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Uchechukwu C. Megwalu, MD, MPH ©; Davud Sirjani, MD; Erin E. Devine, PhD

Objective: To analyze oropharyngeal squamous cell carcinoma incidence and mortality trends in the United States for the years 1973 through 2013.

Study Design: Cross-sectional study using a large population-based cancer database.

Methods: Data on incidence and mortality rates were extracted from the Surveillance, Epidemiology, and End Results (SEER) 9 Database. Annual percentage change in rates was calculated using jointpoint regression analysis (National Cancer Institute, Bethesda, MD).

Results: Incidence rates increased (annual percent change [APC]; 1.52, 95% confidence interval [CI] 0.17 to 2.88) from 1973 to 1983, remained stable (APC −0.52, 95% CI −1.30 to 0.26) from 1983 to 1997, and increased (APC 1.32, 95% CI 0.83 to 1.81) from 1997 to 2013. Overall, incidence rates increased for males (APC 0.73, 95% CI 0.22 to 1.25) but not females (APC −0.77, 95% CI −0.68 to 0.82). Incidence rates increased in the white population (APC 0.79, 95% CI 0.33 to 1.25) but decreased in the black population (APC −0.72, 95% CI −1.41 to −0.02). The incidence rates increased for tongue-base tumors (APC 1.17, 95% CI 0.42 to 1.92) and tonsil tumors (APC 0.47, 95% CI 1.10 to 4.96) but decreased for other sites. Incidence-based mortality decreased (APC −0.78, 95% CI −1.13 to −0.42) from 1993 to 2013.

Conclusion: Oropharyngeal squamous cell carcinoma incidence rates increased in a nonlinear fashion from 1973 to 2013, whereas mortality rates declined. This, along with variation in trends by demographic and tumor factors, suggest that human papilloma virus is the main driver of the recent rise in incidence.

Key Words: Oropharynx cancer, head and neck cancer, incidence, mortality, SEER program.

Level of Evidence: 2b.

INTRODUCTION

Oropharyngeal cancer accounts for 10% to 12% of all upper aerodigestive tract cancers. It is a major cause of mortality and morbidity; approximately 14,000 cases were diagnosed in the United States in 2013, accounting for 2,400 deaths. The majority of these cancers are squamous cell carcinoma. The major risk factors for oropharyngeal cancer are tobacco use, alcohol consumption, and human papilloma virus (HPV) infection.

Several studies have reported an upward trend in oropharyngeal cancer incidence rates in the United States and other parts of the world, mostly attributed to HPV-related tumors. Many of these studies have analyzed incidence trends in a linear fashion, which does not account for variation in trends over time. Moreover, some investigators have reported stable incidence rates, suggesting that incidence trends have not been consistent over the past few decades. The goals of our study were to analyze oropharyngeal squamous cell carcinoma (OPSCC) incidence trends by demographic and tumor characteristics in the United States for the years 1973 through 2013, and to analyze OPSCC incidence-based mortality.

MATERIALS AND METHODS

This study was exempt from review by the Stanford University Institutional Review Board because it was conducted using de-identified public data. Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) 9 Database of the National Cancer Institute, which includes information from nine high-quality, population-based registries: California (San Francisco and Oakland), Connecticut, Georgia (Atlanta only), Hawaii, Iowa, Michigan (Detroit only), New Mexico, Utah, and Washington (Seattle and Puget Sound region). OPSCC age-adjusted incidence rates were calculated for the years 1973 through 2013. The incidence-based mortality analysis was restricted to deaths that occurred between 1993 and 2013 to prevent underestimation of mortality rates in the early years.

The following International Classification of Diseases for Oncology (ICD-O) codes were included: C01.9 (base of tongue, NOS [not otherwise specified]), C02.4 (lingual tonsil), C05.1 (soft palate, NOS), C05.2 (uvula), C09.0 (tonsillar fossa), C09.1 (tonsillar pillar), C09.8 (overlapping lesion of tonsil), C09.9 (tonsil, NOS), C10.0 (vallecula), C10.2 (lateral wall of oropharynx), C10.3 (posterior wall of oropharynx), C10.8 (overlapping lesion of oropharynx), and C10.9 (oropharynx, NOS). The following...
ICD-O histology codes were included: 8070/3, 8071/3, 8074/3, 8075/3, and 8078/3.

Race was recorded in the SEER database as “White”; “Black”; “Other: American Indian, Alaska Native, Asian/Pacific Islander”; or “Unknown.” Tumor site was grouped as “base of tongue,” “soft palate,” “tonsil,” “pharyngeal wall,” and “Other.” Tumor size and lymph node status are recorded in SEER using Extent of Disease codes (Extent of Disease-4 codes for the years 1983 through 1987, Extent of Disease-10 codes for the years 1988 through 2003, and Collaborative Staging codes for the years 2004 through 2013). These codes were used to obtain information on tumor size and lymph node status for cases diagnosed between 1983 and 2013. Demographic data and information on tumor site and distant metastasis were available for cases diagnosed between 1973 and 2013.

The SEER computer software (SEER*Stat version 8.3.4; National Cancer Institute, Bethesda, MD; Information Management Services, Inc., Calverton, MD) was used to calculate incidence and mortality rates. All rates were age-adjusted to the 2000 U.S. standard population and expressed per 100 thousand person-years. Incidence-based mortality rates were calculated as number of OPSCC deaths among cases diagnosed in the SEER-9 registries over person-time at risk among individuals in the SEER areas. Joinpoint regression analysis program (Joinpoint Regression Program version 4.4.0; National Cancer Institute, Bethesda, MD) was used to calculate annual percentage change (APC) and 95% confidence intervals (CI). T tests were used to determine whether APCs were statistically significantly different from zero. The best-fitting log-linear regression model was selected to identify calendar years (joinpoints) when APCs changed significantly. An estimate was considered statistically significant at \( z = 0.05 \).

RESULTS

The SEER database identified 28,623 cases of OPSCC diagnosed among residents of the SEER-9 areas for the years 1973 through 2013. The case counts and incidence rates according to demographic characteristics are shown in Table I. The majority of the cases were male (74.5%). Although the majority of cases were white, the black population had the highest incidence rates (42.84 per 100,000 person-years). The cases were fairly equally distributed among the < 60-year-old (46%) and ≥ 60-year-old (54%) age groups. However, the ≥ 60-year-old age group had higher incidence rate of OPSCC (95.70 vs. 16.33 per 100,000 person-years)

Overall, the incidence of OPSCC increased from 25.98 (95% CI 23.38 to 28.78) per 100,000 person-years from 1973 to 32.29 (95% CI 30.39 to 34.28) per 100,000 person-years in 2013 (average APC 0.72, 95% CI 0.26 to 1.18). The results of Joinpoint regression analysis (National Cancer Institute) are shown in Figure 1 and Tables II and III. OPSCC incidence rates increased annually by 1.52% (95% CI 0.17 to 2.88%) from 1973 to 1983, remained stable (APC -0.52, 95% CI -1.30 to 0.26) from 1983 to 1997, and increased annually by 1.32% (95% CI 0.83 to 1.81%) from 1997 to 2013. OPSCC incidence rates increased in the male population (average APC 0.73, 95% CI 0.22 to 1.25) but remained stable in the female population (average APC -0.77, 95% CI -0.68 to 0.82) from 1973 to 2013. OPSCC incidence rates increased for both the < 60-year-old (average APC 0.65, 95% CI 0.46 to 0.84) and ≥ 60-year-old (average APC 0.76, 95% CI 0.22 to 1.31) age groups from 1973 to 2013. OPSCC incidence rates remained stable (average APC 0.76, 95% CI 0.22 to 1.31) but increased annually by 2.26% (95% CI 2.16% to 2.36%) from 2004 to 2013.

Incidence trends by clinical factors are shown in Table III. The incidence trends varied by tumor site. The incidence rates increased for tongue-base tumors (average APC 1.17, 95% CI 0.42 to 1.92) and tonsil tumors (average APC 0.47, 95% CI 1.10 to 4.96) but decreased for soft palate (average APC -2.87, 95% CI -3.46 to -2.28) and pharyngeal wall (average APC -0.96, 95% CI -1.74 to -0.18) tumors from 1973 to 2013. The incidence rates of tumors with distant metastasis decreased annually by 2.26% (95% CI 1.69% to 2.82%) from 1973 to 2001, remained stable (APC 24.58, 95% CI -10.4 to 73.31) from 2001 to 2004, and then increased annually by 2.76% (95% CI 0.67% to 4.90%) from 2004 to 2013. In contrast, the incidence rates of tumors without distant metastasis increased during the years 1973 to 2013.

Information on tumor size and lymph node status was available for cases diagnosed between 1983 and 2013. The incidence rates increased for all tumor size groups from 1983 to 2013. The incidence trends varied by lymph node status. The incidence rates of tumors
with lymph node metastasis increased annually by 2.00% (95% CI 1.31% to 2.70%) from 1983 to 2001, increased annually by 5.62% (95% CI 2.87% to 8.44%) from 2001 to 2008, and then remained stable (APC −0.19, 95% CI −3.12 to 2.83) from 2008 to 2013. In contrast, the incidence rates of tumors without lymph node metastasis decreased annually by 0.93% (95% CI 0.51% to 1.35%) from 1973 to 2013.

The incidence trends are compared between OPSCC and cervical squamous cell carcinoma in Figure 2.

### TABLE II.

Oropharyngeal Squamous Cell Carcinoma Incidence Trends by Demographic Factors.

<table>
<thead>
<tr>
<th></th>
<th>Overall (1973–2013)</th>
<th>Trend 1</th>
<th></th>
<th>Trend 2</th>
<th></th>
<th>Trend 3</th>
<th></th>
<th>Trend 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average APC (95% CI)</td>
<td>Year</td>
<td>APC (95% CI)</td>
<td>Year</td>
<td>APC (95% CI)</td>
<td>Year</td>
<td>APC (95% CI)</td>
<td>Year</td>
<td>APC (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.72</td>
<td>1973 to</td>
<td>1.52 (0.17, 2.88)</td>
<td>1983 to</td>
<td>−0.52 (−1.30, 0.26)</td>
<td>1997 to</td>
<td>1.32 (0.83, 1.81)</td>
<td>2009 to</td>
<td>−1.67 (−5.01, 1.79)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.73</td>
<td>1973 to</td>
<td>0.49 (0.23, 0.74)</td>
<td>2002 to</td>
<td>3.17 (1.07, 5.31)</td>
<td>2009 to</td>
<td>−0.25 (−1.01, 0.51)</td>
<td>2013 to</td>
<td>−1.67 (−5.01, 1.79)</td>
</tr>
<tr>
<td>Female</td>
<td>−0.77</td>
<td>1973 to</td>
<td>0.07 (−0.88, 0.82)</td>
<td>1992 to</td>
<td>−8.82 (−28.34, 16.02)</td>
<td>1995 to</td>
<td>−0.25 (−1.01, 0.51)</td>
<td>2013 to</td>
<td>−1.67 (−5.01, 1.79)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>0.79</td>
<td>1973 to</td>
<td>0.22 (−0.05, 0.48)</td>
<td>2000 to</td>
<td>3.52 (1.86, 5.22)</td>
<td>2008 to</td>
<td>−0.42 (−2.77, 1.98)</td>
<td>2013 to</td>
<td>−2.77 (1.98)</td>
</tr>
<tr>
<td>Black</td>
<td>−0.72</td>
<td>1973 to</td>
<td>4.61 (2.16, 7.11)</td>
<td>1984 to</td>
<td>−2.66 (−3.09, −2.23)</td>
<td>2013 to</td>
<td>−2.77 (1.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>−0.12</td>
<td>1973 to</td>
<td>−0.12</td>
<td>2013 to</td>
<td>−0.80 (−0.80, 0.57)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, in years</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>&lt; 60</td>
<td>0.65</td>
<td>1973 to</td>
<td>0.65 (0.46, 0.84)</td>
<td>2013 to</td>
<td>0.65 (0.46, 0.84)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>0.76</td>
<td>1973 to</td>
<td>1.91 (0.28, 3.57)</td>
<td>1983 to</td>
<td>−0.83 (−1.50, −0.15)</td>
<td>2000 to</td>
<td>1.98 (1.16, 2.81)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APC = annual percent change; CI = confidence interval.
TABLE III.
Oropharyngeal Squamous Cell Carcinoma Incidence Trends by Clinical Factors.

<table>
<thead>
<tr>
<th>Site</th>
<th>Overall Average APC (95% CI)</th>
<th>Trend 1</th>
<th>Trend 2</th>
<th>Trend 3</th>
<th>Trend 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year</td>
<td>APC (95% CI)</td>
<td>Year</td>
<td>APC (95% CI)</td>
<td>Year</td>
</tr>
<tr>
<td><em>Tongue base</em></td>
<td>1.17 (0.42, 1.92)</td>
<td>1973 to 1983</td>
<td>3.26 (1.47, 5.07)</td>
<td>1983 to 1995</td>
<td>−0.64 (−1.89, 0.63)</td>
</tr>
<tr>
<td>Tonsil</td>
<td>0.47 (1.10, 4.96)</td>
<td>1973 to 1998</td>
<td>0.11 (−0.25, 0.48)</td>
<td>1998 to 2013</td>
<td>1.92 (1.31, 2.53)</td>
</tr>
<tr>
<td>Soft palate</td>
<td>−2.87 (−3.46, −2.28)</td>
<td>1973 to 1990</td>
<td>−0.54 (−1.59, 0.53)</td>
<td>1990 to 2013</td>
<td>−4.56 (−5.28, −3.84)</td>
</tr>
<tr>
<td>Pharyngeal wall</td>
<td>−0.96 (−1.74, −0.18)</td>
<td>1973 to 2013</td>
<td>−0.96 (−1.74, −0.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.35 (0.83, 1.88)</td>
<td>1973 to 2013</td>
<td>1.35 (0.83, 1.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>0.66 (−1.78, 3.17)</td>
<td>1973 to 2001</td>
<td>−2.26 (−2.82, −1.69)</td>
<td>2001 to 2004</td>
<td>24.58 (−10.45, 73.31)</td>
</tr>
<tr>
<td>No distant metastasis</td>
<td>1.03 (0.51, 1.55)</td>
<td>1973 to 1980</td>
<td>3.77 (0.81, 6.82)</td>
<td>1980 to 2013</td>
<td>0.46 (0.25, 0.67)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>0.03 (0.00, 0.06)</td>
<td>1973 to 1997</td>
<td>−15.73 (−27.85, −1.57)</td>
<td>1977 to 1991</td>
<td>−0.15 (−3.06, 2.85)</td>
</tr>
<tr>
<td>unknown</td>
<td>1.78 (0.92, 2.65)</td>
<td>1983 to 1995</td>
<td>0.03 (−1.84, 1.93)</td>
<td>1995 to 2013</td>
<td>2.97 (2.16, 3.78)</td>
</tr>
<tr>
<td>Size: ≤ 2 cm</td>
<td>2.44 (1.89, 2.99)</td>
<td>1983 to 2013</td>
<td>2.44 (1.89, 2.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size: &gt; 4 cm</td>
<td>0.41 (−0.03, 0.85)</td>
<td>1983 to 1996</td>
<td>−0.70 (−1.55, 0.15)</td>
<td>1996 to 2013</td>
<td>1.26 (0.78, 1.75)</td>
</tr>
<tr>
<td>Node: positive</td>
<td>2.46 (1.60, 3.33)</td>
<td>1983 to 2001</td>
<td>2.00 (1.31, 2.70)</td>
<td>2001 to 2008</td>
<td>5.62 (2.87, 8.44)</td>
</tr>
<tr>
<td>Node: negative</td>
<td>−0.93 (−1.35, −0.51)</td>
<td>1983 to 2013</td>
<td>−0.93 (−1.35, −0.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node: unknown</td>
<td>0.41 (−0.03, 0.85)</td>
<td>1983 to 1996</td>
<td>−0.70 (−1.55, 0.15)</td>
<td>1996 to 2013</td>
<td>1.26 (0.78, 1.75)</td>
</tr>
</tbody>
</table>

APC = annual percent change; CI = confidence intervals.
OPSCC incidence rates have surpassed cervical squamous cell carcinoma incidence rates since 2000. Comparing incidence rates from 2009 to 2013 by sex, the incidence of cervical squamous cell carcinoma in women was 41.4 (95% CI 40.0 to 42.9) per 100,000 person-years, whereas the incidences of OPSCC were 55.8 (95% CI 54.1 to 57.5) for men and 11.6 (95% CI 10.9 to 12.4) for women. The incidence of mortality due to OPSCC decreased from 22.58 (95% CI 20.65 to 24.63) per 100,000 person-years in 1993 to 20.63 (95% CI 19.08 to 22.27) per 100,000 person-years in 2013 (average APC 0.78, 95% CI 1.13 to 0.42). This decrease in mortality was consistent throughout this period (Fig. 1).

DISCUSSION

Our study showed an overall increase in OPSCC incidence rates in the United States between 1973 and 2013. However, the incidence trend was not stable throughout this period. Incidence rates increased between 1973 and 1983, remained stable between 1983 and 1997, and then increased again between 1997 and 2013. Incidence trends varied by sex, with an increase in the male population and stable rates in the female population. Incidence trends varied by race, with an overall increase in the white population and a decrease in the black population. Incidence rates increased for both the < 60-year-old and ≥ 60-year-old age groups, and for all tumor sizes. Incidence rates increased for tumors of the tongue base and tonsil but decreased for tumors of other oropharyngeal subsites. Incidence rates increased for lymph node metastasis, while declining for tumors without lymph node metastasis. In spite of the rising OPSCC incidence rates, our study showed a significant decline in the incidence-based mortality rates.

Several studies have reported an increase in OPSCC incidence trends in the United States over the years. Ernster et al. compared the incidence rates of OPSCC between two time periods (1980 to 1990, 1991 to 2001) using SEER data. They found an increase in age-adjusted incidence rates for the U.S. population. Similar to our study, they found an increase in incidence rates for males. They found a decrease in incidence rates for females, contrary to our study, which showed that the incidence rate has remained stable in the female population. Katzel et al. examined incidence rates of oropharyngeal and oral cavity cancer using electronic medical records and the cancer registry of Kaiser Permanente of Northern California (a contributor to the SEER database) from 1995 to 2010. Similar to our study, they found an annual increase in incidence rate of 3.8% per year from 1995 to 2010 for HPV-related oropharyngeal cancers, which they defined as cancers for the following sites: base of tongue, lingual tonsil, palatine tonsil, oropharynx, and Waldeyer’s ring. Interestingly, the incidence rates increased in smokers but remained stable in nonsmokers. In contrast, Gupta et al. performed an analysis of incidence trends of upper aerodigestive tract squamous cell carcinoma in Ontario, Canada, and the United States between 1984 and 2001. Incidence trends were analyzed using joinpoint regression. They found that the incidence rate of OPSCC in the United States remained stable throughout the study period. This is consistent with our study, which shows that, although the incidence rates increased overall from 1973...
to 2013, the incidence rates were stable from 1983 to 1997.

In the Canadian literature, Auluck et al. analyzed OPSCC incidence trends in British Columbia, Canada, for the years 1980 through 2006. APC was calculated for age-adjusted incidence for the entire period of 1980 through 2006. Similar to our study, the incidence rates increased in the male population but remained stable in the female population from 1980 to 2006. The authors did not report on incidence trends for both genders combined. In addition, several studies have reported an increase in OPSCC incidence rates in other parts of the world, such as New Zealand, Australia, and Scotland.

Chaturvedi et al. evaluated incidence trends for oropharyngeal cancers in 23 countries across five continents for the years 1983 through 2001. They found a significant increase in oropharyngeal cancer incidence for men in economically developed countries (including the United States) but no increase in economically developing countries. For women, an increase in incidence rates was observed only in European countries. They found a decrease in incidence rates for women in the United States.

Our study showed an increase in OPSCC incidence rates between 1973 and 1983, stable incidence rates between 1983 and 1997, and then an increase between 1997 and 2013. The reason for this pattern is unclear. However, there are several potential explanations. We hypothesize that the initial rise in rise in the incidence of OPSCC between 1973 and 1983 was due to an increase in tobacco-related cancers. Per capita cigarette consumption rapidly increased between the 1930s and 1970s and has steadily declined since. In addition, we hypothesis that the rise in the incidence of OPSCC since 1997 is primarily due to an increase in the incidence of HPV-related cancers in patients who were sexually active during or after the U.S. sexual revolution of the 1960s and 1970s. Several studies have shown an increase in the number of sexual partners and prevalence of HPV infection in this cohort.

HPV-positive oropharyngeal cancers have distinct demographic and clinicopathologic characteristics. They tend to arise in the tonsils and tongue base. Our study revealed an increase in incidence rates for tumors of the tongue base and tonsil, and a decrease in incidence rates for other oropharyngeal subsites. This is also supported by findings from other studies showing increasing incidence rates for tongue-base and tonsil tumors. HPV-positive tumors usually present with high rates of nodal metastasis.

Our study also showed that incidence rates increased for tumors with lymph node metastasis while declining for tumors without lymph node metastasis. Furthermore, HPV-positive tumors are more common in white males. Our study may explain the racial and gender disparities in OPSCC incidence trends in our study. Our study showed that incidence rates increased in the white population, whereas incidence rates rose sharply in the black population between 1973 and 1984 and then steadily declined between 1984 and 2013. Previous studies have reported on the racial divergence in incidence trends of oropharyngeal cancer.

CONCLUSION

OPSCC incidence rates significantly increased in the United States between 1973 and 2013 but not at a stable rate throughout this period. Incidence rates increased between 1973 and 1983, remained stable between 1983 and 1997, and then increased again between 1997 and 2013. In spite of rising incidence rates, OPSCC incidence-based mortality rate has significantly declined. Differences in incidence trends by demographic and clinical factors, as well as the paradoxical decline in mortality due to OPSCC, are consistent with an increase in the incidence of HPV-related cancers.
HPV vaccines have been available since 2006 and are recommended by the Advisory Committee on Immunization Practices for routine vaccination of adolescent girls and boys aged 11 or 12 years. Future studies are needed to evaluate the impact of these vaccines on OPSCC incidence trends. Given that the average age at OPSCC presentation is approximately 60 years, it may take another 40 to 50 years to appreciate the effects of vaccination on incidence rates.

BIBLIOGRAPHY