

Rising Population of Survivors of Oral Squamous Cell Cancer in the United States

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BACKGROUND: The incidence of oropharyngeal cancer (OPC) and a subset of oral cavity cancer (OCC) is increasing in the United States. To the authors' knowledge, the presumed growing prevalence of survivors of OPC and OCC has not been investigated to date. **METHODS:** Retrospective analysis of Surveillance, Epidemiology, and End Results data (1975-2012) estimated changes in incidence, 5-year cause-specific survival, and prevalence for OPC and OCC. Changes in incidence, cause-specific survival and prevalence were estimated by linear regression and expressed as the percentage change (*B*). Differences in incidence trends over time were determined by joinpoint analysis. **RESULTS:** The incidence of OPC increased by 62.6% from 1975 through 2012. Notable increases in OPC incidence were observed among men, white individuals, and those of younger ages. The 5-year survival for OPC increased significantly for all sexes, races, and individuals aged >30 years, with white individuals and males experiencing the largest increase in survival. By contrast, the incidence of OCC declined by 22.3% during the same time period. OCC incidence decreased across all groups but increased among individuals aged 30 to 39 years. Significant increases in survival were observed for OCC, except for those who were female, black, and aged <40 years. The prevalence of survivors of OPC increased from 2000 to 2012 (*B*, 115.1 per 100,000 individuals per year; *P*<.0001), whereas the prevalence of survivors of OCC significantly decreased (*B*, -15.8 per 100,000 individuals per year; *P*<.0001). **CONCLUSIONS:** The prevalence of survivors of OPC is increasing, whereas the prevalence of survivors of OCC is declining. These data portend significant implications for long-term care planning for survivors of OPC and OCC. *Cancer* 2016;122:1380-7. © 2016 American Cancer Society.

KEYWORDS: human papillomavirus, oral cancer, oropharyngeal cancer, survivors.

INTRODUCTION

Population-based studies in the United States and developed countries have reported significant increases in oral squamous cell cancer (OSCC), which includes oropharyngeal cancer (OPC) and oral cavity cancer (OCC).¹ The epidemiologic shifts in OSCC have been attributed primarily to the increasing incidence of human papillomavirus (HPV)-related OPC.² Indeed, the incidence of OPC in the United States is projected to surpass that of cervical cancer and is responsible for the largest burden of HPV-related malignancy in men.² Patients with OPC are characteristically young and have a good prognosis.³⁻⁹

Although the incidence of OCC overall is declining in the United States,¹⁰ the incidence among young females has increased dramatically in recent decades, the etiology of which is poorly understood and does not appear to be related to HPV infection.¹¹⁻¹⁵ Improvements in survival have been limited to individuals treated with radiotherapy.¹⁶ It is interesting to note that a shift in the treatment paradigm from single modality (surgery or radiotherapy) in the mid-1970s to primary surgery with or without radiotherapy in the late 1990s has been observed.^{10,17}

The improved prognosis of patients with OPC combined with the steadily increasing incidence of both OPC and a subset of OCC¹ suggests a rising prevalence of survivors of OSCC. Despite the growing emphasis on improved understanding of the survivorship trajectory,¹⁸ to our knowledge the extent of the US population comprising survivors of OSCC has not been investigated to date. Population-based prevalence estimates for OSCC are crucial to inform accurate survivorship planning for health care practice, spending, and policy as well as research priorities. In the current study, changes in the prevalence of survivors of OSCC over time are described.

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MATERIALS AND METHODS

Data Set

Data were obtained from Surveillance, Epidemiology, and End Results (SEER) registries for 1975 through 2012. For estimating population-based incidence and limited-duration prevalence (LDP) across this time period, SEER 9 registries were used, in which all regions contributed cases diagnosed in 1975 or later.¹⁹ Cause-specific survival (CSS) was estimated using SEER 18 registries, which included regions that joined the SEER program after 1975.²⁰

Site Classification

The classification of OPC and OCC was consistent with previous studies and American Joint Committee on Cancer anatomic site classifications.^{16,21,22} Briefly, OPC included the tongue (C019), lingual tonsil (C024), palatine tonsil (C090-C099), oropharynx (C100-109), and Waldeyer ring (C142). OCC included the tongue (C020-C023 and C028-C029), gum (C030-039), and oral cavity (C040-049 and C060-069). Cancers of the lip and ill-defined sites were excluded. Analysis was limited to squamous cell histology (*International Classification of Diseases for Oncology, Third Edition* [ICD-0-3] codes 8050-8076, 8078, 8083, 8084, and 8094). All tumors matching the selection criteria were included, regardless of whether the tumor was the patient's first primary malignancy. Survival analysis was based on the time from the diagnosis of the first head and neck primary tumor.

Statistical Analysis

SEER*Stat software (version 8.2.1) was used to estimate the incidence of OPC and OCC, 5-year CSS, 25-year LDP, and the prevalence of 5-year to 10-year survivors overall and modeled separately by sex (males vs females), race (white, black, and other), and decade of life (aged 20-29, 30-39, 40-49, 50-59, and ≥ 60 years). Incidence rates for each year from 1975 to 2012 were calculated as the age-adjusted number of new cases per 100,000 individuals. The 5-year CSS, the probability of surviving the cancer diagnosis of interest in the absence of any other causes of death, was estimated for each year from 1975 to 2007, the last year for which those diagnosed in that year would have at least 5 years of survival (to 2012).

The prevalence of survivors was calculated by the 25-year LDP. The 25-year LDP is defined as the percentage of individuals alive during the year examined who were diagnosed within the past 25 years with the condition of interest.^{23,24} Because the study period begins in 1975, the 25-year LDP was calculated as of January 1 for

each year from 2000 to 2012 only. For example, the LDP for 2000 represents the percentage of patients alive on January 1, 2000 who were diagnosed with cancer between 1975 and 1999. The LDP of 5-year to 10-year survivors was estimated to determine the prevalence of those diagnosed 5 to 10 years earlier than the year of interest and still alive in the year of interest, to ascertain the prevalence of "long-term survivors." This was calculated as of January 1 for each year from 1985 to 2012 using the previous 5 to 10 years (eg, the LDP of those diagnosed from 1975 to 1979 as of January 1, 1985).

To examine the changes in incidence over time, the annual percent change (APC) and percentage change were calculated using SEER*Stat statistical software.²³ Joinpoint software was used to estimate differences in incidence trends over time between patient groups (based on sex, race, and age).^{25,26} Yearly changes in the 5-year CSS, 25-year LDP, and the prevalence of 5-year to 10-year survivors during their respective intervals were summarized using simple linear regression methods. Each outcome from SEER*Stat was modeled as a function of time (continuous yearly) to calculate a slope for the per-year change. Slopes (*B*) were calculated separately for OSCC overall; OPC and OCC; and by sex, age, and racial groups. To explore whether changes over time differed across patient groups, regression models were performed with interactions between time and patient group. Analyses were completed using R statistical software (version 3.1.2).²⁷

RESULTS

Incidence Trends

The incidence of OPC increased by 62.6%, whereas the incidence of OCC declined by 22.3% from 1975 to 2012 (see online Supporting Information Table 1) (Fig. 1). The increase in the incidence of OPC was primarily noted among males, whereas the incidence of OCC declined among both males and females. The incidence of OPC increased among whites and decreased among blacks. A declining incidence of OCC was observed for all races. Notable increases in the incidence of OPC were observed across age groups, most dramatically among younger age groups (eg, a 332.1% increase for those aged 20-29 years). By contrast, significant decreases in the incidence of OCC were observed in all age groups aged >40 years during the period between 1975 and 2012, except for a large 106.3% increase that was observed among individuals aged 30 to 39 years.

Changes in incidence by calendar periods were estimated (see online Supporting Information Table 2). For

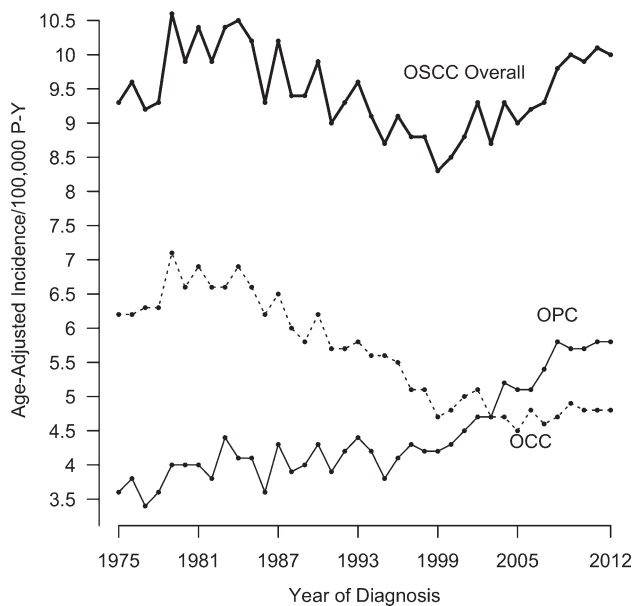


Figure 1. Age-adjusted incidence trends over time for oral squamous cell cancer, oropharyngeal cancer (OPC), and oral cavity cancer (OCC). P-Y indicates per year.

OPC, small but significant increases in incidence from 1975 to 1998 were noted for males and whites, but thereafter dramatically increased from 1998 to 2012 for both males (APC, 3.01; $P > .05$) and whites (APC, 3.29; $P < .05$). By contrast, the incidence of OCC among men from 1975 to 1984 was stable, followed by a significant decrease from 1984 to 2003 (APC, -2.38 ; $P < .05$). The incidence of OCC among women steadily and significantly declined from 1975 to 2009 (APC, -0.79 ; $P < .05$). Among whites, the incidence of OCC was stable from 1975 to 1983, significantly declined from 1983 to 2004 (APC, -1.53 ; $P < .05$), and then significantly increased from 2004 to 2012 (APC, 0.89; $P < .05$). However, among blacks, the incidence of OCC was stable from 1975 to 1990, and then significantly decreased from 1990 to 2012 (APC, -4.58 ; $P < .05$).

Until 1998, the incidence of OPC among individuals aged 50 to 59 years was stable, but it subsequently significantly increased from 1998 to 2005 (APC, 5.25; $P < .05$). Similar increases in the incidence of OPC were observed for those aged ≥ 60 years from 2000 to 2012 (APC, 3.05; $P < .05$). During the entire study period, those aged 30 to 39 years and 40 to 49 years with OPC had significant increases in incidence, albeit a smaller one than individuals in the older age groups (APC, 0.80 and 1.65, respectively; $P < .05$ for each). Similar significant annual increases in the incidence of OCC were observed among individuals aged 50 to 59 years from 2007 to 2012

(APC, 4.05; $P < .05$) and among those aged 30 to 39 years from 1975 to 2012 (APC, 0.83; $P < .05$). There were distinct periods of significant decline in incidence for individuals aged ≥ 50 years before 2007. Between 1975 and 2012, the incidence of OCC increased significantly, albeit slightly, among individuals aged 30 to 39 years, whereas a significant decrease was observed among individuals aged 40 to 49 years (APC, 0.83 and -1.69 , respectively; $P < .05$).

Changes in 5-Year CSS

Significant improvements in 5-year survival were observed for OPC and OCC from 1975 to 2007 (Fig. 2) (Table 1). The 5-year survival for OPC dramatically improved across all genders, races and age groups > 30 years ($P < .005$ for all). An increase of $> 1\%$ in the CSS per year was observed for males and for individuals aged 40 to 49 years with OPC ($B > 1.0$; $P < .0001$). More modest, yet significant, increases in survival were observed for OCC ($P < .001$ for all), except for among females, blacks, and those aged < 40 years. Although survival improved for both OPC and OCC, the annual rate of improvement was significantly more rapid for OPC compared with OCC overall (B , 0.91% vs 0.20%; $\Delta B = 0.71$ [$P < .0001$]). A greater rate of average annual improvement in survival was observed for OPC compared with OCC for males, females, whites, black, and individuals of all ages > 40 years (ΔB range, 0.61-1.00; $P < .0001$).

Prevalence Trends

The prevalence of survivors of OPC increased significantly from 2000 to 2012 (B , 115.1 per 100,000 per year; 95% confidence interval [95% CI], 105.5-124.7 [$P < .0001$]) (Table 2), whereas the prevalence of survivors of OCC significantly decreased (B , -15.8 per 100,000 per year; 95% CI, -19.1 to -12.5 [$P < .0001$]). The most dramatic increases in the number of OPC cases per 100,000 individuals per year were observed among males, whites, and those aged 50 to 59 years ($P < .001$), although significant increases also were observed for females, non-whites, and all age groups examined. By contrast, there were significant decreases in prevalence noted across all demographics of OCC ($P < .0001$ for each), except for individuals aged < 50 years. The growth of survivors of OPC was dramatically increased relative to the decrease in survivors of OCC (ΔB , 130.88; $P < .001$), and was further pronounced among males and whites.

To closely examine the change in the prevalence of long-term survivors, the prevalence of 5-year to 10-year survivors was estimated (Fig. 3) (see online Supporting

Information Table 3). The prevalence of long-term survivors of OPC increased significantly from 1985 to 2012 (B , 18.3; 95% CI, 16.1-20.5). Increases in the prevalence of survivors of OPC were most notable for males, whites, and individuals aged >40 years (B , 4.7-36.3; P <.001 for all). Conversely, the prevalence of long-term survivors of OCC declined overall, and among all demographic

groups of interest except for individuals aged <40 years (B , -1.1 to -20; P <.001 for all).

DISCUSSION

The increasing incidence of OPC combined with significant improvements in 5-year survival rates for OPC and OCC has resulted in a rising population of survivors of OSCC in the United States. The population-based changes for OPC are dramatic. On average, between 2000 and 2012, the number of survivors of OPC per year increased by 115 per 100,000 individuals (Table 2). By contrast, although survival for OCC has improved in recent time periods, the prevalence of survivors of OCC has declined. The rising percentage of the population with OPC portends substantial policy and public health planning implications, particularly for survivorship care and health maintenance needs.^{28,29}

Although previously speculated on and a consideration in planning clinical trials, the dramatically increased prevalence of survivors of OPC in the United States in recent decades to our knowledge has not been described previously.³⁰⁻³² It is important to note that survivor prevalence estimates are based on time periods of greatest relevance to HPV-related OPC.² The greatest increases in survivors of OPC were observed among males (B , 229.9; 95% CI, 211.3-248.5 [P <.001]), white individuals (B , 142.1; 95% CI, 130.7-153.5 [P <.0001]), and individuals aged 50 to 59 years (B , 50.3; 95% CI, 47.8-52.8

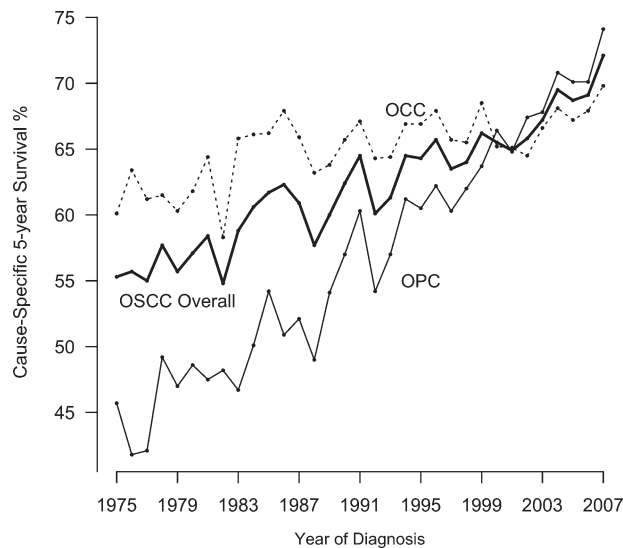


Figure 2. Five-year cause-specific survival over time for oral squamous cell cancer (OSCC), oropharyngeal cancer (OPC), and oral cavity cancer (OCC).

TABLE 1. Average Changes in 5-Year Cause-Specific Survival From 1975 to 2007

| | OSCC Overall | | OPC | | OCC | | OPC Versus OCC | |
|---------------|---------------------------|------------------|---------------------------|------------------|---------------------------|------------------|----------------|------------------|
| | B (95% CI) ^a | P ^b | B (95% CI) ^a | P ^b | B (95% CI) ^a | P ^b | ΔB | P ^c |
| Entire cohort | 0.45 (0.39-0.51) | <.0001 | 0.91 (0.83-0.99) | <.0001 | 0.2 (0.13-0.27) | <.0001 | 0.71 | <.0001 |
| Sex | | | | | | | | |
| Male | 0.59 (0.52-0.66) | <.0001 | 1.06 (0.97-1.15) | <.0001 | 0.28 (0.21-0.35) | <.0001 | 0.77 | <.0001 |
| Female | 0.21 (0.12-0.3) | <.0001 | 0.58 (0.41-0.75) | <.0001 | 0.05 (-0.05-0.15) | .32 | 0.53 | <.0001 |
| Race | | | | | | | | |
| White | 0.48 (0.43-0.53) | <.0001 | 0.95 (0.87-1.03) | <.0001 | 0.22 (0.15-0.29) | <.0001 | 0.73 | <.0001 |
| Black | 0.15 (0.01-0.29) | .04 | 0.51 (0.31-0.71) | <.0001 | -0.1 (-0.27-0.07) | .27 | 0.61 | <.0001 |
| Other | 0.27 (0.03-0.51) | .04 | 0.46 (-0.09-1.01) | .11 | 0.35 (0.05-0.65) | .03 | 0.11 | .73 |
| Age, y | | | | | | | | |
| 20-29 | 2.79 (-0.03-5.61) | .19 | -0.21 (-1.34-0.92) | .72 | 0.23 (-0.48-0.94) | .53 | -0.44 | .51 |
| 30-39 | 0.5 (0.12-0.88) | .02 | 0.79 (0.28-1.3) | .005 | 0.34 (-0.08-0.76) | .12 | 0.45 | .19 |
| 40-49 | 0.65 (0.54-0.76) | <.0001 | 1.23 (1.01-1.45) | <.0001 | 0.23 (0.11-0.35) | <.0001 | 1.00 | <.0001 |
| 50-59 | 0.49 (0.41-0.57) | <.0001 | 0.92 (0.77-1.07) | <.0001 | 0.18 (0.09-0.27) | <.0001 | 0.74 | <.0001 |
| ≥60 | 0.38 (0.31-0.45) | <.0001 | 0.77 (0.67-0.87) | <.0001 | 0.2 (0.11-0.29) | <.0001 | 0.57 | <.0001 |

Abbreviations: 95% CI, 95% confidence interval; OCC, oral cavity cancer; OPC, oropharyngeal cancer; OSCC, oral squamous cell cancer.

^a B represents the percentage change in cause-specific survival per year.

^b P values testing for significantly positive slopes within OPC and OCC.

^cInteraction P values for differences in the slopes between OPC and OCC.

TABLE 2. Average Changes in Age-Adjusted Prevalence^a From 2000 to 2012

| | OSCC Overall | | OPC | | OCC | | OPC Versus OCC | |
|---------------|-------------------------|----------------|-------------------------|----------------|-------------------------|----------------|----------------|----------------|
| | B (95% CI) ^b | P ^c | B (95% CI) ^b | P ^c | B (95% CI) ^b | P ^c | ΔB | P ^d |
| Entire cohort | 98.9 (86.5-111.3) | <.0001 | 115.1 (105.5-124.7) | <.0001 | -15.8 (-19.1--12.5) | <.0001 | 130.88 | <.0001 |
| Sex | | | | | | | | |
| Male | 210.6 (188-233.2) | <.0001 | 229.9 (211.3-248.5) | <.0001 | -18.4 (-23.1--13.7) | <.0001 | 248.26 | <.0001 |
| Female | -5.5 (-10--1) | .04 | 10.2 (7.8-12.6) | <.0001 | -15.6 (-18.2--13) | <.0001 | 25.72 | <.0001 |
| Race | | | | | | | | |
| White | 133.9 (119.7-148.1) | <.0001 | 142.1 (130.7-153.5) | <.0001 | -7.6 (-11.1--4.1) | .001 | 149.64 | <.0001 |
| Black | -58.7 (-70.6--46.8) | <.0001 | 26.8 (19.1-34.5) | <.0001 | -84.9 (-95.5--74.3) | <.0001 | 111.64 | <.0001 |
| Other | 15.4 (8.2-22.6) | .002 | 20.7 (17-24.4) | <.0001 | -4.7 (-10.6-1.2) | .15 | 25.32 | <.0001 |
| Age, y | | | | | | | | |
| 20-29 | 1.1 (0.9-1.3) | <.0001 | 0.2 (0.1-0.3) | .004 | 0.9 (0.7-1.1) | <.0001 | -0.78 | <.0001 |
| 30-39 | 4.3 (3.7-4.9) | <.0001 | 2.3 (1.9-2.7) | <.0001 | 2 (1.3-2.7) | <.0001 | 0.27 | .51 |
| 40-49 | 21.7 (20-23.4) | <.0001 | 20.8 (19.8-21.8) | <.0001 | 1 (0.1-1.9) | .06 | 19.78 | <.0001 |
| 50-59 | 41.3 (37.5-45.1) | <.0001 | 50.3 (47.8-52.8) | <.0001 | -8.9 (-10.4--7.4) | <.0001 | 59.19 | <.0001 |
| ≥60 | 33.5 (22.3-44.7) | <.0001 | 41.9 (33.9-49.9) | <.0001 | -8.7 (-12.4--5) | <.0001 | 50.57 | <.0001 |

Abbreviations: 95% CI, 95% confidence interval; OCC, oral cavity cancer; OPC, oropharyngeal cancer; OSCC, oral squamous cell cancer.

^aThe 25-year limited-duration prevalence is as of January 1 in each given year for the years 2000 through 2012 and expressed as the number of individuals per 100,000 per year.

^bB represents the number of individuals per 100,000 per year.

^cP values testing for significantly positive or negative slopes within OPC and OCC.

^dInteraction P values for differences in the slopes between OPC and OCC.

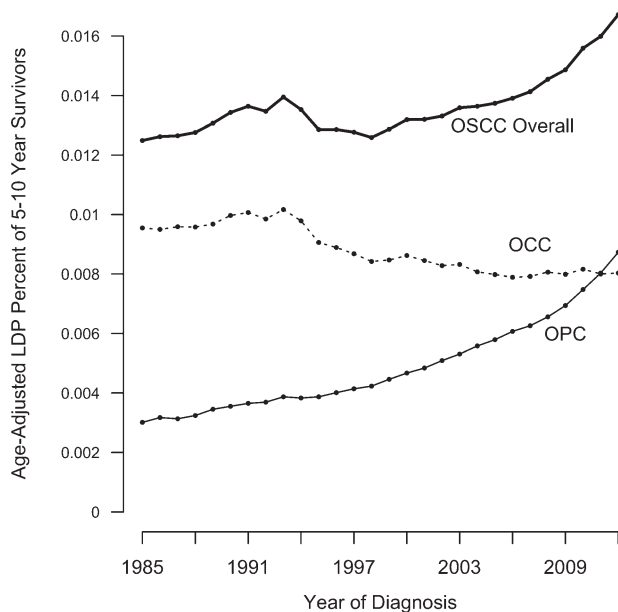


Figure 3. Age-adjusted limited-duration prevalence (LDP) of 5-year to 10-year survivors by calendar year of diagnosis for oral squamous cell cancer, oropharyngeal cancer (OPC), and oral cavity cancer (OCC).

[$P < .0001$]), reflecting the incidence trends in the United States and other countries.^{1,2} Prevalence estimates may have previously been a low priority within the context of

historically poor survival for OPC,^{33,34} but with the recent and projected surge of younger individuals diagnosed with HPV-related OPC and their expected favorable long-term survival, these data are needed to accurately estimate the survivorship trajectory.^{2,35}

Indeed, these prevalence estimates highlight the fact that resources are necessary not only for curative treatment after diagnosis among patients with OPC, but also for anticipating the projected health maintenance needs of this growing survivor population. Along with appreciation of the emerging number of young survivors of OPC is a heightened awareness of the late effects of cancer treatment that impair health-related quality of life.^{28,36,37} As the prevalence of survivors of OPC continues to rise, an increasing percentage of patients will require care plans tailored to the late complications of treatment.^{29,38} Furthermore, to our knowledge to date, the ideal surveillance and screening plans for cancer-related and nonrelated conditions are unknown in this population.

Although the increase in survivors of OPC is not surprising given the increase in the determinants of prevalence (incidence and survival), the paradoxically vanishing population of survivors of OCC is unexpected. Prior data have demonstrated a declining incidence of OCC.^{10,15} Significant yet modest increases in OCC survival have not resulted in an increased prevalence of survivors of OCC. Instead, there has been a significant downtrend in the

prevalence of survivors of OCC. Indeed, the prevalence trajectories of long-term survivors of OCC and OPC are distinct and crossing. Although the prevalence of long-term survivors was previously greater for OCC than OPC, after a steady decline for OCC and a dramatic increase for OPC, in 2012 the prevalence of survivors of OPC overtook that of OCC. The profile of survivors of head and neck cancer is therefore evolving. It can be expected from these estimates that survivor clinics will increasingly be composed of survivors of OPC, and fewer survivors of OCC.

The large and significant increase in 5-year survival in OPC compared with the more modest rise in the CSS of OCC can be explained in part by the growing subset of HPV-related OPCs diagnosed over time.^{2-4,6-9,16,21,22,39,40} However, to the best of our knowledge, the relative contribution of other factors, including temporal changes in treatment, is unknown.¹⁰ Prior observations of improved survival were restricted to the administration of radiotherapy.¹⁶ Improvements in survival for OPC and OCC were greater among males.

The incidence trends reported herein are updated to include the most recent decade.^{2,15,16,41-46} In contrast to the previously reported trends for OCC,¹⁵ although incidence overall has declined ($B, -22.3$), incidence in the most recent calendar periods is stable for males and females (see online Supporting Information Table 2). The recent increased incidence of OCC in white individuals and those of younger ages may reflect a resurgence of tobacco use or the emergence of other carcinogenic exposures.⁴⁷⁻⁵¹ The rise in the incidence of OCC among young people is consistent with prior estimates reported in 2007.¹⁵ The newly noted change is in the incidence of OCC for individuals aged 50 to 59 years ($P = .0002$). As observed previously, divergent trends in the incidence of OPC were observed in white individuals compared with black individuals.^{52,53}

There are several limitations that warrant discussion. SEER estimates have the potential for reporting bias. In addition, HPV tumor status was not available. Prevalence estimates were derived from incidence and survival. Additionally, the data included were overlapping, but to account for 5-year survival since diagnosis, the CSS could only be calculated up to 2007.

The results of the current study demonstrate a steady and significant increase in the prevalence of survivors of OPC and a decline in survivors of OCC in the United States. This finding underscores the need to develop appropriate, evidence-based guidelines for the surveillance and management of cancer-related and non-cancer-

related conditions in this unique and growing population of survivors.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Mira A. Patel: Conceptualization, methodology, validation, formal analysis, investigation, writing—original draft, writing—review and editing, and visualization. **Amanda Blackford:** Conceptualization, methodology, software, validation, formal analysis, writing—original draft, writing—review and editing, visualization, and supervision. **Eleni Rettig:** Writing—review and editing and visualization. **Jeremy D. Richmon:** Conceptualization, writing—original draft, writing—review and editing, visualization. **David W. Eisele:** Writing—review and editing and supervision. **Carole Fakhry:** Conceptualization, methodology, validation, formal analysis, investigation, resources, writing—original draft, writing—review and editing, visualization, supervision, project administration, and funding acquisition.

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