and recurrence free times (Figure 2A-2C). Although current cigarette use appeared associated with worse survival and recurrence free times when compared to never smokers, the amount of recent cigarette use (accumulated within 10 years of diagnosis) was not (Figure 2D-2F). Among smokers, differences in outcome (HR (95% CI) per 10 pack years) by intensity of remote use were significant for worse OST, RFT and for DST survival (1.11 (1.04, 1.18), 1.09 (1.02, 1.17), and 1.11 (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 hazard ratios for each outcome were wide and contained 1.00

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(HR (95% CI) per 10 pack years for OST, RFT, DST: 0.94 (0.68, 1.30), 1.05 (0.75, 1.46), 0.98 (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 while smoking history was no longer statistically significant in the risk-adjusted models (Table 2). Age and BMI remained statistically significant for overall survival. Interestingly, pack years 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, Table 1).

In multivariable analysis, remote (> than 10 years prior to diagnosis) cigarette use was not a significant prognostic variable after adjustment for other prognostic factors (HR (95% CI) per 10 pack years: 1.03 (0.95,1.12), 1.05 (0.97,1.15), 1.08 (0.97,1.20), respectively for OST, RFT, DST).

Tobacco Use, HPV status and Outcome: In HPV(+) patients, for overall (Figure 3A), recurrence-free (Figure 3B), and disease-specific survival (Figure 3C), nonsmokers showed marginal improvements in survival compared to smokers. Outcomes were better for HPV(+) patients compared to all HPV(-) patients, regardless of smoking history. In univariate analysis, HPV(+) nonsmokers had better outcomes compared to HPV(+) smokers though only OST reached statistical significance (HR (95% CI): 0.22 (0.05, 0.94), 0.36 (0.12, 1.08), 0.16 (0.02, 1.20) for OST, RFT, DST respectively). In multivariable analysis, HPV(+) nonsmokers compared to HPV(+) smokers had improvements in outcome that did not achieve statistical significance (HR (95% CI): 0.22 (0.05, 1.04), 0.34 (0.11, 1.06), 0.15 (0.02, 1.31) for OST, RFT, DST respectively), after adjustment for confounding factors.

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

Association of Tobacco Use and Clinical Variables: Smoking status (never, current, 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 remote 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, remote cigarette use (Figure 4B; p<.0001) was more strongly associated with severity of comorbidity score than recent cigarette use (Figure 4C; p=0.88).

DISCUSSION

In this large, prospective cohort of HNSCC patients, we have confirmed the simple association of cigarette use with overall survival (21, 22). When considering only smoking status, never smokers were consistently identified as a prognostically favorable patient group for OST, RFT, and DST survival. Similarly, pack years showed a modest 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

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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 OST, RFT,

or DST 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 remote

use, in bivariate analysis. The univariate effect of remote cigarette use diminishes in multivariate analyses,

and comorbidities have a strong effect on outcome, particularly on overall survival. Since tobacco use is a

likely contributing factor to these comorbidities, it is possible that some of the negative impact of smoking on

outcomes in HNSCC patients 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 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 in 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 OST, 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 information predicted survival better than

pathological TNM staging (31). Management of comorbidities at diagnosis may be a key factor for improving

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survival rates in HNSCC patients. Survivors who continue smoking compared to 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 remote 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 which found alcohol use as a strong prognostic factor for HNSCC patients (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 post-treatment (38). Other studies found obesity to be adversely associated with disease-specific

survival 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(+) disease, had better OST than HPV(-) subjects, regardless of smoking history. In

HPV(+) 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(-)

nonsmokers and ever smokers did not have significantly different OST, RFT, DST. It is an important and unique

finding that HPV(-) 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 between 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 due to the contemporary epidemiologic shift of HPV related oropharyngeal cancer with increasing numbers of non-smokers over the last two 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 OST, RFT and DST. 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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Table 1. Univariate Cox proportional hazards model for survival outcome

		No. of Patients	OST HR (95% CI)	OST p-value	RFT HR (95% CI)	RFT p-value	DST HR (95% CI)	DST p-value
Age at Dx	10 years	687	1.44 (1.26, 1.64)	**<0.0001**	1.26 (1.10, 1.43)	**0.0007**	1.21 (1.02, 1.43)	0.03
Gender[b]	Male (ref)	504	(ref)		(ref)		(ref)	
	Female	183	1.31 (0.94, 1.83)	0.11	1.13 (0.80, 1.60)	0.48	1.21 (0.78, 1.86)	0.39
Married	Married	436	0.55 (0.40, 0.74)	**0.0001**	0.65 (0.48, 0.89)	**0.007**	0.66 (0.44, 0.98)	0.04
	Not Married[a]	251	(ref)		(ref)		(ref)	
Prior Ca[b]		108	1.04 (0.69, 1.57)	0.86	0.86 (0.55, 1.34)	0.51	0.85 (0.48, 1.50)	0.58
Prior HNSCC[c]		31	2.83 (1.60, 5.02)	**0.0004**	3.10 (1.81, 5.30)	**<0.0001**	3.25 (1.63, 6.49)	**0.0008**
Ca Stage	I/Cis (ref)	108	(ref)		(ref)		(ref)	
	II	79	3.24 (1.32, 7.95)	0.01	1.47 (0.58, 3.70)	0.41	2.50 (0.60, 10.47)	0.21
	III	97	4.14 (1.78, 9.61)	**0.0009**	3.04 (1.41, 6.57)	**0.005**	5.66 (1.63, 19.69)	**0.006**
	IV	403	4.90 (2.28, 10.50)	**<0.0001**	3.98 (2.02, 7.84)	**<0.0001**	7.64 (2.41, 24.21)	**0.0005**
Disease Site	oral cavity (ref)	271	(ref)		(ref)		(ref)	
	hypopharynx	24	1.60 (0.80, 3.18)	0.19	1.97 (1.01, 3.82)	0.05	1.91 (0.81, 4.49)	0.14
	larynx	135	0.69 (0.45, 1.05)	0.08	0.80 (0.52, 1.22)	0.30	0.90 (0.54, 1.51)	0.69
	oropharynx	257	0.58 (0.40, 0.83)	**0.003**	0.74 (0.51, 1.06)	0.10	0.64 (0.40, 1.03)	0.07
ACE comorbidity	none (ref)	183	(ref)		(ref)		(ref)	
	mild	322	2.29 (1.44, 3.63)	**0.0005**	1.64 (1.07, 2.52)	0.02	1.71 (1.00, 2.95)	0.05
	moderate	125	2.66 (1.58, 4.47)	**0.0002**	1.96 (1.20, 3.21)	**0.007**	1.93 (1.03, 3.63)	0.04
	severe	57	3.99 (2.20, 7.22)	**<0.0001**	2.61 (1.46, 4.65)	**0.001**	3.13 (1.53, 6.40)	**0.002**
BMI	1 unit increase	683	0.95 (0.92 ,0.98)	**0.001**	0.97 (0.94, 0.99)	0.02	0.95 (0.92 ,0.99)	0.01
HPV status	HPV- (ref)	222	(ref)		(ref)		(ref)	
	HPV+	140	0.39 (0.24, 0.64)	**0.0002**	0.48 (0.30, 0.78)	**0.003**	0.42 (0.23, 0.77)	**0.005**
	Unknown	325	0.91 (0.65, 1.26)	0.56	0.89 (0.64, 1.25)	0.51	0.79 (0.52, 1.22)	0.29
Alcohol Use	never (ref)	67	(ref)		(ref)		(ref)	
	current	450	0.75 (0.45, 1.26)	0.27	0.66 (0.40, 1.07)	0.09	0.72 (0.38, 1.38)	0.33
	former	170	1.11 (0.64, 1.92)	0.72	0.88 (0.52, 1.51)	0.65	1.01 (0.51, 2.02)	0.97
Cigarette Use	never (ref)	184	(ref)		(ref)		(ref)	
	current	282	2.07 (1.32, 3.25)	**0.002**	1.31 (0.87, 1.98)	0.20	1.87 (1.05, 3.31)	0.03
	former	221	2.11 (1.33, 3.36)	**0.002**	1.51 (0.99, 2.30)	0.06	2.18 (1.22, 3.90)	**0.008**
Pack Years	10 unit increase	687	1.10 (1.05, 1.15)	**<0.0001**	1.07 (1.02, 1.12)	0.007	1.09 (1.03, 1.16)	**0.005**
Years Quit	never smoker	184	0.48 (0.31, 0.76)	**0.002**	0.77 (0.51, 1.16)	0.21	0.53 (0.30, 0.94)	0.03
	quit 10+ years	158	0.93 (0.64, 1.37)	0.73	1.09 (0.74, 1.62)	0.67	1.13 (0.70, 1.82)	0.61
	quit <10 years	59	1.26 (0.77, 2.06)	0.36	1.33 (0.79, 2.23)	0.29	1.20 (0.62, 2.32)	0.60
	current smoker	279	(ref)		(ref)		(ref)	
Remote Pack Years	10 unit increase	680	1.13 (1.07, 1.19)	**<0.0001**	1.09 (1.03, 1.16)	**0.004**	1.12 (1.04, 1.20)	**0.002**
Recent Pack Years	10 unit increase	680	1.20 (0.98, 1.64)	0.07	1.10 (0.89, 1.36)	0.40	1.12 (0.86, 1.46)	0.38

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Table 1 Abbreviations: OST=Overall Survival Time, RFT=Recurrence-Free Time, DST=Disease Specific Survival Time, No.=Number, HR=Hazard Ratio, CI=Confidence Interval, HNSCC=Head and Neck Squamous Cell Cancer, Cis=insitu, ACE=Adult Comorbidity Evaluation-27 summary score, BMI=Body Mass Index, HPV= Human papillomavirus

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

		No. of Patients	OST		RFT		DST	
			HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	10 years unit	683	1.30 (1.12, 1.51)	**0.0005**	1.16 (1.00, 1.35)	0.05	1.12 (0.93, 1.36)	0.24
Gender	Male	500	(ref)		(ref)		(ref)	
	Female	183	1.07 (0.74, 1.54)	0.73	0.95 (0.65, 1.39)	0.79	1.08 (0.68, 1.73)	0.74
Married	Married	434	0.77 (0.55, 1.09)	0.14	0.78 (0.55, 1.10)	0.15	0.90 (0.58, 1.39)	0.63
	Not Married	249	(ref)		(ref)		(ref)	
Prior Cancer		108	0.83 (0.53, 1.30)	0.41	0.73 (0.46, 1.16)	0.18	0.67 (0.37, 1.23)	0.20
Prior HNSCC		31	2.31 (1.25, 4.26)	**0.008**	2.73 (1.54, 4.84)	**0.0006**	2.77 (1.31, 5.87)	**0.008**
Ca Stage	I/Cis	107	(ref)		(ref)		(ref)	
	II	78	3.24 (1.31, 8.02)	0.01	1.40 (0.55, 3.54)	0.48	2.37 (0.56, 9.97)	0.24
	III	97	5.02 (2.14, 11.80)	**0.0002**	3.34 (1.53, 7.31)	**0.003**	6.58 (1.87, 23.19)	**0.003**
	IV	401	7.20 (3.29, 15.73)	**<0.0001**	5.03 (2.50, 10.11)	**<0.0001**	10.54 (3.26, 34.05)	**<0.0001**
Disease Site	Oral Cavity	269	(ref)		(ref)		(ref)	
	Hypopharynx	23	0.76 (0.35, 1.66)	0.50	1.11 (0.53, 2.33)	0.79	0.92 (0.37, 2.31)	0.86
	Larynx	135	0.52 (0.33, 0.82)	**0.005**	0.66 (0.42, 1.04)	0.08	0.62 (0.35, 1.08)	0.09
	Oropharynx	256	0.72 (0.47, 1.11)	0.14	0.81 (0.52, 1.25)	0.33	0.72 (0.41, 1.26)	0.25
ACE comorbidity	none	182	(ref)		(ref)		(ref)	
	mild	320	1.63 (1.00, 2.67)	0.05	1.27 (0.81, 2.01)	0.30	1.35 (0.75, 2.41)	0.31
	moderate	125	2.66 (1.58, 4.47)	**0.003**	1.69 (1.00, 2.87)	0.05	1.81 (0.92, 3.54)	0.08
	severe	56	2.69 (1.38, 5.25)	**0.004**	1.95 (1.01, 3.78)	0.05	2.72 (1.21, 6.12)	0.02
BMI	1 unit increase	683	0.96 (0.93, 0.99)	0.01	0.98 (0.95, 1.00)	0.09	0.97 (0.93, 1.00)	0.06
HPV status	HPV-	221	(ref)		(ref)		(ref)	
	HPV+	140	0.41 (0.22, 0.73)	**0.003**	0.48 (0.27, 0.84)	0.01	0.37 (0.17, 0.77)	**0.008**
	Unknown	322	0.83 (0.58, 1.20)	0.32	0.79 (0.55, 1.15)	0.22	0.73 (0.46, 1.17)	0.20
Alcohol Use	never	66	(ref)		(ref)		(ref)	
	current	448	1.21 (0.68, 2.15)	0.51	0.86 (0.50, 1.49)	0.60	0.96 (0.48, 1.92)	0.90
	former	169	1.16 (0.64, 2.12)	0.62	0.90 (0.51, 1.61)	0.72	0.99 (0.47, 2.07)	0.98
Cigarette Use	never	183	0.76 (0.45, 1.28)	0.30	0.95 (0.59, 1.53)	0.83	0.81 (0.42, 1.54)	0.81
Pack Years	10 unit increase	683	1.05 (0.99, 1.11)	0.13	1.05 (0.98, 1.12)	0.14	1.04 (0.96, 1.13)	0.33

Table 2 Abbreviations:

No.=Number, OST=Overall Survival Time, RFT=Recurrence-Free Time, DST=Disease Specific Survival Time, HR=Hazard Ratio, CI=Confidence Interval, HNSCC=Head and Neck Squamous Cell Cancer, Cis=insitu, ACE=Adult Comorbidity Evaluation-27 summary score, BMI=Body Mass Index, HPV= Human papillomavirus

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Table 3. Association of Smoking Status with clinical and epidemiologic characteristics

Variable	Subgroup	No. of Patients	% of Patients Never Smokers	% of Patients Current Smokers	% of Patients Former Smokers	Chi-square p-value
Age Category	<60	345	30	50	21	**<0.001**
	60-75	246	20	39	41	
	>75	96	35	14	51	
Gender	Male	504	26	41	33	0.55
	Female	183	28	43	29	
Married	Married	251	18	56	26	**<0.001**
	Not Married	436	32	33	36	
Prior Cancer	No	579	27	42	31	0.48
	Yes	108	26	37	37	
Prior HNSCC	No	656	27	42	31	**0.07**
	Yes	31	29	23	48	
Stage	I/Cis	108	28	42	31	0.37
	II	79	28	41	32	
	III	97	16	48	35	
	IV	403	29	39	32	
Disease Site	Larynx	135	4	66	30	**<0.001**
	Oral Cavity	271	29	41	30	
	Oropharynx	257	37	27	35	
	Hypopharynx	24	17	46	38	
ACE comorbidity	none	183	40	36	24	**<0.001**
	mild	322	23	43	34	
	moderate	125	19	44	37	
	severe	57	19	42	39	
BMI category	underweight (<18.5)	33	3	76	21	**<0.001**
	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	HPV-	222	20	50	30	**0.001**
	HPV+	140	37	31	31	
	Unknown	325	27	39	34	
Alcohol Use	never	67	48	31	21	**<0.001**
	current	450	29	42	29	
	former (quit >12 months)	170	13	43	44	

Table 3 Abbreviations:

No.=Number. %=proportion of patients within subgroup (row). HNSCC=Head and Neck Squamous Cell Cancer, Cis=insitu, ACE=Adult Comorbidity Evaluation-27 summary score, BMI=Body Mass Index, HPV= Human papillomavirus

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Table 4: Associations of Clinical and Epidemiologic Characteristics with Cumulative Pack Years Remote and Recent among Current and Former Smokers.

Variable	Subgroup	No. of patients	Mean (std) Total Pack years	p-value	Mean (std) Remote Pack Years	p-value	Mean (std) Recent Pack Years	p-value
Age Category	<60	243	30.2 (23.8)	**<0.001**	21.5 (18.5)	**<0.001**	9.1 (7.4)	**<0.001**
	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)	
Gender	Male	372	36.1 (26.5)	0.09	28.8 (22.6)	0.10	7.6 (7.4)	0.23
	Female	131	31.4 (28.8)		24.9 (24.2)		6.7 (6.8)	
Married	Married	206	38.1 (27.1)	**0.03**	29.6 (23.4)	0.14	8.9 (7.1)	**<0.001**
	Not Married	297	32.6 (27.0)		26.5 (22.9)		6.3 (7.1)	
Prior Ca	No	423	34.1 (27.2)	0.18	26.8 (22.7)	**0.03**	7.6 (7.4)	0.09
	Yes	80	38.6 (27.1)		32.9 (24.8)		6.1 (6.3)	
Prior HNCa	No	481	34.7 (27.3)	0.48	27.4 (23.0)	0.12	7.5 (7.3)	**0.01**
	Yes	22	38.9 (25.2)		35.3 (24.6)		3.6 (4.7)	
Stage	I/Cis	78	35.9 (29.2)	0.47	28.0 (23.9)	0.47	7.9 (7.5)	0.55
	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	Larynx	129	42.3 (25.0)	**<0.001**	32.9 (20.9)	**0.002**	9.7 (7.1)	**<0.001**
	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	none	109	26.3 (22.0)	**<0.001**	19.9 (17.4)	**<0.001**	7.0 (6.7)	0.88
	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	underweight (<18.5)	32	40.5 (31.1)	0.16	31.8 (25.7)	0.34	8.7 (6.9)	**0.01**
	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	HPV-	175	38.2 (25.4)	**0.03**	30.2 (21.8)	**0.03**	8.4 (6.8)	0.07
	HPV+	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	never	35	37.6 (33.0)	0.22	29.3 (27.6)	0.07	8.3 (9.8)	0.44
	current	320	33.3 (25.6)		26.0 (21.2)		7.5 (7.1)	
	former (quit >12 months)	148	37.7 (28.8)		31.3 (25.6)		6.8 (6.8)	
Cigarette Use	never							
	current	282	40.4 (26.9)	**<0.001**	29.0 (22.1)	0.19	11.6 (6.3)	**<0.001**
	former (quit >12 months)	221	27.7 (25.9)		26.2 (24.3)		1.9 (4.0)	

<u>Table 4 Abbreviations:</u>

No.=Number, std=standard deviation, HNSCC=Head and Neck Squamous Cell Cancer, Cis=insitu, ACE=Adult Comorbidity Evaluation-27 summary score, BMI=Body Mass Index, HPV= Human papillomavirus

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Supplemental Table 1. Hazard Ratio (95% Confidence Interval) for selected covariates from multivariable Cox model analyses with different strategies for missing HPV status.

			OST	RFT	DST
		Missing Data Strategy	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
HPV Status	HPV(+) vs. HPV(−)	A	0.41 (0.22, 0.73)	0.48 (0.27, 0.84)	0.37 (0.17, 0.77)
		B	0.40 (0.20, 0.82)	0.36 (0.18, 0.74)	0.30 (0.12, 0.72)
		C	0.34 (0.16, 0.72)	0.34 (0.16, 0.74)	0.24 (0.09, 0.63)
		D	0.38 (0.20, 0.72)	0.37 (0.19, 0.72)	0.25 (0.10, 0.63)
Smoking Status	never vs. ever	A	0.76 (0.45, 1.28)	0.95 (0.59, 1.53)	0.81 (0.42, 1.54)
		B	0.93 (0.47, 1.85)	1.04 (0.54, 1.98)	1.01 (0.44, 2.30)
		C	0.91 (0.43, 1.90)	1.16 (0.58, 2.33)	0.93 (0.37, 2.29)
		D	0.81 (0.48, 1.36)	1.14 (0.70, 1.87)	0.87 (0.45, 1.68)
Cigarette Pack Years	10 unit increase	A	1.05 (0.99, 1.11)	1.05 (0.98, 1.12)	1.04 (0.96, 1.13)
		B	1.03 (0.95, 1.11)	1.03 (0.95, 1.13)	1.05 (0.94, 1.16)
		C	1.04 (0.95, 1.13)	1.06 (0.97, 1.16)	1.06 (0.95, 1.18)
		D	1.05 (0.98, 1.11)	1.05 (0.99, 1.12)	1.05 (0.96, 1.14)
Age	10 year increase	A	1.30 (1.12, 1.51)	1.16 (1.00, 1.35)	1.12 (0.93, 1.36)
		B	1.50 (1.21, 1.86)	1.24 (0.99, 1.54)	1.22 (0.94, 1.60)
		C	1.58 (1.25, 1.99)	1.28 (1.01, 1.63)	1.32 (0.98, 1.78)
		D	1.30 (1.11, 1.51)	1.15 (0.98, 1.34)	1.10 (0.90, 1.33)
Stage	IV vs. I	A	7.20 (3.29, 15.73)	5.03 (2.50, 10.11)	10.54 (3.26, 34.05)
		B	5.20 (2.01, 13.48)	3.22 (1.33, 7.80)	8.15 (1.89, 35.15)
		C	6.27 (2.14, 18.33)	3.30 (1.28, 8.52)	10.28 (1.81, 58.51)
		D	7.06 (3.22 15.46)	5.01 (2.49, 10.08)	10.58 (3.26, 34.28)
	III vs. I	A	5.02 (2.14, 11.80)	3.34 (1.53, 7.31)	6.58 (1.87, 23.19)
		B	4.58 (1.61, 13.04)	2.62 (0.98, 7.04)	6.84 (1.46, 32.18)
		C	6.02 (1.85, 19.55)	3.06 (1.06, 8.85)	9.37 (1.49, 58.99)
		D	4.82 (2.03, 11.45)	3.33 (1.51, 7.33)	6.88 (1.94, 24.38)
	II vs. I	A	3.24 (1.31, 8.02)	1.40 (0.55, 3.54)	2.37 (0.56, 9.97)
		B	2.42 (0.78, 7.53)	1.01 (0.30, 3.39)	2.04 (0.34, 12.42)
		C	3.11 (0.90, 10.73)	1.01 (0.28, 3.62)	3.82 (0.54, 26.77)
		D	3.18 (1.28, 7.90)	1.35 (0.53, 3.42)	2.33 (0.55, 9.85)
Disease Site	OP vs. OC	A	0.72 (0.47, 1.11)	0.81 (0.52, 1.25)	0.72 (0.41, 1.26)
		B	0.93 (0.47, 1.87)	1.26 (0.62, 2.56)	0.99 (0.41, 2.35)
		C	0.95 (0.45, 2.02)	1.26 (0.58, 2.75)	1.10 (0.43, 2.81)
		D	0.98 (0.58, 1.66)	1.15 (0.66, 2.03)	1.14 (0.57, 2.29)
	LA vs. OC	A	0.52 (0.33, 0.82)	0.66 (0.42, 1.04)	0.62 (0.35, 1.08)
		B	0.68 (0.38, 1.20)	0.71 (0.39, 1.30)	0.57 (0.27, 1.17)
		C	0.60 (0.31, 1.17)	0.71 (0.36, 1.41)	0.51 (0.22, 1.22)
		D	0.55 (0.34, 0.86)	0.69 (0.43, 1.09)	0.64 (0.36, 1.13)
	HP vs OC	A	0.76 (0.35, 1.66)	1.11 (0.53, 2.33)	0.92 (0.37, 2.31)
		B	1.63 (0.66, 4.07)	2.67 (1.05, 6.77)	1.66 (0.55, 4.99)
		C	2.12 (0.87, 5.16)	3.60 (1.42, 9.12)	2.73 (0.98, 7.55)
		D	0.84 (0.38, 1.85)	1.19 (0.56, 2.52)	1.04 (0.41, 2.66)
Comorbidities	mild vs. none	A	1.63 (1.00, 2.67)	1.27 (0.81, 2.01)	1.35 (0.75, 2.41)
		B	1.63 (0.83, 3.21)	1.24 (0.67, 2.27)	1.74 (0.78, 3.88)
		C	2.03 (0.95, 4.34)	1.17 (0.60, 2.26)	1.97 (0.80, 4.84)
		D	1.64 (0.99, 2.70)	1.26 (0.79, 2.02)	1.34 (0.74, 2.43)
	moderate vs. none	A	2.66 (1.58, 4.47)	1.69 (1.00, 2.87)	1.81 (0.92, 3.54)
		B	2.80 (1.32, 5.94)	1.43 (0.70, 2.93)	2.56 (1.03, 6.35)
		C	3.23 (1.41, 7.42)	1.43 (0.66, 3.07)	2.76 (1.01, 7.51)
		D	2.20 (1.24, 3.89)	1.59 (0.92, 2.73)	1.77 (0.89, 3.53)
	severe vs. none	A	2.69 (1.38, 5.25)	1.95 (1.01, 3.78)	2.72 (1.21, 6.12)
		B	2.98 (1.15, 7.74)	1.81 (0.72, 4.56)	2.45 (0.73, 8.17)
		C	2.49 (0.83, 7.44)	1.48 (0.54, 4.08)	1.65 (0.41, 6.69)
		D	2.70 (1.38, 5.30)	1.93 (0.99, 3.75)	2.54 (1.11, 5.79)
BMI (unit=1)	1 unit increase	A	0.96 (0.93 ,0.99)	0.98 (0.95, 1.00)	0.97 (0.93, 1.00)
		B	0.97 (0.94 ,1.01)	1.00 (0.97, 1.04)	1.00 (0.95, 1.04)
		C	0.98 (0.94, 1.03)	1.01 (0.97, 1.05)	1.01 (0.96, 1.07)
		D	0.97 (0.94, 0.99)	0.98 (0.95, 1.01)	0.97 (0.93, 1.01)
Prior HNSCC	yes vs. no	A	2.31 (1.25, 4.26)	2.73 (1.54, 4.84)	2.77 (1.31, 5.87)
		B	3.50 (1.24, 9.89)	3.80 (1.40, 10.27)	4.80 (1.52, 15.09)
		C	2.72 (1.11, 6.68)	4.09 (1.79, 9.31)	4.04 (1.46, 11.18)
		D	2.28 (1.19, 4.38)	2.60 (1.42, 4.78)	2.69 (1.19, 6.09)

A=Missing Category. **B**=Omit subjects with missing HPV. **C**=Inverse Probability Weighting. **D**=Multiple Imputation
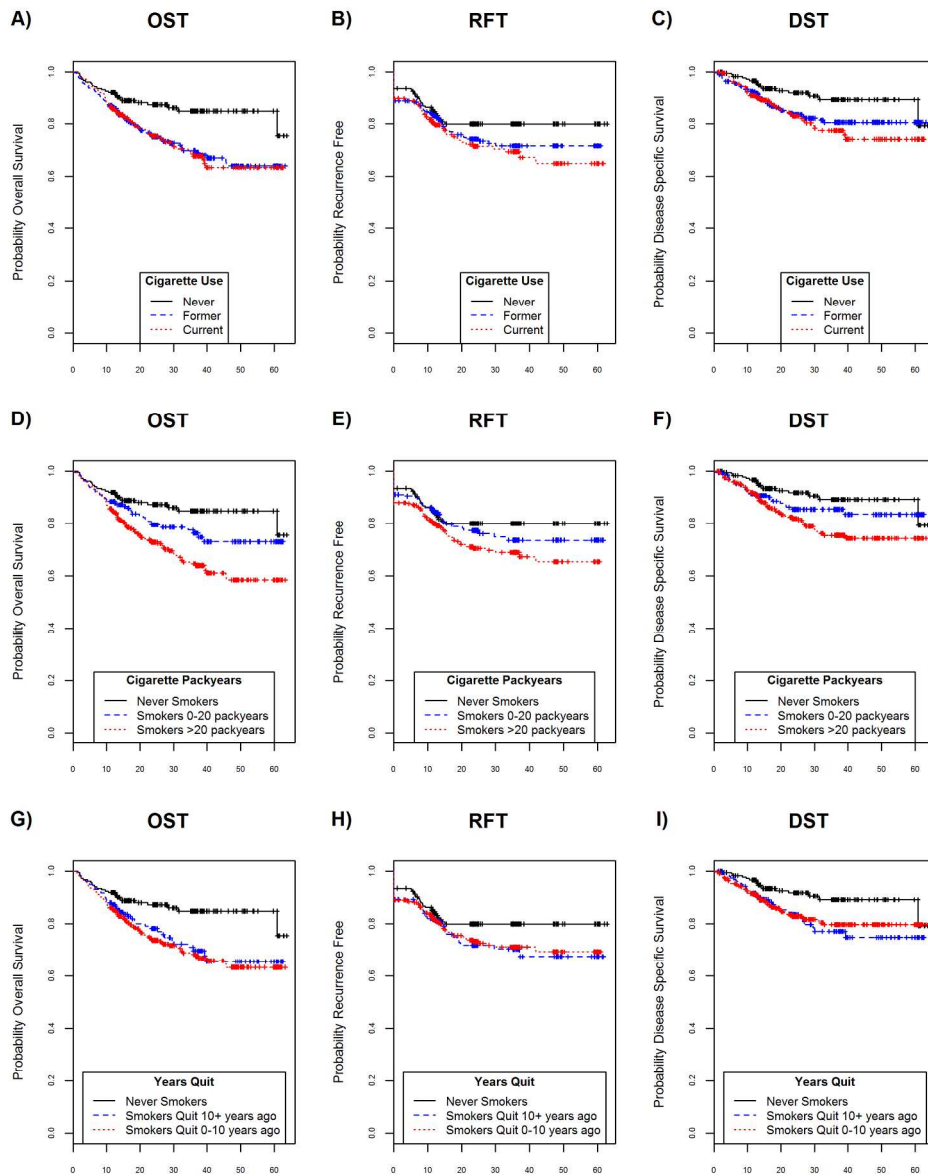
6

Figure 1. Survival benefits according to smoking status (A-C), pack years (D-F), and years since quit (G-I). Panels A, B, C: unadjusted OST, RFT, and DST, respectively, by cigarette use (never, former, 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.
Panels D, E, F: unadjusted OST, RFT, and DST, respectively, by pack years (never smoker, smokers 0-20 pack years, and smokers > 20 pack years). Never smokers had significantly better survival outcomes than smokers (OST p-value=0.01 in univariable Cox model). There were apparent differences in each category of survival events with a 7-10% increase risk of outcome for every 10 pack year increase in cigarette use (Cox Proportional models for OST, RFT, DST; p=0.01, 0.007, 0.005, respectively).
Panels G, H, I: unadjusted OST, RFT, and DST, 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 remote and quitters.
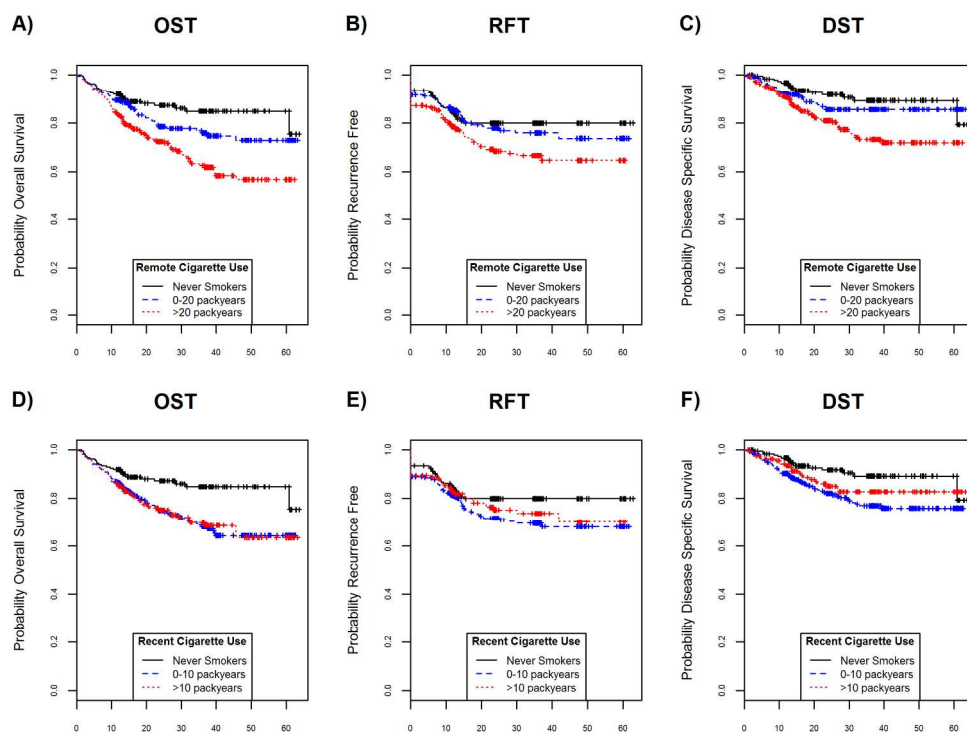
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Figure 2. Association of remote or recent pack years with survival. A, B, C, unadjusted OST, RFT, DST, respectively, for pack years comparing never smokers to 0-20 pack years and >20 pack years for remote use smokers. For remote use, significant differences in OST favored light pack years compared to heavy pack years while RFT and DST were more similar among light and never smokers. D, E, F, unadjusted OST, RFT, DST, respectively, for pack years comparing never smokers to 0-20 pack years and >20 pack years for recent use smokers. For recent use, moderate differences in survival were only observed in RFT comparing light to heavy cigarette use.
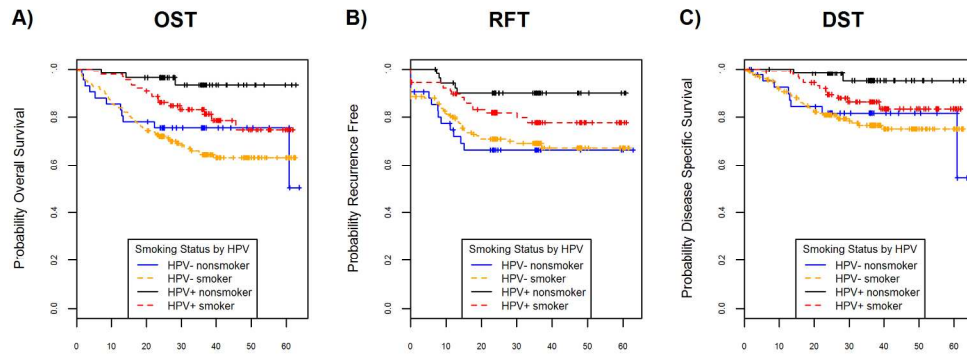
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Figure 3. Survival benefits according to HPV status by smoking history. A, B, C: unadjusted OST, RFT, DST, respectively, for HPV status by smoking history (HPV negative nonsmoker (n=44), HPV negative smoker (n=178), HPV positive nonsmoker (n=52), HPV 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.
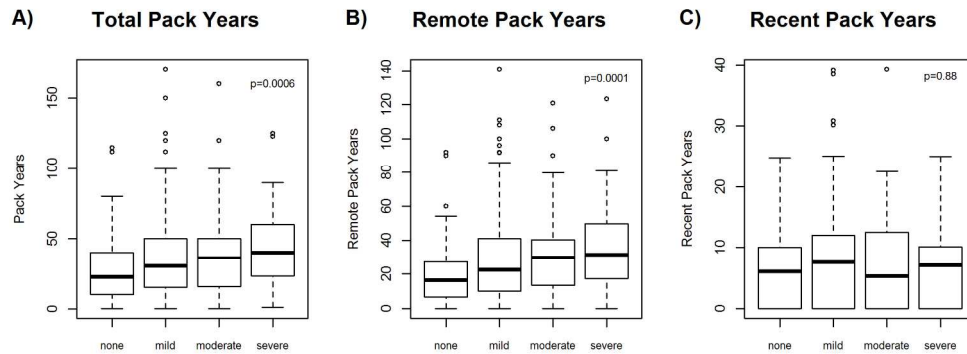203x76mm (300 x 300 DPI)

Figure 4. Pack years and comorbidity score boxplots among ever smokers. A, Overall pack years differ by comorbidity score (none, mild, moderate, severe) with an ANOVA test p-value=0.0006. B, Remote use pack years also differ by comorbidity (none, mild, moderate, severe) with an ANOVA test p-value=0.0001. C, Recent use pack years did not differ significantly by comorbidity score (none, mild, moderate, severe) with an ANOVA test p-value=0.88. Comorbidities were associated with pack years in a monotonic trend when accounting for the intensity and duration of smoking habit.
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ONLINE SUPPLEMENTARY METHODS

Recruitment. The University of Michigan's Head and Neck Specialized Program of Research Excellence (SPORE) approached every previously untreated adult HNSCC patient evaluated in the Head and Neck Oncology Program of the University of Michigan (UM; Ann Arbor, MI) Comprehensive Cancer Center for participation in our longitudinal epidemiology study. The inclusion criterion was a new primary squamous cell carcinoma of the upper aerodigestive tract. Patients with a previous diagnosis of HNSCC within the last 5 years were excluded. Patients with cutaneous squamous cell carcinoma of the head and neck, and cervical esophagus were not included. From November 2008 through July 2013, patients were prospectively screened for eligibility and 92% signed a written informed consent to participate. This unselected study population represented the 28% of incident HNSCC cases in the State of Michigan treated at UM. After consent, subjects completed questionnaires to capture demographics, epidemiologic characteristics, behavior modules, and dietary intake. Subjects completed the questionnaires annually for five years after diagnosis and completed dietary intake surveys annually for two years after diagnosis. Comprehensive smoking status data were collected including types of tobacco used, age of initiation, duration and frequency of use, age of initiation and cessation, and second hand smoke exposure. For the 30% of subjects who did not complete the baseline health survey, we attempted to abstract the information from the medical record. This study was approved by the Institutional Review Board of the University of Michigan Medical School.

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 using the Adult Comorbidity Evaluation 27 (ACE-27) which is a validated score assessing comorbidities in cancer patients [1]. Prior HNCa was defined as a previous primary head and neck tumor more than five years earlier. Median household income was collected from the 2000 Census and rounded to the nearest dollar; subjects without a valid U.S. postal address for identification in a census block were not included in the median household income calculation. Self-reported smoking history included age of initiation, cessation, and smoking status in categories never, current (or quit within 12 months of diagnosis), or former (quit over 12 months prior to diagnosis). Tobacco intensity was characterized by a combination of duration and pack years in proximity to an index date defined a number of years prior to diagnosis. Patient outcomes were analyzed based on index dates for cumulative tobacco use up to 5 years prior to diagnosis of cancer, 10 years prior to diagnosis and 20 years prior diagnosis. Supplemental Figure 1 illustrates how pack years were split into two quantities to

delineate remote and recent cigarette use based on the patient date of diagnosis, an index date of 10 years prior to diagnosis, pack years, and cigarette initiation and cessation dates. Each line begins at the date of initiation and ends at patient reported date of cessation or the date of diagnosis for current smokers. The length of the line indicates duration while the width represents intensity. Quantities are separated into remote and recent based on the index date. For example, patient 1 has quantifiable remote and recent tobacco use. Patient 2 quit smoking more than 10 years prior to diagnosis. For patient 2, recent use would be quantified as zero but remote use was more intense than patient 1 and therefore patient 2 may have a similar, if not higher, quantity for remote use than patient 1. The recent use for patient 3 who began smoking less than 10 years prior to diagnosis is less than that of patient 1.

Follow-up. Patients were followed according to NCCN guideline intervals and tumor status (recurrence, persistent disease, second primary) was updated annually during a medical record review. If subjects did not return to UM for surveillance after treatment, self-reported tumor status from yearly surveys and contact with local physicians was used. A subject was lost to follow-up if we lacked updates after contacting the subject's referring physician(s), address, telephone, and emergency contact and was then censored to the last known contact date. Deaths were confirmed through the Social Security Death Master File, yearly surveys, notification from family, and medical record reviews. Overall survival time was censored to 2/1/14 or the last known contact date for subjects with an invalid SSN and/or lost to follow-up. Tumor status was censored to the last date of each subject's annual medical record review. Persistent disease was given a follow-up time of one day for calculation in time to recurrence. For subjects with concurrent HNSCC primaries, the primary tumor of focus was the tumor with which the patient most clearly presented symptomology.

Other Tobacco Use. Lifetime second hand smoke (SHS) exposure in the home or workplace was experienced by 82% with a mean exposure of 33.0 years (SD: 17.9 years) while SHS exposure in the past seven days was reported by 28%. Ever use of marijuana was suspect to reporting bias and was not considered further in analysis. Former cigarette smokers had fewer mean total pack years (mean: 28.4 pack years, SD: 28.3 pack years) than current smokers (mean: 41.1 pack years, SD: 31.4 pack years). Smokeless tobacco was a combination of chewing tobacco and snuff use, representing the minimum age of initiation, maximum age of cessation, and a sum of duration. There was little reported use of cigar, pipe, or smokeless tobacco use among never cigarette smokers (n=25). Cigar, pipe, and smokeless tobaccos were frequently missing age of initiation and cessation. With the missing data and knowing a previous analysis noted no

increased risk of HNSCC with the added impact of cigar and pipe tobaccos among ever smokers [2], only cigarette data was considered for further analysis.

Study Population. The population was comprised mainly of oral cavity and oropharynx tumor sites (40% and 37%, respectively) and Stage IV (58%) (Table 1). The mean age at diagnosis was 61.1 years (SD: 12.0 years). Among all smokers, the mean age of initiation was 23.7 years (SD: 10.3 years); among former smokers, the mean age of cessation was 46.1 years (SD: 14.7 years). There were 31 subjects diagnosed with a prior HNSCC tumor and 151 subjects diagnosed with a prior other cancer prior to HNSCC diagnosis. The population was mainly males (73%). Most of the population was married (64%) and a significant group of subjects achieved a high school diploma or less education (39%). Household income was $49,287 (SD: $17,891). BMI included 5% underweight, 34% normal, 35% overweight, and 26% obese. All patients were evaluated by our multidisciplinary team and discussed at our tumor board where standardized treatment recommendations were made. Treatment modalities included surgery alone (25%) or surgery with adjuvant radiation or chemoradiation (20%), chemoradiation alone (40%), and radiation alone (7%). A small group (8%) received palliative treatment at baseline or their treatment is unknown. Ten percent of patients were never rendered disease free after curative treatment. Recurrence patterns were local only (25%), regional ± locoregional (36%), and distant ± locoregional (39%). Six percent of subjects developed a second primary in the HN or non-HN region after HNSCC diagnosis. Ten patients had second HNSCC primaries diagnosed concurrently or within one month of their date of diagnosis for the primary HNSCC under study; six patients were diagnosed with a HNSCC second primary while under follow-up with a median time to diagnosis of 33.2 months. Median time to non-HNSCC second primary was 9.4 months. In men over 60 years of age, there was a 16% prevalence of prostate cancer and an 8% prevalence of colon cancer. The cause of most deaths was attributed to malignancy. Median follow-up for overall survival (using the Kaplan-Meier method) was 30 months and the two year overall survival rate estimate was 78%. Among all living patients, median follow-up was 24.4 months. Median follow-up for recurrence free time was 24 months and the two year estimate of the proportion recurrence-free was 74%.

HPV Status. HPV status was determined from biopsy or surgical resection formalin-fixed, paraffin-embedded blocks for 362 subjects using previously reported PCR methods [3]. HPV status was unable to be determined for 325 subjects. Subjects with equivocal or missing HPV status were included in analysis and given an HPV status of

"unknown". Among subjects with adequate DNA or tissue specimens, 84% of oropharynx cancers were HPV(+), 12% of

oral cavity, 13% of larynx, and 25% of hypopharynx.

Statistical Analysis. Chi-square tests were performed to test differences in clinical and epidemiological

characteristics by smoking status (never, current, former). Differences in tobacco use intensity variables by

characteristics were tested with analysis of variance (ANOVA).

The Kaplan-Meier method was used to estimate rates and graphically visualize overall survival (OST), recurrence-

free (RFT), and disease specific survival (DST) time. Time-to-event outcomes were defined from diagnosis to death any

cause (OST), time to disease recurrence (RFT), or time to death from HNSCC malignancy. For patients with persistent

disease, time to recurrence was defined as one day.

The multivariable analysis excluded 4 subjects missing BMI information, resulting in a total of 683 subjects for

analysis. In Table 2 in the paper we present multivariable Cox model results in which we categorized HPV status into

three groups; positive, negative and unknown. While this method for handling missing HPV data is generally considered

preferable in terms of less bias and better efficiency than removal of subjects with unknown HPV status, it can induce

some bias in the estimates. As a sensitivity analysis we undertook alternative analyses, based on statistically justified

approaches, to handle the missing data. One method is inverse probability weighted Cox model analysis applied to the

n=361 patients without any missing data. The weight for each subject is 1/Prob(not missing), where Prob(not missing) is

derived from a logistic regression model including age, stage, disease site, year of diagnosis, history of cancer, sex,

marital status, comorbidity score and BMI as predictors. The second method is multiple imputation followed by Cox

model analyses of the n=687 subjects. The imputed values of HPV were created by the method described in Bartlett et

al [4].

Supplemental Table 1 shows the 95% confidence intervals from the multivariable Cox model results for the three

endpoints of OST, RFT and DST. We show four sets of results for each endpoint: (a) the results from Table 2 in the

paper, (b) the results from the Cox model applied to the n=361 subjects without any adjustment for missing data, (c) the

results from the inverse probability weighted Cox model applied to n=361 subjects and (d) the results after multiple

imputation. The results show similar, but not identical confidence intervals, however for nearly all factors and for all

endpoints there was considerable overlap in the confidence intervals. The strong and clear associations of the

endpoints with stage, age, history of prior HNSCC, comorbidities and HPV status are consistent across analyses. The

generally modest and not statistically significant effects of smoking after multivariable adjustment are also replicated.

All statistical analyses were conducted using SAS software, Version 9.3 of the SAS System for Windows.

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Supplemental Table 1. Hazard Ratio (95% Confidence Interval) for selected covariates from multivariable Cox model analyses with different strategies for missing HPV status. **A**=Missing Category. **B**=Omit subjects with missing HPV. **C**=Inverse Probability Weighting. **D**=Multiple Imputation.

			OST	RFT	DST
			HR (95% CI)	HR (95% CI)	HR (95% CI)
HPV Status	HPV(+) vs. HPV(–)	A	0.41 (0.22, 0.73)	0.48 (0.27, 0.84)	0.37 (0.17, 0.77)
		B	0.40 (0.20, 0.82)	0.36 (0.18, 0.74)	0.30 (0.12, 0.72)
		C	0.34 (0.16, 0.72)	0.34 (0.16, 0.74)	0.24 (0.09, 0.63)
		D	0.38 (0.20, 0.72)	0.37 (0.19, 0.72)	0.25 (0.10, 0.63)
Smoking Status	never vs. ever	A	0.76 (0.45, 1.28)	0.95 (0.59, 1.53)	0.81 (0.42, 1.54)
		B	0.93 (0.47, 1.85)	1.04 (0.54, 1.98)	1.01 (0.44, 2.30)
		C	0.91 (0.43, 1.90)	1.16 (0.58, 2.33)	0.93 (0.37, 2.29)
		D	0.81 (0.48, 1.36)	1.14 (0.70, 1.87)	0.87 (0.45, 1.68)
Cigarette Packyears	10 unit increase	A	1.05 (0.99, 1.11)	1.05 (0.98, 1.12)	1.04 (0.96, 1.13)
		B	1.03 (0.95, 1.11)	1.03 (0.95, 1.13)	1.05 (0.94, 1.16)
		C	1.04 (0.95, 1.13)	1.06 (0.97, 1.16)	1.06 (0.95, 1.18)
		D	1.05 (0.98, 1.11)	1.05 (0.99, 1.12)	1.05 (0.96, 1.14)
Age	10 year increase	A	1.30 (1.12, 1.51)	1.16 (1.00, 1.35)	1.12 (0.93, 1.36)
		B	1.50 (1.21, 1.86)	1.24 (0.99, 1.54)	1.22 (0.94, 1.60)
		C	1.58 (1.25, 1.99)	1.28 (1.01, 1.63)	1.32 (0.98, 1.78)
		D	1.30 (1.11, 1.51)	1.15 (0.98, 1.34)	1.10 (0.90, 1.33)
Stage	IV vs. I	A	7.20 (3.29, 15.73)	5.03 (2.50, 10.11)	10.54 (3.26, 34.05)
		B	5.20 (2.01, 13.48)	3.22 (1.33, 7.80)	8.15 (1.89, 35.15)
		C	6.27 (2.14, 18.33)	3.30 (1.28, 8.52)	10.28 (1.81, 58.51)
		D	7.06 (3.22 (15.46)	5.01 (2.49, 10.08)	10.58 (3.26, 34.28)
	III vs. I	A	5.02 (2.14, 11.80)	3.34 (1.53, 7.31)	6.58 (1.87, 23.19)
		B	4.58 (1.61, 13.04)	2.62 (0.98, 7.04)	6.84 (1.46, 32.18)
		C	6.02 (1.85, 19.55)	3.06 (1.06, 8.85)	9.37 (1.49, 58.99)
		D	4.82 (2.03, 11.45)	3.33 (1.51, 7.33)	6.88 (1.94, 24.38)
	II vs. I	A	3.24 (1.31, 8.02)	1.40 (0.55, 3.54)	2.37 (0.56, 9.97)
		B	2.42 (0.78, 7.53)	1.01 (0.30, 3.39)	2.04 (0.34, 12.42)
		C	3.11 (0.90, 10.73)	1.01 (0.28, 3.62)	3.82 (0.54, 26.77)
		D	3.18 (1.28, 7.90)	1.35 (0.53, 3.42)	2.33 (0.55, 9.85)
Disease Site	OP vs. OC	A	0.72 (0.47, 1.11)	0.81 (0.52, 1.25)	0.72 (0.41, 1.26)
		B	0.93 (0.47, 1.87)	1.26 (0.62, 2.56)	0.99 (0.41, 2.35)
		C	0.95 (0.45, 2.02)	1.26 (0.58, 2.75)	1.10 (0.43, 2.81)
		D	0.98 (0.58, 1.66)	1.15 (0.66, 2.03)	1.14 (0.57, 2.29)
	LA vs. OC	A	0.52 (0.33, 0.82)	0.66 (0.42, 1.04)	0.62 (0.35, 1.08)
		B	0.68 (0.38, 1.20)	0.71 (0.39, 1.30)	0.57 (0.27, 1.17)
		C	0.60 (0.31, 1.17)	0.71 (0.36, 1.41)	0.51 (0.22, 1.22)
		D	0.55 (0.34, 0.86)	0.69 (0.43, 1.09)	0.64 (0.36, 1.13)
	HP vs OC	A	0.76 (0.35, 1.66)	1.11 (0.53, 2.33)	0.92 (0.37, 2.31)
		B	1.63 (0.66, 4.07)	2.67 (1.05, 6.77)	1.66 (0.55, 4.99)
		C	2.12 (0.87, 5.16)	3.60 (1.42, 9.12)	2.73 (0.98, 7.55)
		D	0.84 (0.38, 1.85)	1.19 (0.56, 2.52)	1.04 (0.41, 2.66)
Comorbidities	mild vs. none	A	1.63 (1.00, 2.67)	1.27 (0.81, 2.01)	1.35 (0.75, 2.41)
		B	1.63 (0.83, 3.21)	1.24 (0.67, 2.27)	1.74 (0.78, 3.88)
		C	2.03 (0.95, 4.34)	1.17 (0.60, 2.26)	1.97 (0.80, 4.84)
		D	1.64 (0.99, 2.70)	1.26 (0.79, 2.02)	1.34 (0.74, 2.43)
	moderate vs. none	A	2.66 (1.58, 4.47)	1.69 (1.00, 2.87)	1.81 (0.92, 3.54)
		B	2.80 (1.32, 5.94)	1.43 (0.70, 2.93)	2.56 (1.03, 6.35)
		C	3.23 (1.41, 7.42)	1.43 (0.66, 3.07)	2.76 (1.01, 7.51)
		D	2.20 (1.24, 3.89)	1.59 (0.92, 2.73)	1.77 (0.89, 3.53)
	severe vs. none	A	2.69 (1.38, 5.25)	1.95 (1.01, 3.78)	2.72 (1.21, 6.12)
		B	2.98 (1.15, 7.74)	1.81 (0.72, 4.56)	2.45 (0.73, 8.17)
		C	2.49 (0.83, 7.44)	1.48 (0.54, 4.08)	1.65 (0.41, 6.69)
		D	2.70 (1.38, 5.30)	1.93 (0.99, 3.75)	2.54 (1.11, 5.79)
BMI (unit=1)	1 unit increase	A	0.96 (0.93 ,0.99)	0.98 (0.95, 1.00)	0.97 (0.93, 1.00)
		B	0.97 (0.94 ,1.01)	1.00 (0.97, 1.04)	1.00 (0.95, 1.04)
		C	0.98 (0.94, 1.03)	1.01 (0.97, 1.05)	1.01 (0.96, 1.07)
		D	0.97 (0.94, 0.99)	0.98 (0.95, 1.01)	0.97 (0.93, 1.01)
Prior HNCa	yes vs. no	A	2.31 (1.25, 4.26)	2.73 (1.54, 4.84)	2.77 (1.31, 5.87)
		B	3.50 (1.24, 9.89)	3.80 (1.40, 10.27)	4.80 (1.52, 15.09)
		C	2.72 (1.11, 6.68)	4.09 (1.79, 9.31)	4.04 (1.46, 11.18)
		D	2.28 (1.19, 4.38)	2.60 (1.42, 4.78)	2.69 (1.19, 6.09)
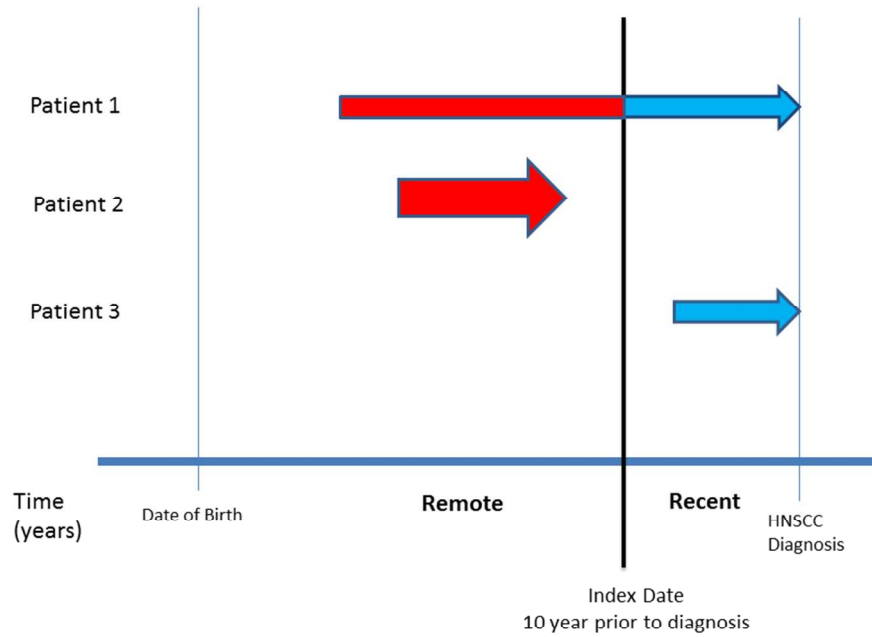
Supplemental Figure 1. Indexing cumulative tobacco use models by proximity to HNSCC diagnosis. Each line begins at the date of initiation and ends at self-reported date of cessation or the date of diagnosis for current smokers. The length of the line indicates duration while the width represents intensity. Quantities are separated into remote and recent based on the index date.

254x190mm (96 x 96 DPI)