Incidence Trends for Human Papillomavirus–Related and –Unrelated Oral Squamous Cell Carcinomas in the United States


ABSTRACT

Purpose
To investigate the impact of human papillomavirus (HPV) on the epidemiology of oral squamous cell carcinomas (OSCCs) in the United States, we assessed differences in patient characteristics, incidence, and survival between potentially HPV-related and HPV-unrelated OSCC sites.

Patients and Methods
Data from nine Surveillance, Epidemiology, and End Results program registries (1973 to 2004) were used to classify OSCCs by anatomic site as potentially HPV-related (n = 17,625) or HPV-unrelated (n = 28,144). Joinpoint regression and age-period-cohort models were used to assess incidence trends. Life-table analyses were used to compare 2-year overall survival for HPV-related and HPV-unrelated OSCCs.

Results
HPV-related OSCCs were diagnosed at younger ages than HPV-unrelated OSCCs (mean ages at diagnosis, 61.0 and 63.8 years, respectively; P < .001). Incidence increased significantly for HPV-related OSCC from 1973 to 2004 (annual percentage change [APC] = 0.80; P < .001), particularly among white men and at younger ages. By contrast, incidence for HPV-unrelated OSCC was stable through 1982 (APC = 0.82; P = .186) and declined significantly during 1983 to 2004 (APC = −1.85; P < .001). When treated with radiation, improvements in 2-year survival across calendar periods were more pronounced for HPV-related OSCCs (absolute increase in survival from 1973 through 1982 to 1993 through 2004 for localized, regional, and distant stages = 9.9%, 23.1%, and 18.6%, respectively) than HPV-unrelated OSCCs (5.6%, 3.1%, and 9.9%, respectively). During 1993 to 2004, for all stages treated with radiation, patients with HPV-related OSCCs had significantly higher survival rates than those with HPV-unrelated OSCCs.

Conclusion
The proportion of OSCCs that are potentially HPV-related increased in the United States from 1973 to 2004, perhaps as a result of changing sexual behaviors. Recent improvements in survival with radiotherapy may be due in part to a shift in the etiology of OSCCs.

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INTRODUCTION

Oral squamous cell carcinomas (OSCCs) arise from the mucosa of the oral cavity and oropharynx.1 OSCCs are the eighth most common cancer among men and the 14th most common among women in the United States.2 Tobacco use and alcohol consumption are known risk factors for OSCCs, and approximately 75% of all OSCCs are attributable to these exposures.3 Recently, human papillomavirus (HPV) infection has been identified as an etiologic agent for a subset of OSCCs, specifically those that arise from the oropharynx, including base of tongue and tonsil.1,4-5 Patients with HPV DNA-positive OSCCs have been shown to be younger in age by 3 to 5 years and are less likely to have a history of tobacco or alcohol use than patients with HPV DNA-negative OSCCs.1 Furthermore, tumor HPV DNA-positivity may confer better prognosis.4-10

Studies in the United States have reported disparate trends in incidence for cancers arising from various anatomic sites in the oral cavity and oropharynx. Whereas the incidence of oral cavity cancers has decreased, oropharyngeal cancer incidence has increased, specifically among younger age groups.11-15 Whereas the declining incidence of oral cavity cancers may be attributed to reductions in tobacco use in the United States,16 reasons underlying the increasing incidence of oropharyngeal cancers are currently unknown. Similar increases in
tonsil cancer incidence from 1970 to 2002 were observed in Sweden.\textsuperscript{17} During the same period, the proportion of HPV DNA-positive tonsil tumors increased from 28% in the 1970s to 68% in the 2000s,\textsuperscript{17} suggesting a dominant role for HPV in the increasing incidence of oropharyngeal cancers.

To explore the potential impact of HPV on the epidemiology of OSCCs in the United States, we used data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program spanning 1973 through 2004.\textsuperscript{18} We classified OSCC anatomic sites as HPV-related and HPV-unrelated based on previously published associations with HPV.\textsuperscript{1,4,5} We assessed differences in patient characteristics, incidence, and survival between HPV-related and HPV-unrelated OSCC sites.

\section*{PATIENTS AND METHODS}

\textbf{Data Sources}

Data on patient demographics, cancer incidence, and overall survival for the period 1973 to 2004 were derived from nine cancer registries covered by the SEER program.\textsuperscript{18} We classified OSCC sites into two groups based on anatomic site-specificity of an etiologic relationship with HPV as follows: sites that are HPV-related (n = 17,625) and sites that are HPV-unrelated (n = 28,144). Molecular and epidemiologic data associate HPV primarily with cancers that arise in the oropharynx, including the lingual and palatine tonsils and base of tongue.\textsuperscript{17} Therefore, HPV-related cancers included the base of tongue (International Classification of Disease for Oncology version-3 [ICD-0-3] topography code: C019), lingual tonsil (C024), palatine tonsil (C090-099), oropharynx (C100-109), and Waldeyer’s ring (C142). The HPV-unrelated sites included cancers of the tongue (C020-023 and C025-029), gum (C030-039), floor of mouth (C040-049), palate (C050-059), and other/unspecified parts of the mouth (C060-069). We excluded cancers of the lip, nasopharynx, salivary gland, hypopharynx, and other and ill-defined sites in the oral cavity and pharynx from all analyses. All analyses were restricted to squamous cell histologies (ICD-0-3 codes: 8050 to 8076, 8078, 8083, 8084, and 8094).

\textbf{Statistical Analyses}

Differences in patient characteristics between HPV-related and HPV-unrelated sites were assessed using the \(\chi^2\) test or student’s \(t\) test. We assessed changes in age at diagnosis by calendar year of diagnosis using linear regression. Incidence rates were age-standardized to the US 2000 standard population.\textsuperscript{18} Time trends by year of cancer diagnosis, expressed as annual percentage change (APC) in incidence, for HPV-related and HPV-unrelated OSCCs overall and across age, sex, and race subgroups were analyzed using log-linear joinpoint regression.\textsuperscript{20}

Incidence data were classified into 13 5-year age groups (ages 20 to 84 years), five 5-year calendar periods (1973 to 1997) and one 7-year period (1998 to 2004), and 18 5-year birth cohorts (1893 to 1978). Age-period-cohort models were used to simultaneously assess the effects of age at diagnosis, calendar period of diagnosis, and birth cohort.\textsuperscript{21-23} In these models, period effects generally denote changes in screening and/or diagnostic practices, whereas cohort effects denote changes in the exposure experiences.\textsuperscript{23} Owing to linear dependencies, the first derivatives (slopes/relative risks) in age-period-cohort models are not uniquely identifiable, however, the second derivatives (changes in slopes) may be uniquely identified using linear contrasts.\textsuperscript{21-23} Therefore, using 10-year intervals, we assessed changes in slopes for the

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Characteristic} & \textbf{HPV-Related} & & \textbf{HPV-Unrelated} & \\
& (n = 17,625) & & (n = 28,144) & \\
& No. & % & No. & % & \(P^t\) & \\
\hline
\textbf{Age at diagnosis, years} & & & & \\
\textbf{Mean} & 61.0 & & 63.8 & & <.001 & \\
\textbf{Standard deviation} & 11.3 & & 12.8 & & & \\
\textbf{Sex} & & & & \\
\textbf{Male} & 12,794 & 72.6 & & 17,416 & 61.9 & <.001 & \\
\textbf{Female} & 4831 & 27.4 & & 10,728 & 38.1 & & \\
\textbf{Race/ethnicity} & & & & \\
\textbf{White} & 14,642 & 83.1 & & 24,030 & 85.4 & <.001 & \\
\textbf{Black} & 2,404 & 13.6 & & 2,673 & 9.5 & & \\
\textbf{Other} & 552 & 3.1 & & 1,338 & 4.7 & & \\
\textbf{Unknown} & 27 & 0.2 & & 103 & 0.4 & & \\
\textbf{Marital status at diagnosis} & & & & \\
\textbf{Never married} & 2,491 & 14.1 & & 3,457 & 12.3 & <.001 & \\
\textbf{Ever married} & 14,299 & 81.1 & & 22,857 & 81.2 & & \\
\textbf{Unknown} & 835 & 4.7 & & 1,830 & 6.5 & & \\
\textbf{Stage at diagnosis} & & & & \\
\textbf{Localized} & 3,054 & 17.3 & & 12,291 & 43.7 & <.001 & \\
\textbf{Regional} & 10,880 & 61.7 & & 11,611 & 41.2 & & \\
\textbf{Distant} & 2,734 & 15.5 & & 1,973 & 7.0 & & \\
\textbf{Unstaged} & 957 & 5.4 & & 2,269 & 8.1 & & \\
\textbf{Radiotherapy} & & & & \\
\textbf{No} & 3,714 & 21.1 & & 14,813 & 52.6 & <.001 & \\
\textbf{Yes} & 13,316 & 75.5 & & 12,552 & 44.6 & & \\
\textbf{Unknown} & 595 & 3.4 & & 779 & 2.8 & & \\
\hline
\end{tabular}
\caption{Characteristics of HPV-Related and HPV-Unrelated Oral Squamous Cell Carcinomas From 1973 to 2004}
\end{table}
period-effect and birth cohort-effect for HPV-related and HPV-unrelated OSCC sites. For example, the test for a change in slope for the 1928 birth cohort denotes the following slope difference: \([1938 to 1928]–[1928 to 1918]\). A statistically significant positive slope difference indicates that an increasing incidence was accelerating (ie, changing more rapidly) or that a decreasing incidence was moderating (ie, changing less rapidly). A statistically significant negative slope difference indicates that an increasing incidence was moderating or that a decreasing incidence was accelerating.13

Radiation treatment for OSCCs, as first course of therapy either alone or in combination with other treatments, was classified into two groups: radiotherapy and no radiotherapy. Differences in 2-year overall survival between HPV-related and HPV-unrelated sites were assessed using life-table methods. Life-table analyses were stratified by stage at diagnosis (SEER historic stage24: localized, regional, and distant), calendar period of diagnosis (1973 to 1982, 1983 to 1992, and 1993 to 2004), and treatment (radiotherapy or no radiotherapy), and differences in survival across strata were assessed using the log-rank test. Using a similar stratification, Cox proportional hazards regression was used to assess differences in 2-year overall survival between HPV-related and HPV-unrelated sites after adjustment for age, race, and sex.

RESULTS

Differences in Demographic Characteristics

Several small but significant differences were observed in demographic characteristics between patients with HPV-related and HPV-unrelated OSCC sites (Table 1). Patients with HPV-related OSCCs were diagnosed at younger ages than patients with HPV-unrelated OSCCs (mean ages at diagnosis, 61.0 and 63.8 years, respectively; \(P < .001\)). Furthermore, age at diagnosis significantly declined from 1973 to 2004 for HPV-related OSCCs (0.5 years decrease per decade; \(P < .001\)), but significantly increased for HPV-unrelated OSCCs (0.7 years increase per decade; \(P < .001\); Fig 1A, online only). Individuals with HPV-related OSCCs were more likely than those with HPV-unrelated OSCCs to be men, black, and never married.

HPV-related OSCCs were predominantly diagnosed at more advanced stages, and likely as a consequence, a substantially higher proportion of patients with HPV-related than HPV-unrelated OSCCs were treated with radiation. The proportions of HPV-related and HPV-unrelated OSCC sites treated with radiation did not appreciably change across calendar periods (78.3% and 49.4%, respectively, for HPV-related and HPV-unrelated OSCCs during 1973 to 1982, and 80.7% and 44.4%, respectively during 1993 to 2004).

Differences in Incidence Trends

Incidence of HPV-related OSCCs increased significantly from 1973 to 2004 (overall APC from 1973 to 2004 = 0.80; \(P < .001\)). In joinpoint regression models, HPV-related OSCC incidence increased significantly from 1973 to 1982 (\(P = .003\)), was stable from 1983 to 1999 (\(P = .854\)), and again increased from 2000 to 2004 (\(P = .016\); Fig 1). In contrast, HPV-unrelated OSCC incidence was stable during 1973 to 1982 (\(P = .186\)) and thereafter significantly decreased during 1983 to 2004 (\(P < .001\)). Notably, there was an equalization of incidence rates for HPV-related and HPV-unrelated OSCCs in year 2004 (3.2/100,000 person-years).

For individual HPV-related anatomic sites, incidence significantly increased during 1973 to 2004 for cancers of base of tongue (APC = 1.27; \(P < .001\)) and tonsil (including lingual tonsil and Waldeyer’s ring, APC = 0.60; \(P < .001\)), but incidence was stable for other cancers of the oropharynx (APC = −0.35; \(P = .196\)). For individual HPV-unrelated anatomic sites, incidence was stable during 1973 to 2004 for tongue cancer (APC = 0.14; \(P = .217\)), and incidence significantly decreased during 1973 to 2004 for cancers of gum (APC = −0.80), floor of mouth (APC = −2.61), palate (APC = −1.77), and other mouth (APC = −1.42; all \(P < .001\)).

Across age groups, HPV-related OSCC incidence was stable in ages 30 to 39 years and 60+ years, whereas incidence increased significantly among ages 40 to 49 years and 50 to 59 years (Fig 2). For HPV-unrelated OSCCs, except an increase in incidence during 1973 to 2004 for the 30 to 39 years group, incidence among all ages (40 to 49 years, 50 to 59 years, and 60+ years) significantly declined during 1973 to 2004 (Fig 2).

Incidence of both HPV-related and HPV-unrelated OSCCs was generally higher among men than women, and among blacks than other races for both sexes (Fig 3). However, incidence trends for HPV-related OSCCs were not consistent across sex and race subgroups. The increasing incidence for HPV-related OSCCs was specifically observed among white men and men of other races (Fig 3A). Incidence of HPV-related OSCC sites among black men increased significantly during 1973 to 1987 and then decreased significantly during 1988 to 2004. Incidence of HPV-unrelated OSCCs among men (Fig 3B) and incidence of HPV-related OSCCs among women (Fig 3C) significantly decreased during 1973 to 2004. For HPV-unrelated OSCCs, incidence declined among white and black women, whereas incidence was stable among women of other races (Fig 3D).

Age-specific incidence rates by birth cohort for HPV-related OSCC sites showed a general pattern of higher incidence among recent birth cohorts as compared with distant birth cohorts (Fig 4A). For example, for ages 40 to 44 years, 45 to 49 years, 50 to 54 years, and
55 to 59 years, incidence rates by birth cohort were lowest for the most distant birth cohorts (cohorts born in the time period from 1918 to 1933); incidence increased thereafter for each successive birth cohort and peaked for the most recent birth cohorts (cohorts born in the time period from 1943 to 1958). Age-specific incidence rates by birth cohort for HPV-unrelated OSCC sites showed a general pattern of decreasing incidence among recent birth cohorts as compared with distant birth cohorts (Fig 4B).

Figure 4C shows slope contrasts for HPV-related and HPV-unrelated OSCC sites derived from models simultaneously adjusting for age, period, and cohort effects. For HPV-related OSCC sites, significant positive changes in slopes were observed for the 1928, 1933, and 1938 birth cohorts, and significant negative changes in slopes were observed for the 1918 and 1948 cohorts. As observed in Fig 4A, the positive changes for 1928, 1933, and 1938 suggest that increasing incidence across these birth cohorts was accelerating, whereas negative changes for 1918 and 1948 suggest that increasing incidence was moderating. For HPV-unrelated OSCC sites, significant negative changes in slopes were observed for the 1908 and 1913 birth cohorts, and a significant positive change in slope was observed for the 1948 cohort. As observed in Fig 4B, the negative changes in slopes for 1908 and 1913 suggest that increasing incidence across these cohorts was moderating, whereas the positive change for the 1948 cohort suggests that declining incidence was moderating. For both HPV-related and HPV-unrelated OSCCs, no significant changes in slopes were observed for period effects, indicating a dominant role for birth cohort effects on the observed incidence patterns.

**Differences in Survival**

Life-table estimates for 2-year overall survival for HPV-related and HPV-unrelated OSCCs after stratification by calendar period of diagnosis, stage at diagnosis, and radiotherapy are listed in Table 2. When treated with radiation, 2-year survival estimates were generally higher for HPV-related OSCCs than HPV-unrelated OSCCs. The survival benefit for HPV-related OSCCs became more apparent in recent calendar periods, and in the most recent calendar period (1993 to 2004), for all stages, patients with HPV-related OSCCs had significantly greater survival rates than those with HPV-unrelated OSCCs. In contrast, when not treated with radiation, 2-year survival was significantly lower for HPV-related than for HPV-unrelated OSCCs. These observations persisted after adjustment for age, sex, and race (data not shown).

For HPV-related (all stages) and HPV-unrelated (localized and distant) OSCC sites treated with radiation, 2-year survival significantly improved across calendar periods, but improvements were more pronounced for HPV-related OSCCs (absolute increase in survival from 1973 through 1982 to 1993 through 2004 for localized, regional, and distant stages = 9.9%, 23.1%, and 18.6%, respectively) than HPV-unrelated OSCCs (5.6%, 3.1%, and 9.9%, respectively). Notably, when treated with radiation, overall improvements in survival across calendar periods for HPV-related OSCCs were observed even when...
analyses were not stratified by stage at diagnosis (2-year survival of 46.3%, 54.4%, and 67.4% in 1973 to 1982, 1983 to 1992, and 1993 to 2004, respectively; P < .01). No significant improvements in survival across calendar periods were observed for either HPV-related or HPV-unrelated OSCCs when not treated with radiation.

**DISCUSSION**

Several of our observations are consistent with the hypothesis that the epidemiology of OSCCs in the United States is actively being changed by HPV. Incidence rates for anatomic sites most strongly associated with HPV (eg, tonsil and base of tongue) are increasing in recent calendar periods and birth cohorts. Likewise, age at diagnosis for HPV-related OSCC sites significantly declined over time, consistent with the reported younger age for individuals with HPV DNA-positive versus HPV DNA-negative OSCCs.\(^1\) As a result of both decreasing incidence for HPV-unrelated OSCC sites and increasing incidence for HPV-related sites, the proportion of all OSCCs that are potentially HPV-related increased over time. Because HPV DNA-positive patients have an improved prognosis,\(^4,6\)-\(^10\) our data suggest that recent improvements in survival may be due in part to a gradual shift in the etiology of the underlying disease.

Our observations of increasing incidence for HPV-related OSCCs, accompanied by decreasing incidence for HPV-unrelated sites, are consistent with previous studies of trends in subsite-specific incidence of constituent OSCCs.\(^11\)-\(^15\) As the procedures for screening, diagnosis, reporting, and coding of OSCCs have not changed significantly over time,\(^15\) it is unlikely that the observed patterns are a result of period effects. The incidence trends by birth cohort and results from age-period-cohort models for both HPV-related and HPV-unrelated OSCCs lend further support to a dominant role for birth cohort effects on the observed incidence patterns. The distinct birth cohort effects we observed for HPV-related and HPV-unrelated OSCCs indicate that the exposure experiences of the underlying populations have significantly changed over time.

The incidence of HPV-unrelated OSCCs declined significantly among recent calendar periods and birth cohorts. This decline in incidence for HPV-unrelated OSCCs may be explained by trends in prevalence of smoking and alcohol consumption among recent birth cohorts.\(^16\),\(^25\) In the United States, smoking prevalence was highest for
cohort year of birth for human papillomavirus (HPV)-related sites and (B) HPV-unrelated sites. (C) Slope contrasts for changes in slopes for birth cohort effects from age-period-cohort models for HPV-related and HPV-unrelated oral squamous cell carcinoma (OSCC) sites. Changes in slopes for birth cohort effects were assessed using 10-year intervals. A statistically significant positive slope difference indicates that an increasing incidence was accelerating (ie, changing more rapidly) or that a decreasing incidence was moderating (ie, changing less rapidly). A statistically significant negative slope difference indicates that an increasing incidence was changing less rapidly or that a decreasing incidence was accelerating.

The incidence of oral tongue cancers among young adults is reportedly increasing.12,13 Further research is needed to understand the reasons underlying this increase.

Smoking and alcohol are also established risk factors for the OSCC subsites we classified as HPV-related. However, the increasing incidence for these sites among recent birth cohorts that have experienced a lower prevalence of smoking and alcohol consumption suggests that the increase is caused by another exposure. Markers of high-risk sexual behavior have increased in recent birth cohorts, including increasing practice of premarital sex, average number of lifetime sex partners, and seroprevalence of herpes simplex virus 2.1,28,29 Such behaviors, including number of lifetime sex partners, oral sex, and a history of sexually transmitted diseases are predictors of oral HPV infections.30 Our observations of increased incidence of HPV-related OSCCs among recent birth cohorts are therefore consistent with changes in sexual behavior in the United States during the 1960s. Perhaps oral HPV prevalence has increased among recent birth cohorts owing to changes in sexual behavior.

Our observation that HPV-related OSCCs were diagnosed at younger ages than HPV-unrelated OSCCs may have arisen from the increasing incidence among recent birth cohorts. Thus, as these recent birth cohorts would age, the increasing incidence of HPV-related OSCCs may be observed among all age groups. The incidence of HPV-related OSCCs was specifically increased among white men and men of other races. These differences in incidence trends across race and sex subgroups may indicate differences in sexual behaviors.

OSCCs with detectable HPV DNA in tumor tissue have better prognosis than HPV DNA-negative OSCCs.4-6,10,31-33 This survival benefit for HPV DNA-positive tumors is believed to arise in part from enhanced sensitivity to radiation and chemotherapy.4,31-33 Consistent with these reports, 2-year overall survival increased appreciably from 1973 to 2004 for HPV-related OSCCs treated with radiation but were more modest for HPV-unrelated cancers. Additionally, significant differences in overall survival for HPV-related versus HPV-unrelated cancers were not observed for any stage during 1973 to 1982 but were observed during 1993 to 2004. Several observations indicate that these survival patterns are not artifactual. As the proportion of HPV-related OSCCs treated with radiation has not appreciably changed over time, the improvement in survival may not be attributed to improved treatment assignment. The improvement in survival for HPV-related OSCCs even when analyses were not stratified by stage at diagnosis argues against stage migration (the so-called Will Rogers phenomenon34,35) as a potential explanation.

We acknowledge, however, that improvements in survival from 1973 to 2004 may be in part attributable to the use of altered fractionated radiotherapy and concurrent chemotherapy during this period, which are associated with significant absolute benefits in 5-year overall survival of 3.4%36 and 8.0%,37,38 respectively. Both of these therapeutic approaches are more likely to be administered to patients with oropharyngeal than oral cavity cancers, and we could not account for this given the available SEER data. However, the absolute benefit in 2-year overall survival of 23.1% we observed for regional stage HPV-related cancers was not observed for any stage during 1973 to 1982 but were observed during 1993 to 2004. Several observations indicate that these survival patterns are not artifactual. As the proportion of HPV-related OSCCs treated with radiation has not appreciably changed over time, the improvement in survival may not be attributed to improved treatment assignment. The improvement in survival for HPV-related OSCCs even when analyses were not stratified by stage at diagnosis argues against stage migration (the so-called Will Rogers phenomenon34,35) as a potential explanation.

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OSCCs owing to increasing presence of HPV DNA in tumors over time.

We note the limitations of our study. Most importantly, our classification of OSCC subsites as potentially HPV-related and HPV-unrelated was based on etiologic evidence from previous studies and not on actual assessment of individual tumor status for presence of HPV DNA. As contemporary estimates for tumor HPV DNA-positivity for sites that we classified as HPV-related are only approximately 70%, our anatomic site-based classification may have resulted in misclassification. However, incidence trends for constituent OSCC subsites were generally similar within the two groups, lending empirical support to our classification. Because our treatment comparisons were observational (ie, not randomized), factors that govern treatment assignment such as anatomic site of cancer and tumor stage may have influenced the observed differences in survival between HPV-related and HPV-unrelated OSCC sites.

In conclusion, our data suggest that the proportion of OSCCs that are potentially HPV-related increased in the United States from 1973 to 2004, particularly among recent birth cohorts, perhaps as a result of changing sexual behaviors. Further research is needed to investigate the role of race and sex on oral sexual behavior, natural history of oral HPV infections, and the immunologic responses to HPV.

The author(s) indicated no potential conflicts of interest.

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**REFERENCES**

Epidemiology of HPV-Related and Unrelated OSCCs in the US

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).