Evolving Association Between Smoked Tobacco Use and Incidence of Glottic Squamous Cell Carcinoma

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Abstract

Introduction: Glottic squamous cell carcinoma has historically had a stringent association with former or active smoked tobacco use. Recent studies meant to investigate the incidence of p16 positivity and oncogenic HPV DNA in laryngeal cancer specimens have stipulated an alternative etiology in a subset of cases. We aimed to determine an updated prevalence of non-smokers among patients diagnosed with glottic cancer contingent on a single-institution's experience.

Methods: Patients diagnosed with glottic squamous cell carcinoma at the authors' institution were identified based on retrospective chart review. Smoking status (never versus current/former smoker), treatment modality, TNM tumor staging, and recurrence data, in addition to standard clinicodemographic information, were recorded. Discrete timeframes were defined (2004-2009, 2010-2015, 2016-2022) to analyze temporal changes in patient smoking status.

Results: Study included 464 patients diagnosed between 2004-2022 with glottic cancer and with known smoking history. Total of 125 patients (26.94%) of patients were non-smokers. No significant association was identified between smoking status and T classification (p=0.673), year of diagnosis (p=0.485), gender (p=0.13), and reflux history (0.94). Non-smokers with glottic cancer were diagnosed at a younger age (61.88 vs. 64.84 years, p=0.021).

Conclusions: A significant proportion (26.94%) of glottic cancer patients were non-smokers; most hallmark clinicodemographic features were similar between non-smokers and current/former smokers. These findings should be considered carefully by clinicians when considering the probability of underlying malignancy among patients with laryngeal complaints and bolster future investigations to identify the precise role of HPV in glottic carcinogenesis.

Introduction

Glottic squamous cell carcinoma comprises approximately 60% of new laryngeal cancer diagnoses, and is associated with the highest 5-year relative survival rate (77%) across stages among the three laryngeal subsites.[1] Smoked tobacco use has historically been considered the single-most significant risk factor for glottic carcinogenesis; in fact, the proportion of larynx cancer diagnoses empirically associated with current or former tobacco use has been reported to be as high as 98%.[2] Although an etiologic shift in oropharyngeal cancer accounting for oncogenic HPV subtypes is well-recognized, an updated analysis of clinicodemographic trends in laryngeal cancer is needed to accommodate for significant changes in tobacco use over the course of the last several decades. Though studies exploring the potential association between HPV and laryngeal carcinogenesis have been published[3], canonical molecular perturbations empirically correlated with HPV-related tumorigenesis have not been well-established in laryngeal tumors. However, a significant change in tobacco-use trends among new glottic cancer diagnoses might corroborate the need for a more deliberate investigation into evolving mechanistic change in laryngeal tumorigenesis.

Methods and Materials

A retrospective review of all patients seen with a diagnosis of laryngeal cancer at the Massachusetts General Hospital Voice Center between 2004 and 2022 was performed. Only patients with a diagnosis of glottic squamous cell carcinoma and with documented smoking status were included. Clinicodemographic parameters accounted for in our retrospective chart review included smoking status recorded as a binary variable (never versus current/former), primary treatment modality, TNM classification, age, and gender. Discrete timeframes were defined (2004-2009, 2010-2015, 2016-2022) in order to elucidate relative changes in historical smoking trends. Differences in clinicodemographic characteristics between never smokers and current or former smokers were assessed via two-sample T-tests for continuous variables, and chi-squared tests for categorical variables. Differences in proportions of never smokers versus former/current smokers by year range were assessed via the chi-squared test. A *p*-value of <0.05 was considered to be the threshold for statistical significance. Other variables of interest that would otherwise be important considerations in evaluating an alternative phenotype of glottic cancer, including tumor grade and HPV status, could not be included in the present analysis due to the significant proportion of missing data.

Results

A total of 426 patients seen at the MGH Voice Center with a glottic squamous cell carcinoma diagnosis and documented smoking history were included in the present analysis. A total of 125 patients (26.94% of all patients with known smoking status) were documented as being never-smokers. No significant differences in clinicodemographic features, including T classification at diagnosis, gender, or year of diagnosis (Figure 1), were identified between smokers and never-smokers. Never-smokers were marginally, but statistically significantly, younger at diagnosis (61.88 versus 64.84 years).

Table 1. Baseline characteristics of the study cohort differentiating between smokers versus non-smokers among glottic cancer patients.

Parameter	Never Smoker (n=125)	Current or Former Smoker (n=339)	P-Value
Age, mean (SD)	61.88 (13.33)	64.84 (12.15)	***0.021***
Male sex, n (%)	112 (89.6%)	284 (83.8%)	0.13
T classification, n (%)			0.673
T1	55 (44%)	141 (41.6%)	
T2	33 (26.4%)	97 (28.6%)	
T3	7 (5.6%)	10 (2.95%)	
T4	3 (2.4%)	10 (2.95%)	
Unknown/Missing Documentation	27 (21.6%)	81 (23.9%)	
Race, n (%)			0.252
White	107 (85.6%)	296 (87.32%)	
Other	11 (8.80%)	27 (7.96%)	
Declined/Unknown	7 (5.6%)	16 (4.72%)	
Married, n (%)	92 (73.6%)	228 (67.26%)	0.19
History of reflux, n (%)	44 (35.2%)	118 (34.81%)	0.937
Date range, n (%)*			0.2
2004-2009	37 (26.06%)	105 (73.94%)	
2010-2015	57 (31.15%)	126 (68.85%)	
2016-2022	31 (22.30%)	108 (77.70%)	

**Frequencies listed as percentages for this parameter represent in-row, versus in-column, frequencies.*

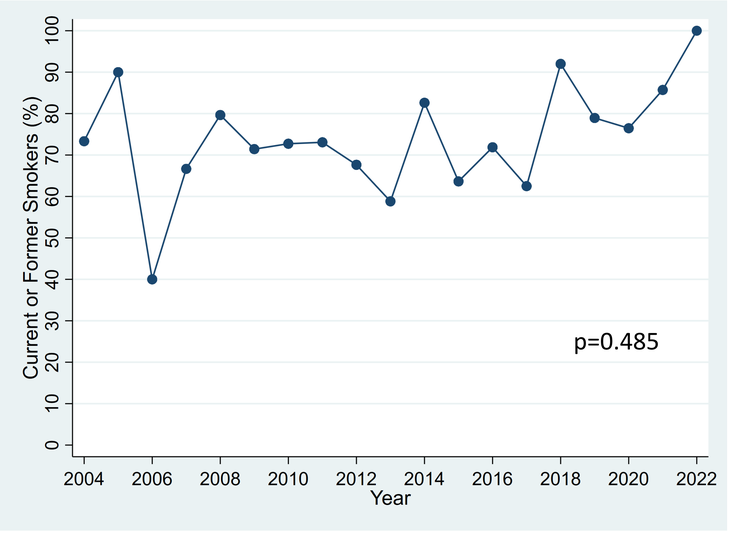

Figure 1. Time-series graph delineating proportions of current or formers smokers among glottic cancer patients by year. P-value corresponds to logistic regression assessing correlation between year of diagnosis and smoking history.

Discussion

Glottic cancer has historically been correlated with tobacco use as a functional pre-requisite for clinical diagnosis. We demonstrate in this single-institution study a significant proportion (26.84%) of patients with glottic cancer were never-smokers, a statistic that stands in stark contrast to historical trends. Information pertaining to histopathologic subtype, grade, and HPV status (inferred either via ISH or p16 positivity) was only sparsely available, making any assertions regarding alternative mechanisms of tumorigenesis impossible. This trend (albeit at a single institution), however, suggests that an updated understanding of possible mechanistic evolution in glottic carcinogenesis might be warranted. Of note, no difference in proportions of never-smokers over the 18 year study period were identified (Figure 1), suggesting that the relative over-representation of never smokers in the study cohort may very well be a reflection of a unique patient population treated at the MGH Voice Center. Future investigations, including institutions from other regions, accounting for additional patient-centric and disease-specific data (e.g. grade, recurrence, disease-specific survival) are necessary to corroborate the findings in the present study.

Conclusions

The rate of current or historical tobacco use among glottic cancer patients may be changing, as suggested by this single-institution study. Future multi-institutional studies are necessary to corroborate the trend identified in the analysis herein, and to appreciate differentiating molecular characteristics between glottic tumors derived from smokers and non-smokers. Moreover, rates of recurrence and disease-specific survival should be considered as outcomes to understand the clinical implications of this possible demographic shift among glottic cancer patients.

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