



Published in final edited form as:

J Natl Cancer Inst. 2025 July 01; 117(7): 1492–1497. doi:10.1093/jnci/djae320.

The role of HPV16 in oral cavity and laryngeal cancers in the United States

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Abstract

In addition to oropharyngeal cancers, evidence suggests there may be an etiologic role for human papillomavirus (HPV) in some other head and neck cancers arising from the oral cavity and larynx. We estimated the burden of HPV16-attributable cancers of the oral cavity (ICD-O-3 site codes C02.0-C02.3, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.8, C05.9, C06.0-C06.2, C06.8, C06.9) and larynx (C32.0-C32.3, C32.8, C32.9) in the United States by pooling estimates from published case studies to calculate HPV16-attributable fractions (HPV16-AFs) and applying the HPV16-AFs to 2016–2020 US Cancer Statistics data. During 2016–2020, of an average annual number of 12,612 oral cavity cancers, 3.9% (n = 497) were estimated to be attributable to HPV16. Of an average annual number of 11,170 laryngeal cancers, 2.8% (n = 309) were estimated to be attributable to HPV16. This information can improve surveillance of HPV16-attributable cancers in the US population and inform our understanding of the potential impact of HPV vaccination on cancers at these two sites.

Persistent infection with human papillomavirus (HPV) causes several cancers, including cervical, penile, anal, and oropharyngeal cancers (1,2). HPV vaccination has been

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Disclaimer: The findings and conclusions are those of the authors and do not necessarily represent the official position of the National Cancer Institute or Centers for Disease Control and Prevention.

Conflicts of Interest

Mona Saraiya is currently employed at Merck but was employed at CDC for her contributions to this article.

recommended in the United States since 2006 (3). Currently, vaccination is recommended for boys and girls aged 11–12 years and can be started at age 9 years (4,5). Catch-up vaccination is recommended through age 26 for those not vaccinated at the routine age (4,5). The 9-valent HPV vaccine (licensed in 2014 and the only vaccine currently available in the United States) was initially indicated for prevention of anogenital cancers attributable to HPV. In 2020, the US Food and Drug Administration expanded the indication to include prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the 9-valent HPV vaccine (6).

The Centers for Disease Control and Prevention (CDC) estimates that over 70% of oropharyngeal cancers in the United States are caused by HPV (7). In addition to oropharyngeal cancers, there is some evidence to suggest that HPV also causes other head and neck cancers arising from the oral cavity and larynx. Based on this evidence, the International Agency for Research on Cancer (IARC) has been providing global estimates for potentially HPV-caused oral cavity and laryngeal cancers since 2017 (8,9). In 2018, an estimated 5900 oral cavity and 4100 laryngeal cancers worldwide were attributable to high-risk HPV types (8). The estimated fraction of HPV-attributable oropharyngeal cancers varies widely worldwide, with much higher estimates in the United States (9). However, analogous estimates of HPV-attributable oral cavity and laryngeal cancers in the US population do not currently exist.

Extending the work of IARC, the purpose of our study was to estimate the US burden of HPV16-attributable oral cavity and laryngeal cancers. HPV16 is a high-risk HPV type and the type most frequently detected in oral cavity and laryngeal cancers (10). Given this fact, and because limited data exist on other types, we focused on HPV16. Institutional Review Board approval was exempted under the Common Rule (45 CFR §46) because we used de-identified data.

First, we calculated HPV16-attributable fractions (HPV16-AFs) from previous case studies. To identify case studies, we referred to previous IARC reports (11), performed a narrative literature review, and consulted with experts in the field. For the narrative review, we searched for studies from the United States published during 2017–2022 that reported HPV16-attributable estimates for oral cavity and laryngeal cancers. We chose this time period because the methodology used by IARC for AF calculation was published in 2016 (11). We also wanted to capture case studies from the most recent 5 years at the time of our review.

We only included studies that used HPV E6/E7 mRNA detection methods to detect HPV16 in oral cavity and laryngeal cancer tissue, as these methods are considered the gold standard for detecting HPV oncogenesis in non-anogenital cancers (11–14). To calculate HPV16-AFs, we pooled estimates by summing the number of HPV16-positive cases across case studies and dividing by the sum of the total number of cases. We used the Clopper-Pearson Exact method (15) to calculate 95% confidence intervals (CIs) of the HPV16-AFs.

Second, we used 2016–2020 US Cancer Statistics (USCS) incidence data to estimate the burden of oral cavity and laryngeal cancers overall and by age, sex, and race and ethnicity.

These demographic data are reported by cancer registries and collected through various methods, including from medical records and pathology reports. USCS combines cancer registry data from CDC's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (16). Cancer registries demonstrate that data are of high quality by meeting USCS publication criteria (17). During 2016–2020, data from 49 cancer registries met these criteria, covering 97% of the US population (17).

The USCS analysis included new cases of primary invasive, histologically confirmed oral cavity cancer and laryngeal cancer diagnosed during 2016–2020. Oral cavity cancer was defined by the following *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3) (18) site codes: C02.0–C02.3, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.8, C05.9, C06.0–C06.2, C06.8, and C06.9. Laryngeal cancer was defined by ICD-O-3 site codes C32.0–C32.3, C32.8, and C32.9. We restricted our analysis to oral and laryngeal cancers of squamous cell carcinoma histology (codes 8050–8086 and 8120–8131).

The definitions of oral cavity and laryngeal cancers used in our analysis are for sites etiologically likely to be HPV-related and in line with methods used in a previously published CDC population-based study to assess HPV types in cancers by anatomic site (10). The site codes listed above differ from SEER Site Recode definitions (19), which mix oral cavity and oropharyngeal cancer sites; for example, tongue includes base of tongue and other mouth includes soft palate and uvula—all of which are part of the oropharynx (see Supplementary Table 1). Given this, routinely used cancer reporting and data visualization tools are suboptimal for nuanced classification of oral cavity and oropharynx cases, which is essential for accurate estimation of HPV-associated fractions for these anatomic sites.

We reported average annual number and age-adjusted incidence rates for oral cavity and laryngeal cancers. We multiplied our HPV16-AFs and corresponding 95% CIs by the number of cases at each cancer site to estimate the average annual number of cases attributable to HPV16.

Nine studies were used to calculate HPV16-AFs (Table 1). Seven studies reported data on oral cavity, 6 on larynx, and 4 on both sites. The total number of samples tested for HPV16 was 1894: 1065 for oral cavity and 829 for laryngeal cancers. Based on these studies, the pooled HPV16-AF was 3.9% (95% CI = 2.9 to 5.3) for oral cavity cancer and 2.8% (95% CI = 1.8 to 4.1) for laryngeal cancer. The average annual number of oral cavity cancers was 12 612, with an age-adjusted incidence rate of 3.3 per 100 000 standard population (Table 2). For laryngeal cancer, the average annual number of cases was 11 170, with an age-adjusted incidence rate of 2.8 per 100 000 standard population. Based on our HPV16-AFs, we estimate that 497 (95% CI = 361 to 667) oral cavity cancers and 309 (95% CI = 198 to 461) laryngeal cancers were potentially attributable to HPV16 each year.

In summary, our pooled analysis of the published literature indicated that 3.9% of oral cavity cancer cases and 2.8% of laryngeal cancer cases in the United States are attributable to HPV16 infection, accounting for 806 total cases annually during the 5-year study

period (2016–2020). Combined, the burden of these cancers is similar to penile cancer. During 2012–2016, an average annual number of 700 penile cancers were estimated to be attributable to HPV types targeted by the 9-valent HPV vaccine (20).

Our estimates are smaller than those reported in previous HPV typing studies based on DNA detection. Notably, Saraiya et al. (10) detected HPV16 using PCR-based genotyping based on any assay format in 20.4% of oral cavity cancers and 6.1% of laryngeal cancers. The difference in findings could be explained in part by inclusion of only studies that used E6/E7 mRNA detection methods in our study. DNA PCR may overestimate the causal fraction because detection of HPV DNA does not indicate its oncogenic activity (21). In contrast, mRNA RT-PCR do indicate transcriptional activity of HPV but require preservation of RNA, which is more susceptible to degradation than DNA (22). As a result, the AFs reported here may be underestimated.

The results from our study have potential implications for estimates of HPV-attributable cancers. Current CDC estimates of potentially HPV-attributable cancers (23) have not included oral cavity and laryngeal cancers because of limited data on optimal AFs. This study provides AFs that could be applied to future data collected on incidence to estimate the burden of these cancers and, in turn, increase accuracy of the overall reported number of HPV-attributable cancers in the United States.

Our estimated HPV16-AFs also provide insight into the percentage of oral cavity and larynx cancers that might be prevented by HPV vaccination (4). While HPV vaccination might lead to fewer cancer cases at these sites, given the relatively small number of estimated HPV16-attributable cases, the maximum potential benefit from HPV vaccination is likely in the prevention of oropharynx, cervical, and anogenital cancers. Vaccination should be promoted among groups at higher risk for HPV, including people with HIV or who are immunocompromised (24).

The results of this study should be interpreted in the context of its limitations. First, we were unable to calculate the percentage of oral cavity and laryngeal cancers attributable to other HPV types, as genotyping studies that examine RNA for these cancers are lacking. Additional genotyping studies like BROADEN (25,26), which aims to provide robust estimates of HPV-attributable head and neck cancers in European and Asian counties, may be beneficial to other countries, as well, to understand the full extent to which oral cavity and laryngeal (or other head and neck) cancers are attributable to HPV, including HPV16. At the present time, our study provides the best estimates of the proportion of oral cavity and laryngeal cancers potentially attributable to HPV16 in the United States.

Second, the COVID-19 pandemic created challenges in healthcare delivery, leading to delays in cancer screening and diagnosis (27), and may have affected the average annual case counts in our USCS analysis. Although additional data may be needed to understand the impact of the COVID-19 pandemic on cancer incidence, when we excluded year 2020 from the analysis, we did not identify large differences in incidence rates.

Third, the same HPV16-AFs were applied across all subgroups. Given this, our estimates may not reflect actual differences in the number of HPV16-attributable cases across

subgroups. Lastly, we excluded cancer cases with no histologic confirmation from our USCS analysis. While these cases represent a very small percentage of cases, excluding them may result in misclassification with an unknown impact on the HPV16-AFs reported here.

Despite these potential limitations, our study provides new knowledge on HPV-attributable oral cavity and laryngeal cancers. In particular, our results contribute to the data on the overall burden of HPV-attributable cancers in the United States that could be prevented by vaccination. The low AFs observed also suggest that non-HPV-based prevention strategies are needed to control oral cavity and laryngeal cancer in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank Dr. Maura Gillison for her feedback during the planning of this project.

Data Availability Statement/Data Sharing Plan

The data are not publicly available because of privacy and legal restrictions. Information about accessing public use United States Cancer Statistics data can be found at <https://www.cdc.gov/cancer/uscs/>.

References

- Centers for Disease Control and Prevention. Cancers caused by HPV. National Center for Chronic Disease and Health Promotion, Centers for Disease Control and Prevention; Accessed February 14, 2023. <https://www.cdc.gov/hpv/parents/cancer.html>
- International Agency for Research on Cancer [IARC]. IARC monographs on the evaluation of carcinogenic risks to humans: Biological agents. Volume 100 B. A review of human carcinogens. World Health Organization; 2012.
- Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. Mar 23 2007;56(RR-2):1–24.
- Centers for Disease Control and Prevention. HPV vaccination recommendations. National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention; Accessed July 13, 2023. <https://www.cdc.gov/vaccines/vpd/hpv/hcp/recommendations.html>
- Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. Aug 16 2019;68(32):698–702. doi:10.15585/mmwr.mm6832a3 [PubMed: 31415491]
- US Food and Drug Administration. FDA adds prevention of oropharyngeal cancer to HPV vaccine's indication. Accessed April 7, 2023. <https://www.fda.gov/media/150779/download>.
- Centers for Disease Control and Prevention. HPV and oropharyngeal cancer. Division of Cancer Prevention and Control, Centers for Disease Control and Prevention; Accessed June 20, 2024. <https://www.cdc.gov/cancer/hpv/oropharyngeal-cancer.html>
- de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. Feb 2020;8(2):e180–e190. doi:10.1016/S2214-109X(19)30488-7 [PubMed: 31862245]

9. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*. Aug 15 2017;141(4):664–670. doi:10.1002/ijc.30716 [PubMed: 28369882]
10. Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst*. Jun 2015;107(6):djv086. doi:10.1093/jnci/djv086 [PubMed: 25925419]
11. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Health*. Sep 2016;4(9):e609–16. doi:10.1016/S2214-109X(16)30143-7 [PubMed: 27470177]
12. Bishop JA, Ma XJ, Wang H, et al. Detection of transcriptionally active high-risk HPV in patients with head and neck squamous cell carcinoma as visualized by a novel E6/E7 mRNA in situ hybridization method. *Am J Surg Pathol*. Dec 2012;36(12):1874–82. doi:10.1097/PAS.0b013e318265fb2b [PubMed: 23060353]
13. Cohen E, Coviello C, Menaker S, et al. P16 and human papillomavirus in sinonasal squamous cell carcinoma. *Head Neck*. Aug 2020;42(8):2021–2029. doi:10.1002/hed.26134 [PubMed: 32149447]
14. Venuti A, Paolini F. HPV detection methods in head and neck cancer. *Head Neck Pathol*. Jul 2012;6 Suppl 1(Suppl 1):S63–74. doi:10.1007/s12105-012-0372-5 [PubMed: 22782225]
15. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26(4):404–413.
16. Centers for Disease Control and Prevention. United States Cancer Statistics (USCS). Division of Cancer Prevention and Control, Centers for Disease Control and Prevention; Accessed October 19, 2023. <https://www.cdc.gov/cancer/uscs/index.htm>
17. Centers for Disease Control and Prevention. Registries that met U.S. Cancer Statistics publication criteria. Division of Cancer Prevention and Control, Centers for Disease Control and Prevention; Accessed June 13, 2024. <https://www.cdc.gov/united-states-cancer-statistics/technical-notes/publication-criteria.html>
18. Fritz A, Percy C, Jack A, et al. International Classification of Diseases for Oncology. 3rd ed. World Health Organization; 2000.
19. National Cancer Institute Surveillance Epidemiology and End Results Program. Site recode ICD-O-3/WHO 2008 definition. National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services; Accessed December 5, 2023. https://seer.cancer.gov/siterecode/icdo3_dwhohome/
20. Senkomago V, Henley SJ, Thomas CC, Mix JM, Markowitz LE, Saraiya M. Human Papillomavirus-Attributable Cancers - United States, 2012–2016. *MMWR Morb Mortal Wkly Rep*. Aug 23 2019;68(33):724–728. doi:10.15585/mmwr.mm6833a3 [PubMed: 31437140]
21. Williams J, Kostiuk M, Biron VL. Molecular Detection Methods in HPV-Related Cancers. *Front Oncol*. 2022;12:864820. doi:10.3389/fonc.2022.864820 [PubMed: 35574396]
22. Hall JS, Taylor J, Valentine HR, et al. Enhanced stability of microRNA expression facilitates classification of FFPE tumour samples exhibiting near total mRNA degradation. *Br J Cancer*. Aug 7 2012;107(4):684–94. doi:10.1038/bjc.2012.294 [PubMed: 22805332]
23. Centers for Disease Control and Prevention. Cancers associated with human papillomavirus, United States—2015–2019. Accessed July 13, 2023. USCS Data Brief, no. 32. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services
24. Garland SM, Brotherton JML, Moscicki AB, et al. HPV vaccination of immunocompromised hosts. *Papillomavirus Res*. Dec 2017;4:35–38. doi:10.1016/j.pvr.2017.06.002 [PubMed: 29179867]
25. Morais E, Kothari S, Chen YT, et al. The BROADEN study: The design of an observational study to assess the absolute burden of HPV-related head and neck cancers. *Contemp Clin Trials*. Apr 2022;115:106631. doi:10.1016/j.cct.2021.106631 [PubMed: 34838716]
26. Nibu KI, Oridate N, Saito Y, et al. Human papillomavirus-driven head and neck cancers in Japan during 2008–2009 and 2018–2019: The BROADEN study. *Cancer Sci*. Aug 2024;115(8):2808–2818. doi:10.1111/cas.16230 [PubMed: 38847353]
27. Centers for Disease Control and Prevention. U.S. Cancer Statistics: Highlights from 2020 mortality and incidence with comparison to 2019 incidence to assess the effect of the COVID-19

- pandemic. USCS Data Brief, no. 35. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services.
28. Chernock RD, Wang X, Gao G, et al. Detection and significance of human papillomavirus, CDKN2A(p16) and CDKN1A(p21) expression in squamous cell carcinoma of the larynx. *Mod Pathol.* Feb 2013;26(2):223–31. doi:10.1038/modpathol.2012.159 [PubMed: 22996374]
 29. 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.* May 1 2017;123(9):1566–1575. doi:10.1002/cncr.30353 [PubMed: 28241096]
 30. Hernandez BY, Lynch CF, Chan OTM, et al. Human papillomavirus DNA detection, p16(INK4a), and oral cavity cancer in a U.S. population. *Oral Oncol.* Apr 2019;91:92–96. doi:10.1016/j.oraloncology.2019.03.001 [PubMed: 30926069]
 31. Lewis JS Jr., Ukpo OC, Ma XJ, et al. Transcriptionally-active high-risk human papillomavirus is rare in oral cavity and laryngeal/hypopharyngeal squamous cell carcinomas--a tissue microarray study utilizing E6/E7 mRNA in situ hybridization. *Histopathology.* May 2012;60(6):982–91. doi:10.1111/j.1365-2559.2011.04169.x [PubMed: 22360821]
 32. Lingen MW, Xiao W, Schmitt A, et al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. *Oral Oncol.* Jan 2013;49(1):1–8. doi:10.1016/j.oraloncology.2012.07.002 [PubMed: 22841678]
 33. Saleh W, Cha S, Banasser A, et al. Localization and characterization of human papillomavirus-16 in oral squamous cell carcinoma. *Oral Dis.* Mar 2023;29(2):436–444. doi:10.1111/odi.13920 [PubMed: 34022097]
 34. Schlecht NF, Brandwein-Gensler M, Nuovo GJ, et al. A comparison of clinically utilized human papillomavirus detection methods in head and neck cancer. *Mod Pathol.* Oct 2011;24(10):1295–305. doi:10.1038/modpathol.2011.91 [PubMed: 21572401]
 35. Taberna M, Resteghini C, Swanson B, et al. Low etiologic fraction for human papillomavirus in larynx squamous cell carcinoma. *Oral Oncol.* Oct 2016;61:55–61. doi:10.1016/j.oraloncology.2016.08.009 [PubMed: 27688105]

Table 1. Case study characteristics, including HPV16-positive cases, and HPV16-attributable fractions in oral cavity and larynx cancers

Citation	Study Design	Sample	Year of Diagnosis	Age	Sex	Race and Ethnicity	Detection Method	HPV Types Tested	Oral Cavity Cancers			Larynx Cancers		
									HPV16+	No. Tested	% (95% CI) ^a	HPV16+	No. Tested	% (95% CI) ^a
Bishop et al. 2012 (12)	Multiple institution retrospective case series	282 FFPE	1996–2005	Not reported	Not reported	Not reported	E6/E7 mRNA ISH	16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82	0	109	0.0 (0.0 to 3.3)	1	64	1.6 (0.4 to 8.4)
Chernock et al. 2013 (28)	Single institution retrospective case series	76 FFPE	1997–2007	57.5 (mean)	Female: 29% Male: 71%	African American: 33% White: 67%	E6/E7 mRNA ISH and RT-PCR	16, 18, 31, 33, 35, 39, 45, 52, 56, 58, 59, 66, 68	N/A	N/A	N/A	3	60	5.0 (1.0 to 13.9)
Fakhry et al. 2017 (29)	Multiple institution retrospective case series	860 FFPE	1995–2012	58 (median)	Female: 36% Male: 64%	Asian, non-Hispanic: 20% Black, non-Hispanic: 32% White, non-Hispanic: 37% Hispanic, any race: 12%	E6/E7 mRNA ISH	16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82	5	253	2.0 (0.7 to 4.6)	8	243	3.3 (1.4 to 6.4)
Hernandez et al. 2019 (30)	Population-based study of two cancer registries	122 FFPE	1993–2004	59% ≥60 years old	Female: 51% Male: 49%	Asian: 31% White: 55% Other race: 14%	E6/E7 RT-PCR	16, 18, 39, 51, 52, 66	0	106	0.0 (0.0 to 3.4)	N/A	N/A	N/A
Lewis et al. 2012 (31)	Single institution retrospective cohort study	87 FFPE	1998–2004	58.7 (mean) 58.3 (median)	Female: 25% Male: 75%	African American: 20% White: 77% Other race: 4%	E6/E7 mRNA ISH	16, 18, 31, 33, 35, 52, 58	0	45	0.0 (0.0 to 7.9)	2	31	6.5 (0.8 to 21.4)
Lingen et al. 2013 (32)	Multiple institution retrospective case series	409 FFPE	2005–2011	61 (median, HPV+) 64 (median, HPV-)	Female: 42% Male: 58%	Not reported	E6/E7 RT-PCR	16, 18, 31, 33, 35, 39, 45, 51, 52, 56,	15	409	3.7 (2.1 to 6.0)	N/A	N/A	N/A

Citation	Study Design	Sample	Year of Diagnosis	Age	Sex	Race and Ethnicity	Detection Method	HPV Types Tested	Oral Cavity Cancers			Larynx Cancers		
									HPV16+	No. Tested	% (95% CI) ^a	HPV16+	No. Tested	% (95% CI) ^a
Saleh et al. 2021 (33)	Single institution retrospective cohort study	114 FFPE	2011–2020	65.1 (mean)	Female: 51% Male: 49%	Not reported	E6/E7 mRNA ISH	58, 59, 68, 73, 82	14	114	12.3 (6.9 to 19.8)	N/A	N/A	N/A
Schlecht et al. 2011 (34)	Single institution prospective case series	110 matched FF and FFPE	Not reported	62–63 (median)	Female: 30% Male: 70%	African American, non-Hispanic: 24% White, non-Hispanic: 39% Hispanic White: 26% Other race: 11%	E6/E7 RT-PCR	16	8	29	27.6 (12.7 to 47.2)	5	27	18.5 (6.3 to 38.1)
Taberna et al. 2016 (35)	Single institution retrospective case series	404 FFPE	2005–2014	Not reported	Female: 23% Male: 77%	Not reported	E6/E7 mRNA RT-PCR	16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82	N/A	N/A	N/A	4	404	1.0 (0.3 to 2.5)
TOTAL									42	1,065	3.9 (2.9 to 5.3)	23	829	2.8 (1.8 to 4.1)

CI = confidence interval; FF = fresh frozen; FFPE = formalin-fixed paraffin-embedded; HPV+ = HPV-positive; HPV- = HPV-negative; ISH = in situ hybridization; mRNA = messenger ribonucleic acid; RT-PCR = reverse transcription-polymerase chain reaction.

^aConfidence intervals calculated using the Clopper-Pearson exact method.

Average annual number, age-adjusted incidence, and HPV16-attributable estimates of oral cavity and laryngeal cancer, United States, 2016–2020^a

Table 2.

Variable	Oral cavity squamous cell carcinoma ^b			Laryngeal squamous cell carcinoma ^c		
	Average annual no.	Rate	Estimated average annual no. HPV16-attributable cases (95% CI) ^e	Average annual no.	Rate	Estimated average annual no. HPV16-attributable cases (95% CI) ^e
Total	12 612	3.3	497 (361 to 667)	11 170	2.8	309 (198 to 461)
Age						
<50 years	1276	0.7	50 (36 to 68)	607	0.3	17 (11 to 25)
≥50 years	11 336	10.0	447 (324 to 600)	10 564	9.2	293 (187 to 436)
Sex						
Female	5218	2.5	206 (149 to 276)	2275	1.1	63 (40 to 94)
Male	7394	4.1	291 (211 to 391)	8895	4.8	246 (157 to 367)
Race and ethnicity						
Non-Hispanic Black	691	1.6	27 (20 to 37)	1573	3.6	44 (28 to 65)
Hispanic, all races	806	2.0	32 (23 to 43)	773	1.9	21 (14 to 32)
Non-Hispanic other race ^f	693	3.0	27 (20 to 37)	258	1.1	7 (5 to 11)
Non-Hispanic White	9950	3.7	392 (285 to 526)	8250	2.9	229 (146 to 341)

CI = confidence interval; HPV = human papillomavirus; HPV16-AF = HPV16-attributable fraction.

^aData are from the US Cancer Statistics (USCS), which combines cancer registry data from the Centers for Disease Control and Prevention’s National Program of Cancer Registries and the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program. Data meet USCS data quality standards for years 2016–2020, covering 97% of the US population. Rates are per 100 000 persons and age-adjusted to the 2000 US standard population. Numbers might not sum due to rounding. CI = confidence interval; HPV = human papillomavirus; HPV16-AF = HPV16-attributable fractions.

^bDefined by *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3) site codes C02.0–C02.3, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.8, C05.9, C06.0–C06.2, C06.8, and C06.9. Limited to histologically confirmed cases of squamous cell carcinoma (histology codes 8050–8086 and 8120–8131).

^cDefined by ICD-O-3 site codes C32.0–C32.3, C32.8, and C32.9. Limited to histologically confirmed cases of squamous cell carcinoma (histology codes 8050–8086 and 8120–8131).

^dCalculated by multiplying the average annual number of cases by the HPV16-AF and corresponding 95% confidence intervals for each cancer site. The same HPV16-AF were applied across all subgroups, so these estimates may not reflect actual differences in the number of HPV16-attributable cases across subgroups.

^fIncludes Non-Hispanic American Indian or Alaska Native and Non-Hispanic Asian or Pacific Islander. Race and ethnicity data are suppressed for North Dakota and Wisconsin.