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Association of Human Papillomavirus Status at Head and Neck Carcinoma Subsites With Overall Survival

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IMPORTANCE Data are limited on the prognostic value of human papillomavirus (HPV) status for head and neck carcinoma subsites.

OBJECTIVE To determine whether HPV positivity at each head and neck subsite is associated with improved overall survival.

DESIGN, SETTING, AND PARTICIPANTS This retrospective population-based cohort study used the National Cancer Database to identify patients diagnosed with head and neck squamous cell carcinomas from January 1, 2010, to December 31, 2014. Patients were classified according to the location of their primary malignancy into 1 of the 6 main subsites of the upper aerodigestive tract: oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, and sinonasal tract. Patients were also classified by their HPV status. Data collection for this study took place from January 1, 2010, to December 31, 2014. Data analysis was conducted from August 1, 2017, to September 30, 2017.

MAIN OUTCOMES AND MEASURES The difference in 5-year overall survival between patients with HPV-positive status and those with HPV-negative status in various head and neck carcinoma subsites; the role of HPV status in an unadjusted Cox multivariate regression model.

RESULTS Of the 175 223 total number of patients identified (129 634 [74.0%] male; 45 589 [26.0%] female; mean [SD] age, 63.1 [11.9] years), 133 273 (76.1%) were ineligible and 41 950 (23.9%) were included in the sample. This sample included 16 644 patients (39.7%) with HPV-positive tumors and 25 306 (60.3%) with HPV-negative tumors. Patients with an HPV-positive status were more likely to be younger, be white, be male, present with local T category tumors, and have poor differentiation on histologic examination. HPV-positive status was associated with survival at 4 tumor subsites: oral cavity (hazard ratio [HR], 0.76; 95% CI, 0.66-0.87), oropharynx (HR, 0.44; 95% CI, 0.41-0.47), hypopharynx (HR, 0.59; 95% CI, 0.45-0.77), and larynx (HR, 0.71; 95% CI, 0.59-0.85). The HPV status was the greatest factor in survival outcome between the HPV-positive and -negative cohorts at the oropharynx subsite (77.6% vs 50.7%; survival difference, 26.9%; 95% CI, 25.6%-28.2%) and hypopharynx subsites (52.2% vs 28.8%; survival difference, 23.4%; 95% CI, 17.5%-29.3%). For the nasopharynx (HR, 1.03; 95% CI, 0.75-1.42) and sinonasal tract (HR, 0.63; 95% CI, 0.39-1.01) subsites, HPV-positive status was not an independent prognostic factor.

CONCLUSIONS AND RELEVANCE Human papillomavirus positivity was associated with improved survival in 4 subsites (oropharynx, hypopharynx, oral cavity, and larynx), and the largest survival difference was noted in the oropharynx and hypopharynx subsites. In the nasopharynx and sinonasal tract subsites, HPV positivity had no association with overall survival. Given these results, routine testing for HPV at the oropharynx, hypopharynx, oral cavity, and larynx subsites may be warranted.

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Head and neck cancers are the sixth most common solid cancer worldwide, with more than 60 000 new cases per year.[1] Human papillomavirus (HPV) infection is now accepted to be a previously unrecognized cause of head and neck squamous cell carcinoma (HNSCC).[2] In the case of oropharyngeal squamous cell carcinoma (OPSCC), there has been as much as a 225% increase in HPV-positive cancers between 1988 and 2004,[3] and up to 70% of new cases are caused by HPV.[2,4,5] In general, patients with HPV-positive OPSCC use less tobacco and alcohol and are more likely to be younger than their counterparts who are negative for HPV.[3,5] HPV-positive status is associated with a significant beneficial impact on prognosis,[6-8] with 1 study reporting a 25% increase in survival at 3 years.[9] HPV-positive OPSCC responds more positively to radiotherapy, which may be associated with defects in double-strand break repair.[10-12] This improvement has led to calls for deintensified treatments,[13] which are currently being investigated.[14-16] However, investigations into non-OPSCC subsites, such as the hypopharynx, nasopharynx, oral cavity, larynx, and sinonasal cavity, are relatively scarce.

The literature on HPV in non-OPSCC subsites is controversial. Studies revealed that HPV is present in these subsites, albeit estimated to be 5 times less prevalent in non-OPSCC than OPSCC.[17-21] A 2016 study that compared the gene expression and DNA methylation profiles of HPV in non-OPSCC subsites with those in OPSCC subsites found them to be identical, leading to the conclusion that HPV can drive carcinogenesis in non-OPSCC.[22] The same study concluded that HPV-driven non-OPSCC has a distinct tumor microenvironment compared with HPV-driven OPSCC. Few studies have looked at the role of HPV at each individual non-OPSCC subsite. Tumors of some subsites, particularly nasopharyngeal tumors, are rare; thus, accurately characterizing the prognostic role of HPV has been difficult.

The purpose of this study was to identify the prognostic role of HPV in all HNSCC subsites. Its results will elucidate HPV's value and importance as a prognostic tool at other subsites, which may help inform treatment decisions and reduce the future burden of HNSCC.

Key Points

Question What is the prognostic role of the human papillomavirus (HPV) at each unique head and neck carcinoma subsite?

Findings In this population-based cohort study involving 41 950 patients with head and neck squamous cell carcinoma, human papillomavirus–positive status was associated with improved overall survival from tumors at oral cavity, oropharynx, hypopharynx, and larynx subsites but not at the nasopharynx and sinonasal tract subsites.

Meaning Routine testing for human papillomavirus may be warranted in tumors originating from the oral cavity, oropharynx, hypopharynx, and larynx subsites.

Methods

Data

Data on a large sample of patients diagnosed with HNSCC were extracted from the National Cancer Database (NCDB). The NCDB is a joint project of the Commission on Cancer and the American Cancer Society[23] that represents more than 70% of incidences of cancer in the United States. Cases in the NCDB are recorded by more than 1500 accredited hospitals in the United States and Puerto Rico. This study was exempt from review by the Yale University Human Research Protection Program because it used a preexisting, deidentified public database. Patient informed consent was not necessary. Data collection for this study took place from January 1, 2010, to December 31, 2014. Data analysis was conducted from August 1, 2017, to September 30, 2017.

Patient Population

Our study population comprised 41 950 patients in the NCDB whose primary malignancy was diagnosed as HNSCC between January 1, 2010, and December 31, 2014. We identified patients using the *International Classification of Diseases for Oncology, Third Edition*, histology codes for squamous cell carcinoma (M8070-8073), and we classified patients according to the following topography codes for the 6 main subsites of the upper aerodigestive tract: oropharynx (C09.0-09.1, C09.8-09.9 [tonsil], C10.0, C10.2-10.4 [other oropharynx], and C-01.9 [base of tongue]), oral cavity (C00.0-00.9 [lip], C02.0-02.4, C02.8-02.9 [other/unspecified parts of the tongue], C03.0-03.1, C03.9 [gum], C04.0-04.1, C04.8-04.9 [floor of mouth], C05.0-05.1, C05.8-05.9 [palate], C06.0-06.2, and C06.8-06.9 [other/unspecified parts of the mouth]), nasopharynx (C11.0-11.3, C11.8, and C11.9 [nasopharynx]), hypopharynx (C12.9 [pyriform sinus], C13.0-13.2, C13.8, and C13.9 [hypopharynx]), sinonasal tract (C30.0, C30.1 [nasal cavity and middle ear], C31.0-31.3, C31.8, and C31.9 [accessory sinuses]), and larynx (C32.0-32.3, C32.8, and C32.9 [larynx]).

We categorized HPV status as negative, positive for low-risk HPV types, positive for high-risk HPV types (HPV-16 and/or HPV-18), or unknown. Patients were classified as HPV-positive if they tested positive for high-risk HPV types or as HPV-negative if they received a negative HPV test result. Patients were excluded if they had low-risk HPV types or unknown HPV status.

We examined patient demographic and tumor data, including age at diagnosis, race/ethnicity, Charleson/Deyo comorbidity score (score range: 0-2, with the highest score indicating a patient with 2 or more comorbidities), primary tumor site, TNM classification by the American Joint Commission on Cancer and the International Union Against Cancer, tumor grade, primary treatment type, insurance status, median income quartiles, treatment facility type and location, and rural or urban classification of primary county of residence. Patients were excluded if they were younger than 18 years, their TNM classification was unknown, or their primary treatment type was unknown. Primary treatment types were as follows: no treatment; radiation only; chemotherapy only; surgery only; radiation and chemotherapy; surgery and radiation; and surgery, radiation, and chemotherapy.

Statistical Analysis

Data analyses were performed using SPSS, version 19.0 (IBM Corp). To compare the distribution of characteristics between patients with HPV-positive status and those with HPV-

negative status, we used 2-sample *t* tests and χ^2 tests. The comparison of mean age at diagnosis was analyzed using a 2-sample *t* test. The proportional distribution of race/ethnicity, primary tumor site, T and N classification, lymph node metastasis, primary treatment type, insurance status, median income quartiles, treatment facility type and location, and rural or urban classification of patient's primary country of residence was determined using χ^2 tests. Survival analysis was performed using the Kaplan-Meier (KM) method. An unadjusted Cox proportional hazards regression model was used for multivariable survival analysis. Age, sex, race/ethnicity, TNM classification, Charleson/Deyo score, HPV status, primary treatment type, insurance status, and median income were entered a priori into the model. A 2-sided $P < .05$ was considered to be statistically significant. Effect-size measures and 95% CIs around the effect-size measures were included to provide estimates of the precision of observed effect size and whether the data were compatible with clinically meaningful differences.

Association of HPV Status With Survival

To determine the association of HPV status with survival among patients with HNSCC, we performed 3 analyses: (1) 5-year unadjusted survival rate, (2) KM survival curve, and (3) unadjusted Cox proportional hazards regression. Subsites in which HPV positivity was found to be associated with improved outcome in the Cox model were further classified as having strong or moderate association on the basis of the difference in 5-year unadjusted survival rates between the HPV-positive and HPV-negative cohorts. A difference greater than 20% survival was classified as strong, and a difference less than 20% was classified as moderate. Subsites in which HPV positivity was found to have no association with improved outcome in the Cox model were classified as having no association.

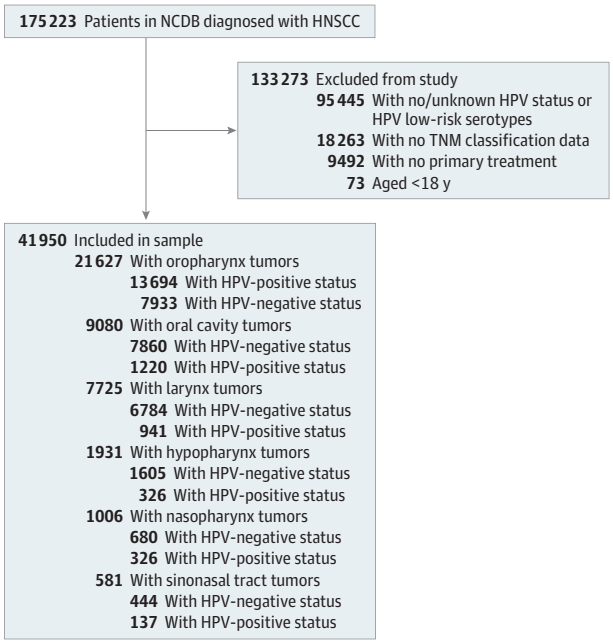
Results

We identified a total of 175 223 patients (129 634 [74.0%] male; 45 589 [26.0%] female; mean [SD] age, 63.1 [11.9] years) diagnosed with HNSCC between January 1, 2010, and December 31, 2014 (**Figure 1**). Of this total, 133 273 patients (76.1%) were ineligible and 41 950 (23.9%) were included in the sample. This sample included 16 644 patients (39.7%) with HPV-positive tumors and 25 306 (60.3%) with HPV-negative tumors). Baseline patient, hospital, clinical, and treatment characteristics by each subsite are shown in eTables 1-6 in the Supplement. In general, patients in the HPV-positive cohort were more likely than their HPV-negative counterparts to be white, be younger, be male, present with local T category tumors, and have poor differentiation on histologic examination.

Survival Outcomes Analyses

The 5-year unadjusted survival rates and KM survival curves for each subsite are shown in the **Table** and **Figure 2**, respectively. Large survival differences (Δ) between the HPV-positive and the HPV-negative cohorts were noted in the oropharynx subsite (77.6% vs 50.7%; Δ, 26.9%; 95% CI, 25.6%-28.2%) and hypopharynx subsite (52.2% vs 28.8%; Δ, 23.4%; 95% CI, 17.5%-29.3%).

Figure 1. Flow Diagram of Patient Selection and Exclusion



Smaller survival differences between the HPV-positive and HPV-negative cohorts were found in the oral cavity subsite (59.4% vs 53.1%; Δ, 6.3%; 95% CI, 3.3%-9.3%), larynx subsite (57.2% vs 48.7%; Δ, 8.5%; 95% CI, 5.1%-11.9%), and sinonasal tract subsite (63.1% vs 45.1%; Δ, 18.0%; 95% CI, 8.7%-27.3%). No statistically significant survival difference was noted in the nasopharynx 5-year unadjusted survival rates (52.5% vs 58.7%; Δ, −6.2%; 95% CI, −12.8% to 0.4%).

On multivariate analysis, after accounting for age, sex, race/ethnicity, Charleson/Deyo score, insurance status, median income, T and N classification, and primary treatment type, we observed that HPV-positive status remained an independent prognostic factor for the oral cavity (hazard ratio [HR], 0.76; 95% CI, 0.66-0.87), oropharynx (HR, 0.44; 95% CI, 0.41-0.47), hypopharynx (HR, 0.59; 95% CI, 0.45-0.77), and larynx (HR, 0.71; 95% CI, 0.59-0.85) subsites. For the nasopharynx (HR, 1.03; 95% CI, 0.75-1.42) and sinonasal tract (HR, 0.63; 95% CI, 0.39-1.01) subsites, HPV-positive status was not an independent prognostic factor.

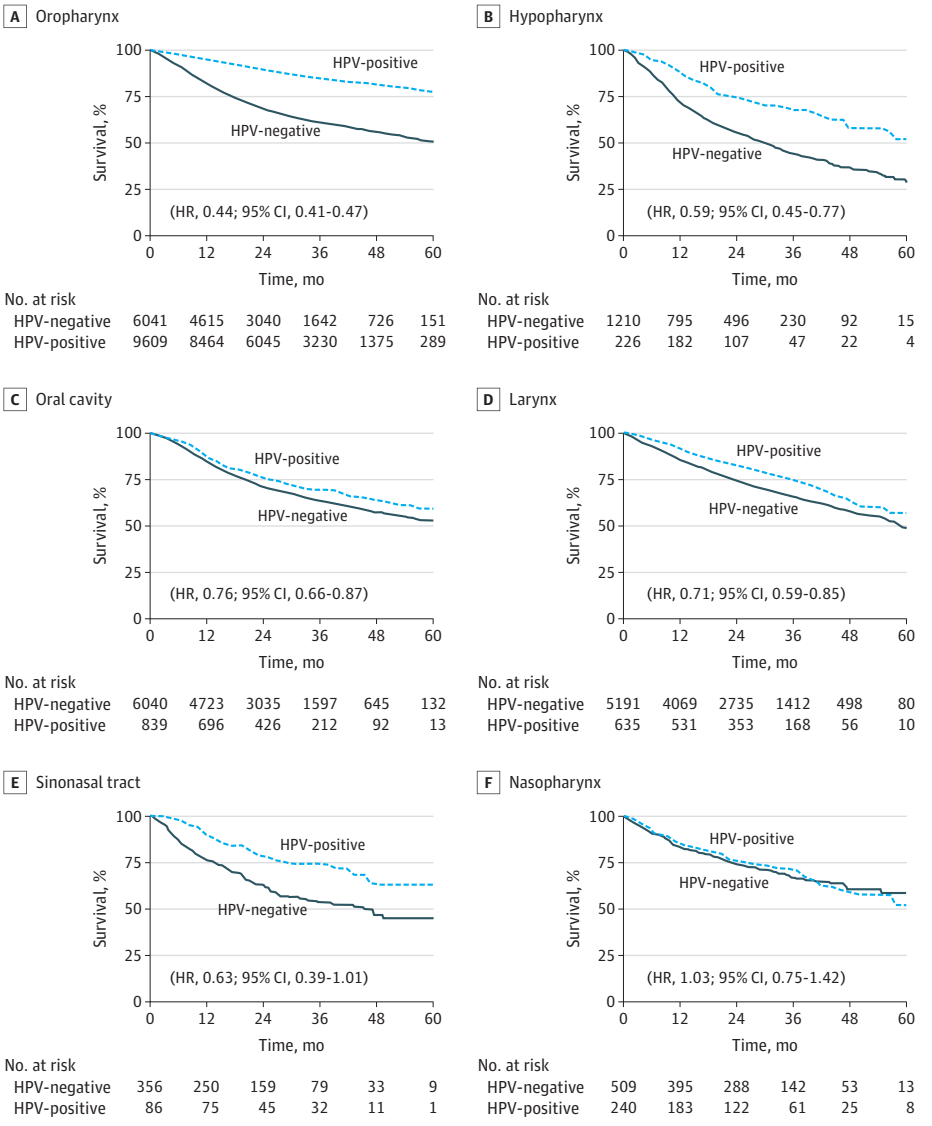
Other factors associated with survival at each subsite are shown in eTables 7-12 in the Supplement. Receiving any treatment other than chemotherapy alone was associated with improved survival in 5 of the 6 subsites. The HRs ranged between 0.07 and 0.7, and the 95% CIs did not include unity (1.0) when comparing treatment groups with the baseline no treatment. Receiving chemotherapy alone did not affect survival in 5 of the 6 subsites; the HRs ranged between 0.8 and 1.1, and the 95% CI included unity. Having a score of 2 on the Charlson/Deyo scale was associated with worse survival at all subsites; the HRs ranged between 1.4 and 2.1, and the 95% CIs were larger than unity.

Table. Year Unadjusted Survival Rates by Human Papillomavirus Status and Cancer Subsite

Subsite	Survival Rate, %		Survival Difference, % (95% CI)
	HPV-Positive Status	HPV-Negative Status	
Oropharynx	77.6	50.7	26.9 (25.6 to 28.2)
Hypopharynx	52.2	28.8	23.4 (17.5 to 29.3)
Oral cavity	59.4	53.1	6.3 (3.3 to 9.3)
Larynx	57.2	48.7	8.5 (5.1 to 11.9)
Sinonasal tract	63.1	45.1	18 (8.7 to 27.3)
Nasopharynx	52.5	58.7	−6.1 (−12.8 to 0.4)

Abbreviation: HPV, human papillomavirus.

Figure 2. Kaplan-Meier Survival Curves by Human Papillomavirus (HPV) Status



Unadjusted hazard ratios (HRs) for HPV status and its association with overall survival are shown for each subsite. HPV-positive status is compared with baseline HPV status.

Discussion

To our knowledge, this study was the largest and most comprehensive retrospective study examining the role of HPV and its association with overall survival at all head and neck subsites. We used a combination of survival differences between the HPV-positive and the HPV-negative cohorts and multivariate models to develop 3 categories for measuring this association: strong, moderate, and no association. We found HPV to have a strong association with overall survival in the oropharynx and hypopharynx subsites, moderate association with improved survival in the

oral cavity and larynx subsites, and no association in the nasopharynx and sinonasal tract subsites.

These results suggest that a variance in the magnitude of survival benefit existed between the subsites, providing a foundation for further study. Why HPV plays a bigger prognostic role in the oropharynx and hypopharynx than in the oral cavity and larynx is unknown, although perhaps it is because the anatomy and function of each subsite differ substantially. This theory may partly explain the similarity in the role of HPV between the adjacent oropharynx and hypopharynx. Preclinical studies alluded to differences in the microtumor environment between OPSCC and non-OPSCC,[22] which may explain the contrast seen between the oral cavity and larynx as well as the oropharynx and hypopharynx subsites.

Recent studies have found that mutations in *TRAF3* (OMIM 601896) and *CYLD* (OMIM 605018) occur only in HPV-associated HNSCC[24] and correlate with survival.[25,26] The absence of viral genome integration is also associated with improved survival[27] and was predicted by mutations in *TRAF3* or *CYLD*.[26] Together, these data suggest that HPV carcinogenesis can occur through HPV integration or through maintenance of the HPV episome[26] and that tumors lacking HPV integration have improved survival. Future studies are required to determine whether laryngeal and oral cavity subsites are more likely to lack mutations in *TRAF3* or *CYLD* and have HPV integration, which could explain why HPV is not associated with as large a survival advantage in these subsites.

The sinonasal tract is unique because it may be at lower risk of exposure to HPV. It is hypothesized that oral HPV infection is transferred by oral sexual contact.[28] However, whether high-risk sexual behavior also affects cancers of the sinonasal tract is not known. A histological analysis of 131 sinonasal carcinomas found high-risk HPV DNA in 21% of tumors.[29] Of interest, although nonkeratinizing squamous cell carcinoma was found to be the most common histological type, the study also reported multiple tumors that were basaloid, papillary, and adenosquamous variants, and some contained features of a salivary gland neoplasm. This study, in combination with our results, suggests that sinonasal carcinomas confer distinct biological and clinical characteristics worthy of further investigation.

The prognostic role of HPV in oropharynx cancers is well established,[9] but a body of conflicting evidence regarding its role in other sites of the head and neck is now emerging.[30-36] Most studies of the prognostic role of HPV at each non-OPSCC subsite had small sample sizes and varied results.[37-39] Many trials have reported the strong association of p16 with improved progression survival, overall survival, and relapse-free survival in oral cavity, hypopharynx, and larynx cancers.[30-33] Some studies have grouped together all the associations by non-OPSCC subtypes, as opposed to delineating the associations by subsite. The results of such studies range from minimal change[34,35] to a substantial increase in survival.[36]

Our data are supported by a recent study by Ko and colleagues[36] that examined the role of HPV at non-OP subsites (oral cavity, hypopharynx, and larynx). The investigators aggregated the 3 subsites and examined the 2 cohorts on the basis of disease staging (I and II; III and IV). Favorable prognosis was identified in both groups for patients with HPV-positive status. However, the investigators did not specifically examine the role of HPV at each subsite by running a multivariate analysis for each subsite cohort, although KM studies were done by subsite. Our study more thoroughly examined the association of HPV because we isolated patient cohorts by subsite to determine the role of HPV. In this way, we were able to exclude the associations of interactions between the primary location of the tumor and HPV status with overall survival.

Our study and many others[30-33] have found an association between improved outcomes and HPV-positive non-OPSCC, but 2 studies offer evidence to the contrary. A recent 2-institution pooled analysis found no survival advantage for patients with larynx, oral cavity, and nasopharynx cancers.[34] Another study comparing advanced p16 and non-p16 tumors in the larynx with hypopharynx tumors demonstrated no outcome differences.[35] These conflicting results may be attributable to a difference in patient population (median age, sex distribution, race/ethnicity, and inclusion criteria) between the aforementioned studies and our own. In addition, the utilization of p16 as a surrogate for HPV status is another factor that differed from our study.

The role of HPV in the nasopharynx is still controversial. One study involving 90 patients (9 HPV-positive patients) found survival benefit with HPV-positive tumors,[40] but another recent study with 125 patients (13 HPV-positive patients) found no survival benefit with HPV-positive tumors.[34] One case series of 45 cases found that HPV-positive nasopharyngeal tumors may represent primary oropharyngeal tumors with extension to the nasopharynx site.[41] This is one of the largest studies examining the role of HPV in nasopharyngeal cancers. Although we found no survival benefit associated with HPV-positive nasopharyngeal tumor status, because of the retrospective and database-use design of our study, we were unable to determine the level of primary site misclassification. Historically, the role of the Epstein-Barr virus has been well characterized in the pathogenesis of nasopharynx tumors. The role of Epstein-Barr virus and its interaction with HPV were outside the scope of our study and not captured by the NCDB; data suggest, however, that Epstein-Barr virus–associated nasopharyngeal cancers have improved prognosis compared with virus-negative tumors,[42] which could confound the analysis of the HPV-negative status factor.

Limitations

The NCDB has well-documented limitations as a source of data.[43] We were limited by the variables captured by the NCDB, such as known risk factors including alcohol and tobacco use. We were also unable to determine the type of testing used for HPV status (eg, polymerase chain reaction, in situ hybridization for HPV DNA vs p16), as this may vary by each reporting institution and agency. Selection bias may exist in our data because routine HPV testing at non-OPSCC subsites is not the current standard of care. Furthermore, the source of the sample may not necessarily be the primary site. Our retrospective study focused on overall survival and not cancer-specific survival; thus, we were unable to distinguish between deaths due to head and neck cancer and deaths due to other causes. The rate of misclassification was likely low because of the nature of the

registry of the data; however, any misclassification was likely to have been evenly distributed across the cohorts.

Conclusions

We identified a variance in the role of HPV and its association with outcomes in HNSCC. Although HPV-positive status was associated with improved disease survival outcomes for 4 subsites, it played the greatest prognostic role at the oropharynx and hypopharynx subsites. Human papillomavirus does not appear to affect the prognosis for the nasopharynx and sinonasal tract subsites. Given these results, we recommend routine testing for HPV status in HNSCC at the oropharynx, hypopharynx, oral cavity, and larynx subsites.

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Study concept and design: Li, Yarbrough, Mehra, Judson.
Acquisition, analysis, or interpretation of data: Li, Torabi, Osborn, Judson.
Drafting of the manuscript: Li, Torabi, Yarbrough.
Critical revision of the manuscript for important intellectual content: Li, Torabi, Mehra, Osborn, Judson.
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REFERENCES

1. American Cancer Society. *Cancer Facts & Figures 2017*. Atlanta, GA: American Cancer Society; 2017.

2. Ang KK, Sturgis EM. Human papillomavirus as a marker of the natural history and response to therapy of head and neck squamous cell carcinoma. *Semin Radiat Oncol*. 2012;22(2):128-142.

3. Deschler DG, Richmon JD, Khariwala SS, Ferris RL, Wang MB. The "new" head and neck cancer patient-young, nonsmoker, nondrinker, and HPV positive: evaluation. *Otolaryngol Head Neck Surg*. 2014;151(3):375-380.

4. 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.

5. Anantharaman D, Abedi-Ardekani B, Beachler DC, et al. Geographic heterogeneity in the prevalence of human papillomavirus in head and neck cancer. *Int J Cancer*. 2017;140(9):1968-1975.

6. Licitra L, Perrone F, Bossi P, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. *J Clin Oncol*. 2006;24(36):5630-5636.

7. 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.

8. Rischin D, Young RJ, Fisher R, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. *J Clin Oncol*. 2010;28(27):4142-4148.

9. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35.

10. Marcu LG. Future treatment directions for HPV-associated head and neck cancer based on radiobiological rationale and current clinical evidence. *Crit Rev Oncol Hematol*. 2016;103:27-36.

11. Weaver AN, Cooper TS, Rodriguez M, et al. DNA double strand break repair defect and sensitivity to poly ADP-ribose polymerase (PARP) inhibition in human papillomavirus 16-positive head and neck squamous cell carcinoma. *Oncotarget*. 2015;6(29):26995-27007.

12. Rieckmann T, Tribius S, Grob TJ, et al. HNSCC cell lines positive for HPV and p16 possess higher cellular radiosensitivity due to an impaired DSB repair capacity. *Radiother Oncol*. 2013;107(2):242-246.

13. Quon H, Forastiere AA. Controversies in treatment deintensification of human papillomavirus-associated oropharyngeal carcinomas: should we, how should we, and for whom? *J Clin Oncol*. 2013;31(5):520-522.

14. Frank SJ, Rosenthal DI, Petsuksiri J, et al. Intensity-modulated radiotherapy for cervical node squamous cell carcinoma metastases from unknown head-and-neck primary site: M. D. Anderson Cancer Center outcomes and patterns of failure. *Int J Radiat Oncol Biol Phys*. 2010;78(4):1005-1010.

15. Chen AM, Li BQ, Farwell DG, Marsano J, Vijayakumar S, Purdy JA. Improved dosimetric and clinical outcomes with intensity-modulated radiotherapy for head-and-neck cancer of unknown primary origin. *Int J Radiat Oncol Biol Phys*. 2011;79(3):756-762.

16. Shoushtari A, Saylor D, Kerr KL, et al. Outcomes of patients with head-and-neck cancer of unknown primary origin treated with intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2011;81(3):e83-e91.

17. Combes J-D, Franceschi S. Role of human papillomavirus in non-oropharyngeal head and neck cancers. *Oral Oncol*. 2014;50(5):370-379.

18. Isayeva T, Li Y, Maswahu D, Brandwein-Gensler M. Human papillomavirus in non-oropharyngeal head and neck cancers: a systematic literature review. *Head Neck Pathol*. 2012;6(suppl 1):S104-S120.

19. Ibieta-Zarco BR, Carrillo-García A, Ponce-de-León-Rosales S, Flores-Miranda MM, Mohar A, Lizano M. Frequency and genotype distribution of multiple human papillomavirus infections in cancer of the head and neck in a Mexican population. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114(3):350-357.

20. Herrero R, Castellsagué X, Pawlita M, et al; IARC Multicenter Oral Cancer Study Group. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst*. 2003;95(23):1772-1783.

21. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst*. 2000;92(9):709-720.

22. Chakravarthy A, Henderson S, Thirdborough SM, et al. Human papillomavirus drives tumor development throughout the head and neck: improved prognosis is associated with an immune response largely restricted to the oropharynx. *J Clin Oncol*. 2016;34(34):4132-4141.

23. Raval MV, Bilimoria KY, Stewart AK, Bentrem DJ, Ko CY. Using the NCDB for cancer care improvement: an introduction to available quality assessment tools. *J Surg Oncol*. 2009;99(8):488-490. Accessed March 21, 2018. doi:10.1002/jso.21173

24. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature*. 2015;517(7536):576-582.

25. Parfenov M, Pedamallu CS, Gehlenborg N, et al; Cancer Genome Atlas Network. Characterization of HPV and host genome interactions in primary head and neck cancers. *Proc Natl Acad Sci U S A*. 2014;111(43):15544-15549.

26. Hajek M, Sewell A, Kaech S, Burtness B, Yarbrough WG, Issaeva N. TRAF3/CYLD mutations identify a distinct subset of human papillomavirus-associated head and neck squamous cell carcinoma. *Cancer*. 2017;123(10):1778-1790.

27. Koneva LA, Zhang Y, Virani S, et al. HPV integration in HNSCC correlates with survival outcomes, immune response signatures, and candidate drivers. *Mol Cancer Res*. 2017;16(1):90-102.

28. D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *J Infect Dis*. 2009;199(9):1263-1269.

29. Bishop JA, Guo TW, Smith DF, et al. Human papillomavirus-related carcinomas of the sinonasal tract. *Am J Surg Pathol*. 2013;37(2):185-192.

30. Chung CH, Zhang Q, Kong CS, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J Clin Oncol*. 2014;32(35):3930-3938.

31. Harris SL, Thorne LB, Seaman WT, Hayes DN, Couch ME, Kimple RJ. Association of p16(INK4a) overexpression with improved outcomes in young patients with squamous cell cancers of the oral tongue. *Head Neck*. 2011;33(11):1622-1627.

32. Shaughnessy JN, Farghaly H, Wilson L, et al. HPV: a factor in organ preservation for locally advanced larynx and hypopharynx cancer? *Am J Otolaryngol*. 2014;35(1):19-24.

33. Sivars L, Bersani C, Grün N, et al. Human papillomavirus is a favourable prognostic factor in cancer of unknown primary in the head and neck region and in hypopharyngeal cancer. *Mol Clin Oncol*. 2016;5(6):671-674.

34. 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.

35. Lassen P, Primdahl H, Johansen J, et al; Danish Head and Neck Cancer Group (DAHANCA). Impact of HPV-associated p16-expression on radiotherapy outcome in advanced oropharynx and non-oropharynx cancer. *Radiother Oncol*. 2014;113(3):310-316.

36. Ko HC, Harari PM, Sacotte RM, et al. Prognostic implications of human papillomavirus status for patients with non-oropharyngeal head and neck squamous cell carcinomas. *J Cancer Res Clin Oncol*. 2017;143(11):2341-2350.

37. Morshed K. Association between human papillomavirus infection and laryngeal squamous cell carcinoma. *J Med Virol*. 2010;82(6):1017-1023.

38. Duray A, Descamps G, Arafa M, et al. High incidence of high-risk HPV in benign and malignant lesions of the larynx. *Int J Oncol*. 2011;39(1):51-59.

39. Sugiyama M, Bhawal UK, Kawamura M, et al. Human papillomavirus-16 in oral squamous cell carcinoma: clinical correlates and 5-year survival. *Br J Oral Maxillofac Surg*. 2007;45(2):116-122.

40. Dogan S, Hedberg ML, Ferris RL, Rath TJ, Assaad AM, Chiosea SI. Human papillomavirus and Epstein-Barr virus in nasopharyngeal carcinoma in a low-incidence population. *Head Neck*. 2014;36(4):511-516.

41. Singhi AD, Califano J, Westra WH. High-risk human papillomavirus in nasopharyngeal carcinoma. *Head Neck*. 2012;34(2):213-218.

42. Stenmark MH, McHugh JB, Schipper M, et al. Nonendemic HPV-positive nasopharyngeal carcinoma: association with poor prognosis. *Int J Radiat Oncol Biol Phys*. 2014;88(3):580-588.

43. Boffa DJ, Rosen JE, Mallin K, et al. Using the National Cancer Database for outcomes research: a review. *JAMA Oncol*. 2017;3(12):1722-1728.

Invited Commentary

Human Papillomavirus in the Mouth and Throat
More Widespread Than Expected?

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In this issue of *JAMA Otolaryngology–Head & Neck Surgery,* Li et al[1] shows that human papillomavirus–positive squamous cell carcinoma (SCC) may be associated with improved overall survival not only in the oropharynx but also possibly in the upper aerodigestive tract subsites—oral cavity, larynx, and hypopharynx. This finding is persuasive given the large sample size used, which was obtained from the National Cancer Database (NCDB), and the multivariate analysis performed. Previous studies with smaller sample sizes have similarly suggested the favorable prognostic role of HPV in cancer in nonoropharyngeal head and neck sites,[2] although other studies have refuted this possibility.[3]

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The authors assessed the differences in survival outcomes by the presence or absence of HPV in a sample of 41 950 patients with head and neck SCC, various proportions of whom had HPV-positive tumors of the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, and sinonasal tract. Greater differences in 5-year overall survival were found between patients with HPV-positive and those with HPV-negative cancers of the oropharynx (survival difference, 26.9%) and hypopharynx (survival difference, 23.4%). There were smaller differences in overall survival between patients with HPV-positive SCC and those with HPV-negative SCC in the oral cavity (survival difference, 6.3%) and the larynx (survival difference, 8.5%). Furthermore, a multivariate analysis showed that HPV positivity in SCC of the oral cavity, oropharynx, hypopharynx, and larynx was an independent prognostic factor even in the context of several other influential variables, such as patient age, comorbidity score, tumor stage, and treatment type. These findings are similar to previous research conducted by Ko et al,[2] who also used the NCDB, but conflict with the findings by Fakhry et al,[3] who studied patients from 2 separate comprehensive cancer centers. In the study by Fakhry et al,[3] the prognostic value of HPV status was not observed in patients with nonoropharyngeal cancers.

These findings encourage the practice of systematic HPV testing for patients with SCC in the oral cavity, larynx, and hypopharynx as well as in the oropharynx. If we do not test patients with cancers in other head and neck subsites, we may miss important HPV-associated therapeutic and prognostic information. Perhaps with more detailed, corroborative evidence, we could consider select deintensified treatment efforts for these nonoropharyngeal SCC subsites on the basis of HPV positivity. At present, many such efforts are under investigation for oropharyngeal SCC. However, it is still too early to tell whether such efforts exist for the other sites. Because this study found only modest survival differences (less than 10%) between patients with HPV-positive and those with HPV-negative cancers in the oral cavity and larynx, deintensified therapies for these subsites may be premature. Future research should focus on whether HPV is particularly relevant in only certain subdivisions of the oral cavity (eg, tongue), larynx (eg, supraglottis), and hypopharynx (eg, piriform sinus) but not in others.

The quality of the information reported in any study depends on the rigor of the data collection from which the interpretations are gleaned. The NCDB, in existence since 1985, compiles cancer-related information on more than 70% of pa-