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INCREASING PREVALENCE OF HPV-POSITIVE OROPHARYNGEAL CANCERS AMONG OLDER ADULTS

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Abstract

Background—The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is increasing among older adults. It is unknown whether these trends are explained by human papillomavirus (HPV) and if HPV-related tumors remain associated with improved prognosis among older patients.

Methods—In a retrospective study of OPSCCs diagnosed from 1995–2013 at two NCCN-designated Cancer Centers, p16 immunohistochemistry and in-situ hybridization (ISH) for HPV16, high-risk DNA and/or E6/E7 RNA was performed. Median age at diagnosis was

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compared by p16 and ISH tumor status. Trends in age were analyzed using non-parametric trends. Survival was analyzed using Kaplan-Meier method and Cox proportional hazards models.

Results—Among 239 patients, 144 (60%) were p16-positive. During 1998–2013, median age increased among p16-positive (p_{trend}=0.01), but not p16-negative (p_{trend}=0.71) patients. The median age of p16-positive patients increased from 53 (interquartile range [IQR] 45–65, 1995–2000) to 58 (IQR 53–64, 2001–2013). Among patients ≥65 years old, the proportion of OPSCCs that were p16-positive increased from 41% during 1995–2000 to 75% during 2007–2013 (p_{trend}=0.04). Among all age groups, including older patients, p16-positive tumor status conferred improved overall survival compared with p16-negative.

Conclusions—The median age of diagnosis of HPV-related OPSCC is increasing as the proportion of OPSCCs caused by HPV rises among older adults. The favorable survival conferred by HPV-positive tumor status persists in older adults.

Keywords

HPV; OPSCC; HNSCC; elderly; ISH; p16

Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is rising in the United States and other developed countries, and this is driven by human papillomavirus (HPV).[1–3] OPSCC incidence is increasing most dramatically among younger age groups[4] consistent with the recognized demographics of the disease. Past research showed that patients with HPV-positive OPSCC (HPV-OPSCC) had a lower median age at diagnosis than HPV-negative OPSCC.[5,6] Indeed, earlier studies showed that the median age of OPSCC diagnosis decreased during 1973–2004[4] and 1977–2012,[7] likely due to the growing proportion of HPV-positive OPSCCs. However, a recent population-based study reported an increase in OPSCC incidence among adults over age 65 in the United States between 2000 to 2012, with a concomitant decrease in non-oropharyngeal head and neck cancer among adults of the same age.[8] This suggests the increase in OPSCC incidence among older adults may be driven by HPV, although this has not been well studied.

HPV-positive tumor status is a well-established marker of improved prognosis for OPSCC both at the time of diagnosis and disease recurrence.[9–13] Of note, age is also an important independent marker of prognosis for most cancers, including OPSCC.[14,15] Therefore, we were interested in exploring whether the prevalence of HPV-positive tumors is increasing, and whether the prognostic advantage of HPV is retained among older patients.

Materials and Methods

This was a retrospective analysis of squamous cell carcinomas of the oropharynx diagnosed between 1995 and 2013 at two NCCN-designated Comprehensive Cancer Centers, the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital (Baltimore, MD) and the University of California San Francisco Helen Diller Family Comprehensive Cancer Center (San Francisco, CA). This analysis focuses on a subset of head and neck squamous cell carcinoma cases previously described[13] in a study enriched for female and non-White

participants. Medical record abstraction was performed to summarize clinical variables including age, sex, race/ethnicity, ever tobacco use, and to confirm tumor sites and American Joint Committee on Cancer (AJCC) 7th edition tumor and nodal stage.

Testing Methods

Tumor testing was performed centrally in 2014 and 2015 and was interpreted by a single pathologist (W.H.W.). Sampling and testing methods have been previously described.[16] P16 immunohistochemistry was performed (MTM Laboratories, Heidelberg, Germany) and p16 expression was considered positive if ≥70% strong and diffuse nuclear and cytoplasmic staining pattern was observed. In situ hybridization (ISH) was performed for HPV16 DNA (Dako GenPoint, Carpinteria, CA). In cases that were p16 positive and HPV16 ISH negative, either high risk HPV DNA (Dako GenPoint) or HPV E6/E7 RNA ISH (RNAscope®, Advanced Cell Diagnostics, Hayward, CA) was performed. Given that p16 is now considered to be a surrogate marker for HPV-positive tumor status[6,17,18] and will be used to establish HPV tumor status in the AJCC Cancer Staging Manual 8th edition,[19] the primary tumor outcome was defined using p16 status. Secondary analyses were also conducted using ISH tumor status, which is previously described.[13]

Statistical Analysis

Descriptive statistics were reported at N (%) or median (interquartile range [IQR]). Age at diagnosis was categorized into three groups: 18–54 (‘younger’), 55–64 (‘middle-aged’), and ≥65 years of age (‘older’). Demographic and disease-related characteristics were compared across age groups using chi-squared tests. Race/ethnicity was categorized as White non-Hispanic (NH) (hereafter referred to as ‘White’), Black NH (‘Black’), and Asian NH or Hispanic any race (‘Asian/Hispanic’). Asian NH and Hispanic any race were combined due to small numbers in each. For some analyses, trends over time were explored by comparing consecutive calendar periods defined as 1995–2000, 2001–2006, and 2007–201*3.* Age group cutoffs were based on the age distribution of the available study population, to retain balanced numbers of study participants across categories. Trends in age and prevalence of HPV-positive tumor status across calendar periods were determined using non-parametric tests of trends across ordered groups. Linear regression models were also used to analyze change (β) in mean age at diagnosis by calendar year. The effect of HPV tumor status on overall survival (OS) was evaluated using Kaplan-Meier and Cox proportional hazards methods. In multivariate analysis, hazard ratios (HRs) were adjusted for sex, race, ever tobacco use, AJCC Cancer Staging Manual 7th edition tumor stage and nodal stage. Statistical significance refers to two-sided p-value <0.05.

Results

This study population was comprised of 239 patients with OPSCC. Most patients were male (67%), ever tobacco users (64%), p16-positive (n=144, 60%) and ISH-positive (n=134, 56%). The three age groups included 98 ‘younger’ (ages 18–54 years, n=98), 83 ‘middle-aged’ (ages 55–64, n=83), and 58 ‘older’ (age ≥65, n=58) adults. Patient characteristics were statistically similar across age groups (Table 1).

Trends in Prevalence of HPV-positive tumors among OPSCCs

Among all age groups including older adults, the proportion of p16-positive tumors increased over the study period (Figure 1). In younger patients, the prevalence of p16-positive tumors increased over time from 50% to 61%, then 70% during 1995–2000, 2001–2006, and 2007–2013, respectively (p_{trend}= 0.10). In middle-aged patients, significant increases were observed in the proportion of p16-positive tumors, from 24% to 77% (p_{trend}<0.001). Increases were similarly notable among patients over 65, with only 41% of OPSCCs being p16-positive in 1995–2000, increasing to 62% and 75% in 2001–2006 and 2007–2013 (p_{trend}=0.04), respectively. Similar increases in prevalence among all age groups were observed when considering ISH-positive tumor status.

Trends in Median Age at Diagnosis of OPSCC over Time

The median age at diagnosis was compared across time periods for p16-positive and p16-negative OPSCC. Median age at diagnosis for patients with p16-positive OPSCC increased over time from 53 (IQR 45–65) to 57 (IQR 50–63), and then 58 (IQR 53–64) between 1995–2000, 2001–2006, and 2007–2013, respectively (1995–2013 p_{trend}=0.10, 1998–2013 p_{trend}=0.01). A similar increase in age was observed among ISH-positive patients (1995–2013 p_{trend}=0.14, 1998–2013 p_{trend}=0.04). In contrast, the median age at diagnosis for p16-negative OPSCC (1995–2013 p_{trend}=0.54, 1998–2013 p_{trend}=0.71) and ISH-negative OPSCC (1995–2013 p_{trend}=0.80, 1998–2013 p_{trend}=0.72) remained stable over time.

Trends in the mean age at diagnosis over time were also explored (Figure 2). Among p16-positive OPSCC, age at diagnosis decreased by 3 years of age for each calendar year during 1995–2000 (β= −3.0, p=0.07). A non-significant increase in age (β= 1.2, p=0.30) during 2001–2006 was followed by a dramatic and significant increase of the mean age by 2 years for every calendar year (β= 2.0, p=0.01) during 2007–2013 (Figure 2a). Age at diagnosis of p16-negative OPSCC remained stable over time (Figure 2b; p-values>0.30). Similar trends were observed when considering tumor ISH status.

Survival Differences by HPV Tumor Status and Age

Median follow up time was 3.5 years (IQR 1.3–6.9). By Kaplan-Meier analysis, p16-positive OPSCC had improved overall survival (OS) as compared with p16-negative patients among all age groups (5-year OS: 77% vs. 40%, p<0.001). Overall survival was better for p16-positive patients in every age group including: younger (5-year OS: 77% vs. 42%; HR 0.43, 95% CI 0.22–0.83; p=0.01), middle-aged (5-year OS: 87% vs. 40%; HR 0.18, 95%CI 0.08–0.42; p<0.001) and older (5-year OS: 59% vs. 34%; HR 0.45, 95%CI 0.23–0.89; p=0.02) patients (Figure 3; Table 2). After controlling for other factors, p16 conferred substantially improved survival within the entire study population (adjusted hazard ratio [aHR] 0.31, 95% CI 0.19–0.51, p<0.001), among younger (aHR 0.31, 95% CI 0.13–0.73, p=0.01), and middle-aged (aHR=0.09, 95% CI 0.01–0.60, p=0.01) patients. Among older adults, p16-positive tumor status was non-significantly associated with improved survival (aHR=0.46, 95% CI 0.17–1.27, p=0.14). The survival benefit of p16 tumor status was possibly less among the older age group, but this difference was not statistically significant ($p_{interaction\ age\ and\ p16}$ =0.24). Exploring only p16-negative OPSCC, overall survival at five years was similar in the younger, middle-aged and older adults (5-year OS: 42%, 95% CI

24–60% vs. 40%, 95% CI 22–58% vs. 34%, 95% CI 14–56%; p=0.34). Findings were similar when ISH tumor status was considered.

Discussion

This is the first study to demonstrate that the observed rise in OPSCC among older adults is driven by increased prevalence of p16-positive tumors (from here forward, HPV), indicating that HPV-OPSCC is no longer a disease of young individuals. Notably, the age at diagnosis of HPV-OPSCC has increased in recent years, and HPV remains a biomarker of improved prognosis among older patients.

The relatively younger median age (53 years) at diagnosis of HPV-OPSCC in the earliest calendar period, 1995–2000, is consistent with the average age reported in the literature.[5,6] This has led to the conclusion that HPV-OPSCC patients are younger than their HPV-negative counterparts. Several earlier epidemiologic studies reported a dramatic increase in incidence of OPSCC among younger age groups compared with middle and older age groups across time periods including 1973–1995,[20] 1974–2004[15] and 1983–2002.[1] This trend appeared to arise from a combination of the younger age of diagnosis for HPV-positive OPSCC (relative to HPV-negative OPSCC) and increasing incidence of HPV-OPSCC overall. In SEER data during 1973–2004, the median age of diagnosis of OPSCC declined by 0.5 years per decade ($p<0.001$).[4] Similar findings have been reported in some other countries. For example, in Denmark the average age of diagnosis with OPSCC decreased over time during 1977–2012.[7]

More recent analyses of SEER data, however, have reported an increase in OPSCC incidence in older adults as well.[8,21] Although incidence in this age group had been stable for 25 years (1975–2000), there was a significant increase in incidence of OPSCC among older adults in the United States between 2000–2012.[8] Consistent with these incidence trends, the increase in age observed in the present analysis appears to be driven by the most recent calendar period (2007–2013). Although it has been recently hypothesized that the prevalence of HPV-related tumors have increased among older adults,[8] this was not established prior to the current study. The present analysis, using gold standard tumor detection methods and centralized testing, demonstrates an increasing proportion of OPSCC are caused by HPV in all age groups, including older adults. This suggests that the recent increase in OPSCC incidence in older adults is indeed due to HPV.

This is the first study to identify that the median age of HPV-OPSCC patients is now increasing. This finding presents a paradigm shift; HPV-OPSCC is no longer a disease solely of younger patients, but one that affects adults across the age spectrum. Previous literature has focused on the distinct demographic characteristics of HPV-positive OPSCC patients. Our data, in the context of recent reports regarding incidence trends, suggest that the clinical presentation of OPSCC is evolving. Reasons for the increase in incidence of OPSCC among older patients and increase in prevalence of HPV-positive tumors among older (and younger) patients were not explored in the present analysis, but may potentially be explained by a cohort effect.

Consistent with prior literature, HPV-positive tumor status was an independent marker of improved overall survival.[13] After stratification by age group, HPV-positive tumor status remains associated with a reduction in risk of death for younger, middle-age, and older age groups. The magnitude of the survival benefit conferred by HPV-positive tumor status appears to possibly be reduced for older patients as compared with either younger or middle-aged patients. The magnitude of the reduction in risk of death conferred by HPV-positive tumor status among older patients in this study (aHR=0.46) is similar to that observed in a recent Princess Margaret Cancer Centre analysis restricted to patients greater than 70 years of age (HR=0.58).[22] This finding may reflect competing risks for mortality among older patients. Since information on disease-specific survival was not available for all patients, this outcome could not be explored in this analysis, but should be part of future study designs.

The observation that survival differences may be attenuated in older patients is of clinical importance. Treatment de-intensification is the focus of present clinical trials, in an attempt to reduce the long-term morbidity for younger and middle-aged OPSCC patients who are expected to have long-term survival.[23] However, acknowledgement of the worse overall survival of older compared with younger patients and potentially reduced prognostic benefit of HPV-positivity raises the question whether such an approach should be adopted for older patients.

Toxicities of multi-modality treatment are thought to be increased among older patients.[24] It is suspected that older patients have a lower threshold for toxicities and a resultant narrower therapeutic ratio for treatment, and indeed this demographic tends to receive less treatment.[25,26] However, patients over age 65 are underrepresented in clinical trials.[27] A recent meta-analysis showed that the few studies examining treatment outcomes by age have mixed findings. The majority were unable show a significant difference in overall survival with each treatment modality by chronological age, yet substantive correlation with patient functional status instead.[28] Older adults require more supportive care[29] and have unique psychosocial experiences.[30] They may potentially have distinct goals of treatment in the context of aging, a greater number of comorbidities,[31,32] and a shorter post-treatment life expectancy. Therefore, understanding the goals of treatment in this growing population emerges as an important consideration. Additional prospective trials are needed to delineate the response to therapy and optimum treatment paradigms for older adults with HPV-OPSCC.

This study had several benefits and limitations. The current analysis provides a large sample from two cancer centers spanning eighteen years with centralized testing. Limitations include the retrospective nature, the potential decreased ability to generalize trends at these centers to the US population, and absence of treatment data and disease-specific survival. We acknowledge that the competing risks of mortality for older patients are greater than for younger patients; thus, a limitation of this analysis is that conclusions are based on overall survival.

In summary, HPV-OPSCC should no longer be considered a disease associated with younger patients. The age at diagnosis of HPV-OPSCC has increased over recent years whereas that of HPV-negative OPSCC has remained stable. This reflects the rise in HPV-positive OPSCC

in all age groups, including older adults, over time, and establishes a basis for additional population-based studies. Lastly, the survival benefit conferred by HPV-positive tumor status as determined by p16 and ISH appears to endure, with increasing age at diagnosis, although it is possible this benefit may attenuate with increasing age. Further investigation is needed to assess this possible trend. We emphasize the importance of including older patients in clinical trials and anticipating the needs unique to this new and growing older demographic. Our results should inform allocation of health care spending as well as future research directions.

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References

1. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol. 2013; 31(36):4550–4559. [PubMed: 24248688]
2. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011; 29(32):4294–4301. [PubMed: 21969503]
3. Rettig E, Kiess AP, Fakhry C. The role of sexual behavior in head and neck cancer: implications for prevention and therapy. Expert Rev Anticancer Ther. 2015; 15(1):35–49. [PubMed: 25193346]
4. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol. 2008; 26(4):612–619. [PubMed: 18235120]
5. Worden FP, Kumar B, Lee JS, et al. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: Response and survival positively associated with HPV16 copy number. J Clin Oncol. 2008; 26(19):3138–3146. [PubMed: 18474879]
6. Ang KK, Harris J, Wheeler R, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. N Engl J Med. 2010; 363:24–35. [PubMed: 20530316]
7. Fakhry C, Andersen KK, Eisele DW, Gillison ML. Oropharyngeal cancer survivorship in Denmark, 1977–2012. Oral Oncol. 2015; 51:982–984. [PubMed: 26319353]
8. Zumsteg ZS, Cook-Wiens G, Yoshida E, et al. Incidence of Oropharyngeal Cancer Among Elderly Patients in the United States. JAMA Oncol. 2016; 2(12):1617–1623. [PubMed: 27415639]
9. Fakhry C, Zhang Q, Felix Nguyen-Tan P, et al. Human Papillomavirus and Overall Survival After Progression of Oropharyngeal Squamous Cell Carcinoma. J Clin Oncol. 2014; 32:3365–3373. [PubMed: 24958820]
10. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008; 100:261–269. [PubMed: 18270337]
11. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. J Clin Oncol. 2015; 33(29):3235–3242. [PubMed: 26351338]
12. Fakhry C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancers. J Clin Oncol. 2006; 24(17):2606–2611. [PubMed: 16763272]
13. Fakhry C, Westra WH, Wang SJ, et al. The Prognostic Role of Sex, Race, and Human Papillomavirus in Oropharyngeal and Nonoropharyngeal Head and Neck Squamous Cell Cancer. Cancer. 2017; 123(9):1566–1575. [PubMed: 28241096]
14. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008; 100(4):261–269. [PubMed: 18270337]

15. Nguyen NP, Ly BH, Betz M, Vinh-Hung V. Importance of age as a prognostic factor for tonsillar carcinoma. Ann Surg Oncol. 2010; 17(10):2570–2577. [PubMed: 20559738]
16. Rooper LM, Gandhi M, Bishop JA, Westra WH. RNA in-situ hybridization is a practical and effective method for determining HPV status of oropharyngeal squamous cell carcinoma including discordant cases that are p16 positive by immunohistochemistry but HPV negative by DNA in-situ hybridization. Oral Oncol. 2016; 55:11–16. [PubMed: 27016012]
17. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide: A Systematic Review. Cancer Epidemiol Biomarkers Prev. 2005; 14(2):467–475. [PubMed: 15734974]
18. Rischin D, Young RJ, Fisher R, et al. Prognostic Significance of p16 INK4A and Human Papillomavirus in Patients With Oropharyngeal Cancer Treated on TROG 02.02 Phase III Trial. J Clin Oncol. 2010; 28:4142–4148. [PubMed: 20697079]
19. Amin, MB., Edge, SB., Greene, FL., et al. AJCC Cancer Staging Manual. 8. New York: Springer; 2017.
20. Frisch M, Hjalgrim H, Jaeger AB, et al. Changing Patterns of Tonsillar Squamous Cell Carcinoma in the United States. Canc Causes Contr. 2000; 11:489–495.
21. Patel MA, Blackford AL, Rettig EM, Richmon JD, Eisele DW, Fakhry C. Rising population of survivors of oral squamous cell cancer in the United States. Cancer. 2016; 122(9):1380–1387. [PubMed: 26950886]
22. Caparrotti F, Bratman SV, Ringash J, et al. Exploring the Impact of Human Papillomavirus Status, Comorbidity, Polypharmacy, and Treatment Intensity on Outcome of Elderly Oropharyngeal Cancer Patients Treated With Radiation Therapy With or Without Chemotherapy. Int J Radiat Oncol Biol Phys. 2017; 98(4):858–867. [PubMed: 28258893]
23. Bhatia A, Burtness B. Human papillomavirus-associated oropharyngeal cancer: Defining risk groups and clinical trials. J Clin Oncol. 2015; 33(29):3243–3250. [PubMed: 26351343]
24. Daly ME, Lau DH, Farwell DG, et al. Feasibility and toxicity of concurrent chemoradiation for elderly patients with head and neck cancer. American J Otolaryngol. 2013; 34:631–635.
25. VanderWalde N, Meyer A-M, Liu H, Tyree S, et al. Patterns of Care in Older Patients with Squamous Cell Carcinoma of the Head and Neck: A Surveillance Epidemiology and End Results-Medicare Analysis. J Geriatr Oncol. 2014; 4(3):262–270.
26. Camilon PR, Stokes WA, Nguyen SA, Lentsch EJ. Are the elderly with oropharyngeal carcinoma undertreated? Laryngoscope. 2014; 124(9):2057–2063. [PubMed: 24591144]
27. Pignon J-P, Le Maître A, Maillard E, Bourhis J, Group C. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients on behalf of the MACH-NC. Radiother Oncol. 2009; 92:4–14. [PubMed: 19446902]
28. VanderWalde NA, Fleming M, Weiss J, Chera BS. Treatment of older patients with head and neck cancer: a review. Oncologist. 2013; 18(5):568–578. [PubMed: 23635557]
29. Michal S, Adelstein D, Rybicki L, et al. Multi-agent concurrent chemoradiotherapy for locally advanced head and neck squamous cell cancer in the elderly. Head Neck. 2012; 34(8):1147–1152. [PubMed: 22021098]
30. D'Souza G, Zhang Y, Merritt S, et al. Patient experience and anxiety during and after treatment for an HPV-related oropharyngeal cancer. Oral Oncol. 2016; 60(2016):90–95. [PubMed: 27531878]
31. Syrigos KN, Karachalios D, Karapanagiotou EM, Nutting CM, Manolopoulos L, Harrington KJ. Head and neck cancer in the elderly: An overview on the treatment modalities. Cancer Treat Rev. 2009; 35(3):237–245. [PubMed: 19100689]
32. Sanabria A, Carvalho AL, Vartanian JG, Magrin J, Ikeda MK, Kowalski LP. Comorbidity is a prognostic factor in elderly patients with head and neck cancer. Ann Surg Oncol. 2007; 14(4): 1449–1457. [PubMed: 17235712]

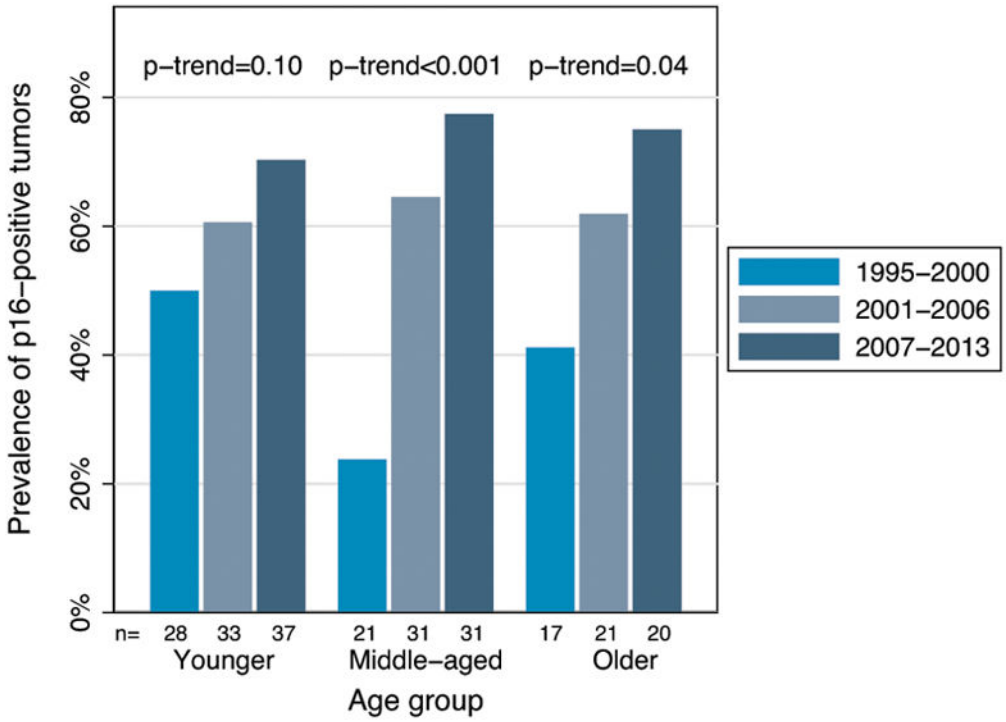

Figure 1.
Prevalence of p16-positive oropharyngeal tumors by age group and calendar period during 1995–2013.

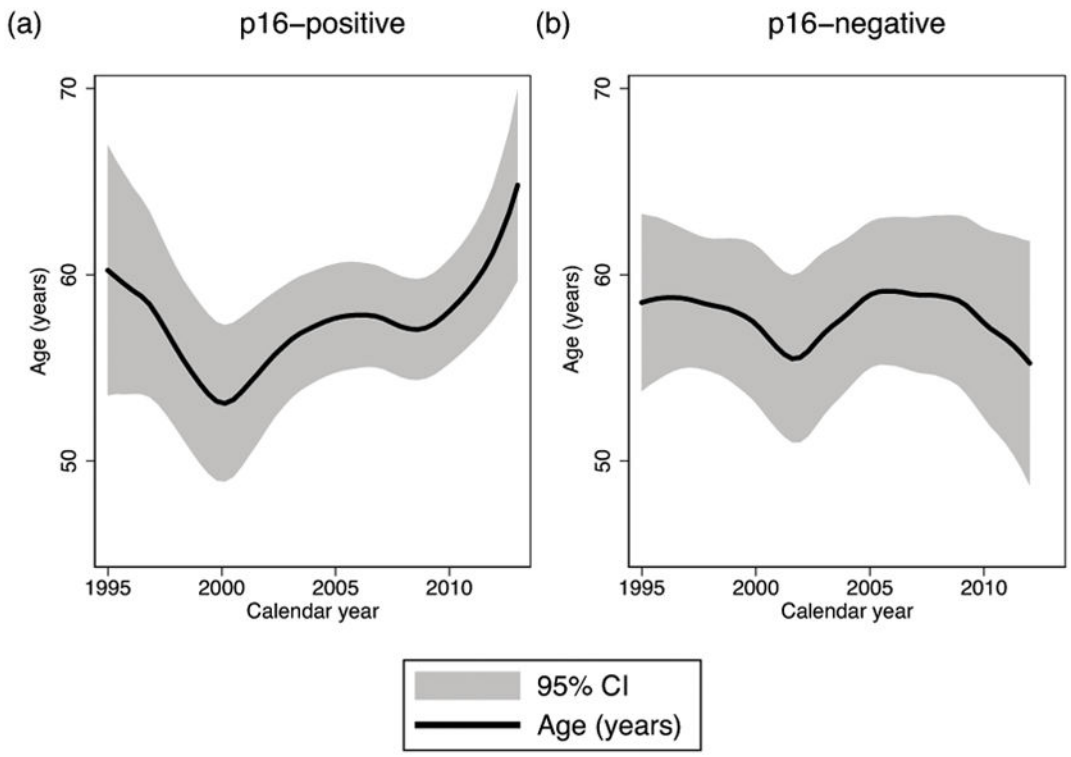

Figure 2.

Mean patient age at diagnosis with (a) p16-positive and (b) p16-negative oropharyngeal squamous cell carcinoma during 1995–2013. CI indicates confidence interval.

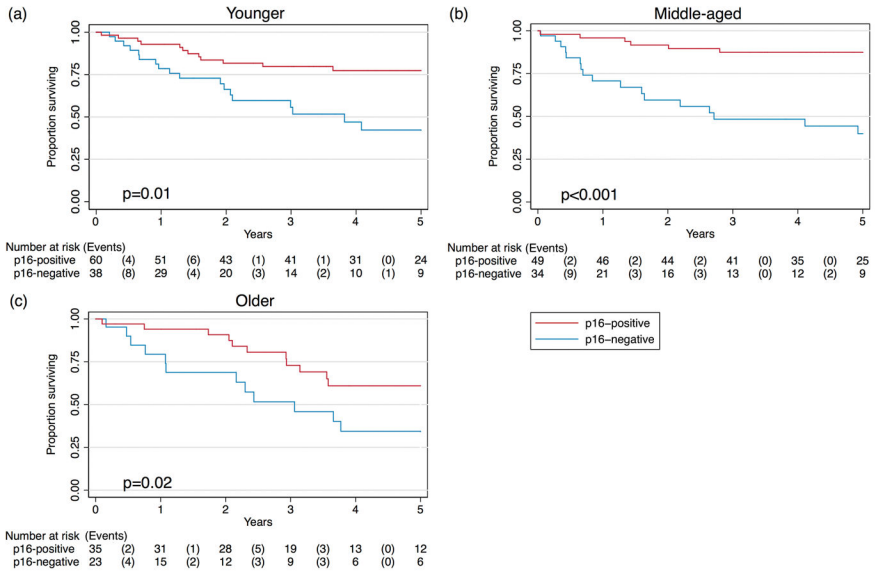

Figure 3.

Survival by p16 tumor status and age group. (a) For younger patients (age 18–54), overall survival for p16-positive (n=98) and p16-negative (n=38) patients was 82% and 66%, respectively, at 2 years and 77% and 42%, respectively, at 5 years. (b) For middle-aged patients (age 55–64), overall survival for p16- positive (n=83) and p16-negative (n=34) patients was 92% and 60%, respectively, at 2 years and 87% and 40%, respectively, at 5 years. (c) For older patients (age >65), overall survival for p16-positive (n=58) and p16-negative (n=23) patients was 88% and 69%, respectively, at 2 years and 59% and 34%, respectively, at 5 years.

Table 1

Characteristics of Study Population, across age groups.

Characteristic	Younger (18–54 years) N=98 N (%)	Middle-aged (55–64 years) N=83 N (%)	Older (≥65 years) N=58 N (%)	p-value (chi^2)
Sex				0.47
Female	37 (38)	25 (30)	17 (29)	
Male	61 (62)	58 (70)	41 (71)	
Race and ethnicity				0.21
White	38 (39)	37 (45)	28 (48)	
Black	47 (48)	28 (34)	19 (33)	
Asian NH	4 (4)	8 (10)	9 (16)	
Hispanic any race	9 (9)	10 (12)	2 (3)	
Study site				0.23
JHH	65 (66)	45 (54)	35 (60)	
UCSF	33 (34)	38 (46)	23 (40)	
Ever tobacco use				0.98
No	19 (19)	17 (20)	10 (17)	
Yes	62 (63)	53 (64)	37 (64)	
Unknown	17 (17)	13 (16)	11 (19)	
p16 tumor status				0.96
Positive	60 (61)	49 (59)	35 (60)	
Negative	38 (39)	34 (41)	23 (40)	
ISH tumor status				
Positive	55 (56)	48 (58)	31 (53)	
Negative	43 (44)	35 (42)	27 (47)	
AJCC 7^{th} edition tumor stage				0.88
T1	30 (31)	20 (24)	17 (29)	
T2	32 (33)	26 (31)	14 (24)	
T3	17 (17)	16 (19)	11 (19)	
T4	17 (17)	18 (22)	13 (22)	
Unknown	2 (2)	3 (4)	3 (5)	
AJCC 7^{th} edition nodal stage				0.76
N0	12 (12)	13 (16)	10 (17)	
N1, N2a, N2b	60 (61)	54 (65)	36 (62)	
N2c, N3	22 (22)	13 (16)	11 (19)	
Unknown	4 (4)	3 (4)	1 (2)	

* Percentages may not add to 100 due to rounding.

Table 2

Overall survival by p16 tumor status and age group.

Age cohort and p16 tumor status	N	HR (95%CI)	p-value	aHR (95%CI)*	p-value
Younger (18–54 years)					
p16-negative	38	-		-	
p16-positive	60	0.43 (0.22–0.83)	**0.01**	0.31 (0.13–0.73)	**0.01**
Middle-aged (55–64 years)					
p16-negative	34	-		-	
p16-positive	49	0.18 (0.08–0.42)	**<0.001**	0.09 (0.01–0.60)	**0.01**
Older (≥65 years)					
p16-negative	23	-		-	
p16-positive	35	0.45 (0.23–0.89)	**0.02**	0.46 (0.17–1.27)	0.14

*adjusted for sex, race and ethnicity, ever tobacco use, AJCC 7th edition tumor stage, AJCC 7th edition nodal stage.

HR indicates hazard ratio; aHR indicates adjusted hazard ratio. Bolding indicates statistical significance.