

Tongue and Tonsil Carcinoma

Increasing Trends in the U.S. Population Ages 20–44 Years

Caroline H. Shiboski, D.D.S., M.P.H., Ph.D.^{1,2}

Brian L. Schmidt, D.D.S., M.D., Ph.D.^{2,3}

Richard C. K. Jordan, D.D.S., Ph.D.^{1,2,4}

¹ Department of Stomatology, Division of Oral Pathology, Oral Medicine, Oral Radiology, School of Dentistry, University of California San Francisco, San Francisco, California.

² Comprehensive Cancer Center, University of California San Francisco, San Francisco, California.

³ Department of Oral and Maxillofacial Surgery, School of Dentistry, University of California San Francisco, San Francisco, California.

⁴ Department of Pathology, School of Medicine, University of California San Francisco, San Francisco, California.

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Address for reprints: Caroline H. Shiboski, D.D.S., Ph.D., Department of Stomatology, Division of Oral Pathology, Oral Medicine, Oral Radiology, Box 0422, Room S612, 513 Parnassus Avenue, University of California San Francisco, San Francisco, CA 94143-0422; Fax: (415) 476-4204; E-mail: caro@itsa.ucsf.edu

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BACKGROUND. An increasing incidence of oral carcinoma among young adults has been reported in the U.S. and Europe. Although the association between human papillomavirus infection and tonsillar carcinoma is now well established, to the authors' knowledge little is known about incidence trends in tonsillar carcinoma among younger adults. The objective of the current study was to explore the trends in both oral cavity and pharyngeal squamous cell carcinoma (SCC) in younger U.S. populations, in particular tongue and tonsillar SCC.

METHODS. Using the 1973–2001 Surveillance, Epidemiology and End Results (SEER) database, we computed age, race, and site-specific trends of oral and pharyngeal (excluding nasopharynx) carcinoma incidence rates. The percent change (PC) and annual percent change (APC) were computed to explore trends in incidence rates over time.

RESULTS. There were 2262 SCC of the oral cavity and 1251 SCC of the pharynx reported to the SEER program from 1973 to 2001 in adults aged 20–44 years. There was a statistically significant increase in the incidence of oral tongue SCC (APC = +2.1; $P < 0.001$), base of tongue SCC (APC = +1.7; $P = 0.04$), and palatine tonsil SCC (APC = +3.9; $P < 0.001$) among younger white individuals, whereas the incidence of SCC in all other oral and pharyngeal sites decreased or remained constant.

CONCLUSIONS. The increase in tonsil SCC incidence from 1973 to 2001 paralleled the increase in tongue SCC, whereas SCC in all other oral and pharyngeal sites remained constant or decreased. This may suggest similar etiologic factors for SCC affecting the palatine tonsils and tongue in younger populations. *Cancer* 2005;103:1843–9. © 2005 American Cancer Society.

KEYWORDS: oral carcinoma, pharyngeal carcinoma, tongue carcinoma, tonsil carcinoma, epidemiology, young adults, trends, relative survival.

Between 1992 and 2001, cancer of the oral cavity and pharynx was the 7th most common cancer among men in the U.S., with an incidence rate of 16.7 per 100,000.¹ It was the fourth most common cancer and ranked tenth among the most common causes of death among African American men. During the last decade, investigators in the U.S. and Europe reported increasing incidence rates of tongue squamous cell carcinoma (SCC) among young adults < 45 years of age.^{2–8} A recent analysis was conducted on combined tumor registry data from Denmark, Sweden, Norway, and Finland.⁸ Scandinavian tumor registries, which are nearly all inclusive with 95% of cancers diagnosed being reported, provide an opportunity for high-quality, population-based studies of cancer incidence and trends. Among 5024 oral tongue SCC reported between 1960 and 1994, 276 (5.5%) occurred among young adults (ages 20–39 years). The incidence of oral tongue SCC increased 5-fold among young men (0.06–0.32 per

100,000) and 6-fold among young women (0.03–0.19 per 100,000) compared with only a 2-fold increase in older age groups.

Even though oral SCC is strongly associated with a lifetime history of cigarette smoking and alcohol consumption in older adults (age > 55 years), to our knowledge little is known about potential risk factors associated with this disease in younger patients. Conversely, the association between human papillomavirus (HPV) infection and the occurrence of tonsil SCC is now well established among adult patients,^{9–14} but to our knowledge little is known about trends in incidence rates of tonsil SCC in younger adults. An analysis of Swedish cancer registry data (1958–1996) showed that husbands of women with cervical carcinoma had a significantly increased risk of developing either tongue or tonsil carcinoma.¹⁵ Therefore, because age-specific tongue and tonsil SCC may share certain etiologic factors, we sought to explore national cancer registry data over the past three decades to determine whether the trend in tonsil SCC rates mirrors the increasing trend of tongue SCC in younger populations in the U.S., and whether these trends differ from trends of SCC in other oral cavity and pharyngeal sites.

MATERIALS AND METHODS

Data Source and Variables

We obtained 1973–2001 oral and pharyngeal cancer incidence data from the Surveillance, Epidemiology and End Results (SEER) program.¹⁶ The SEER program was established by the National Cancer Institute in 1973, in response to the 1971 National Cancer Act.¹⁷ It currently collects data from population-based cancer registries in 11 geographic areas that together represent an estimated 14% of the U.S. population: 5 states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and 6 standard metropolitan statistical areas (Atlanta, Detroit, San Francisco–Oakland, Seattle–Puget Sound, San Jose–Monterey, and Los Angeles County). The completeness of reporting of cancer cases to the SEER program was estimated to be 97% for 6 of the geographic areas for the year 1987.¹⁸ The SEER registry includes data on patient demographics, primary tumor site, morphology/histology, stage at diagnosis, and first course of treatment. Information on vital status is actively followed. For the current analysis, we extracted the following cases from the 1973–2001 database: adults \geq 20 years with invasive SCC (no in situ cases) affecting the oral cavity (salivary glands excluded) and the pharynx (nasopharynx excluded). Both salivary gland and nasopharynx cancers were excluded because the majority of cancers affecting these sites are not SCC. In the SEER database, oral

cavity sites are grouped as lip, tongue (including base of tongue), floor of mouth, and “other mouth” (gingiva/palate/buccal mucosa/vestibule) whereas the pharyngeal sites are grouped as tonsil (palatine tonsil), oropharynx, hypopharynx, and pharynx not otherwise specified. For the current analysis, we separated oral tongue, which we grouped with oral cavity carcinomas, from base of tongue, which we grouped with pharyngeal carcinomas. Young adults were defined as persons ages 20–44 years of age.

Statistical Analysis

We used the SEER*Stat version 5.3.1 software¹⁶ and Stata version 8.0 (Stata Corporation, College Station, TX) for the analyses presented in the current study. Counts and proportions of carcinomas of the oral cavity and pharynx were summarized by age group and specific site, and in the younger age group by race. We computed incidence rates of SCC of both the oral cavity and pharynx, defined as the number of new cases per 100,000 persons, and age adjusted to the U.S. standard million population of 2000. We first explored the trend of these incidence rates by gender over the 1973–2001 time period in the entire adult population (age \geq 20 years). We then examined the trend in oral tongue SCC compared with other oral cavity sites, and the trend in tonsil SCC incidence compared with base of tongue and other pharyngeal sites over the 1973–2001 time period in the younger age group (ages 20–44 years) by race. We computed the percent change (PC) and the annual percent change (APC) from 1973 to 2001. The APC is computed by fitting a least-squares regression line to the natural logarithm of the rates, using calendar year as a regressor variable.¹⁷ Testing the hypothesis that the APC is equal to zero is equivalent to testing the hypothesis that the regression slope parameter is equal to zero. The hypothesis is rejected at the 0.05 significance level. The computation of the APC, and the testing of the hypothesis that the APC is equal to zero, relies on the assumption of a linear change of the trends in log rates over time. To assess whether this assumption was reasonable, we fitted a Poisson regression model in which year of diagnosis was included as a continuous variable, and other Poisson regression models using a spline function with various numbers of breakpoints or knots to allow the categorization of time after different distributions. We then compared the log-likelihood of these various models against the log-likelihood of the strictly linear model, and found no statistically significant difference between the models using the likelihood ratio test.

We used a life table method to compute survival rates. The 5-year relative survival rate is defined as the

TABLE 1
Oral and Pharyngeal SCC Cases Reported to the SEER Program, 1973–2001: Distribution by Age and Site

Age (yrs)	Sites				
	Oral cavity ^a No. (%) ^c		Pharynx ^b No. (%) ^c		
20–44	2262 (7)		1251 (5)		
45–54	5296 (16)		4636 (20)		
55–64	9254 (27)		7664 (33)		
≥ 65	17,052 (50)		9909 (42)		
Total	33,864		23,460		

Oral cavity ^a					
	Tongue No. (%) ^d	Lip No. (%) ^d	FOM No. (%) ^d	Gingiva/palate No. (%) ^d	Other No. (%) ^d
20–44	871 (39)	711 (31)	355 (16)	189 (8)	136 (6)
≥ 45	7216 (23)	8468 (27)	6697 (21)	5383 (17)	3838 (12)

Pharyngeal sites ^b					
	Tonsil No. (%) ^d	Base of tongue No. (%) ^d	Oropharynx No. (%) ^d	Hypopharynx No. (%) ^d	Other pharynx No. (%) ^d
20–44	554 (44)	382 (31)	64 (5)	184 (15)	67 (5)
≥ 45	6562 (30)	5657 (25)	1789 (8)	6242 (28)	1959 (9)

SCC: squamous cell carcinoma; SEER: Surveillance, Epidemiology and End Results program; FOM: floor of mouth.

^a Salivary glands were excluded.^b Nasopharynx was excluded.^c Column percentage (may not add to 100% because of rounding).^d Row percentage (may not add to 100% because of rounding).

likelihood that a person will not die of cancer (or related cause) 5 years after the date of diagnosis.¹⁷ We computed 5-year relative survival rates for both the 20–44 years and the ≥ 45 years age groups with site-specific SCC of the oral cavity and pharynx. We also explored the distribution of cases of both tongue and tonsil SCC in both age groups, by stage at diagnosis (localized vs. metastasis to regional lymph nodes or to a distant site).

RESULTS

Distribution of SCC Cases by Age, Site, and Race

A total of 2262 SCC of the oral cavity and 1251 SCC of the pharynx (excluding the nasopharynx) were reported to the SEER program between 1973 and 2001 in the 20–44 years age group (Table 1). Thus, 7% of all adult oral cavity SCC cases ($n = 33,864$) and 5% of all adult pharyngeal SCC cases ($n = 23,460$) were diagnosed in the younger age group during that period. The proportion of oral tongue SCC was higher than any other oral cavity sites in the younger age group (39%), but not in the older age group (23%). Similarly, the proportion of tonsil SCC was also higher than any other pharyngeal sites both in the younger age group (44%) and in the older age group (30%), followed by

TABLE 2
Oral and Pharyngeal SCC Cases Reported to the SEER Program, 1973–2001: Distribution by Race among 20–44-Year-Olds

Race	Sites	
	Oral cavity ^a No. (%) ^c	Pharynx ^b No. (%)
White	1835 (81)	848 (68)
Black	271 (12)	350 (28)
Asian/Pacific Islander	112 (5)	49 (4)
Native American	5 (< 1)	2 (< 1)
Unknown	39 (2)	2 (< 1)
Total	2262	1251

Results program.

^a Salivary glands were excluded.^b Nasopharynx was excluded.^c Column percentage (may not add to 100% because of rounding).

base of tongue (31% and 25%, respectively). Greater than two-thirds of both oral cavity and pharyngeal SCC cases occurred among whites (Table 2).

Exploration of Trends

Between 1973 and 2001, the incidence of oral SCC decreased by 52% among adult men, from 12.1 per

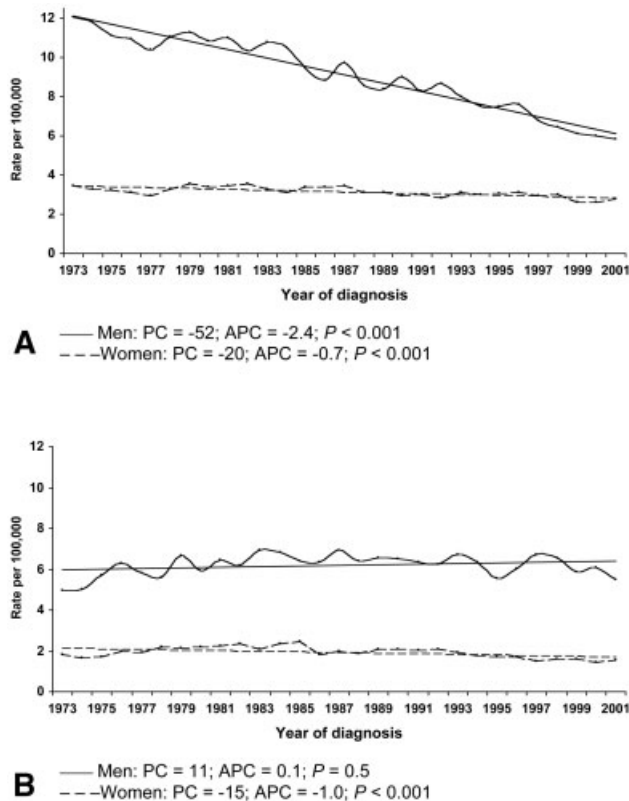


FIGURE 1. (A) Trends in age-adjusted oral squamous cell carcinoma (SCC) rates among adults (age ≥ 20 years) by gender, 1973–2001. (B) Trends in age-adjusted pharyngeal (nasopharynx excluded) SCC rates among adults (age ≥ 20 years) by gender, 1973–2001 (note that base of tongue SCC cases are included in the pharyngeal cases). PC: percent change; APC: annual percent change.

100,000 to 5.8 per 100,000 with an APC of -2.4 ($P < 0.001$) (Fig. 1A). The incidence rate among women was less than one-third of the rate among men in 1973, and the decrease over time was only slight (from 3.5 per 100,000 in 1973 to 2.8 per 100,000 in 2001). The annual incidence rates of SCC in pharyngeal sites stayed constant among men and decreased only slightly among women over time (Fig. 1B). However, during the same period, there was a statistically significant increase in the incidence of oral tongue SCC, from 0.09 per 100,000 to 0.48 per 100,000 (APC = $+2.1$; $P < 0.001$), among younger whites ages 20–44 years, whereas the incidence of SCC in all other oral cavity sites decreased (Fig. 2A). Similarly, the incidence of tonsil SCC increased, from 0.18 per 100,000 to 0.38 per 100,000 in 2000 and 0.25 per 100,000 in 2001 (APC = $+3.9$; $P < 0.001$), as did the incidence of SCC affecting the base of tongue, whereas the incidence of all other pharyngeal sites remained constant over time (Fig. 2B). The annual incidence rates of oral tongue

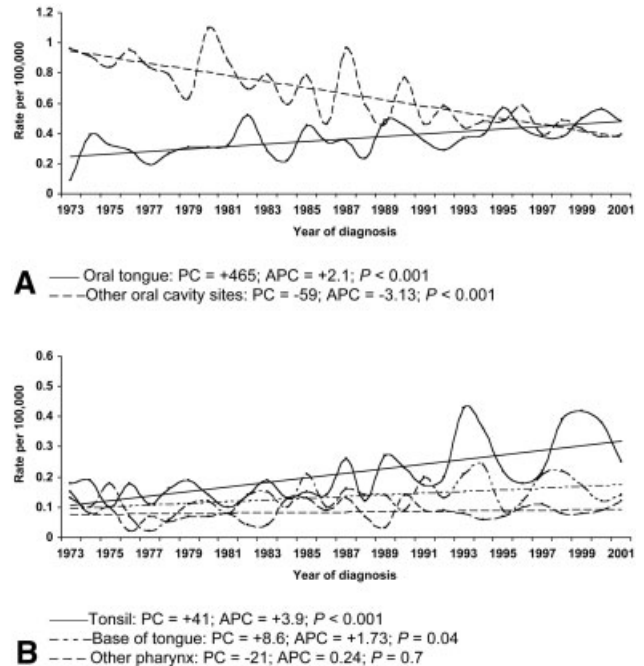


FIGURE 2. (A) Trends in oral squamous cell carcinoma (SCC) rates among whites ages 20–44 years, 1973–2001. Oral tongue SCC was compared with SCC occurring in other oral cavity sites. (B) Trends in pharyngeal SCC rates among whites ages 20–44 years, 1973–2001. Tonsil SCC was compared with SCC in other pharyngeal sites and with base of tongue SCC (nasopharynx excluded). PC: percent change; APC: annual percent change.

SCC between 1973 and 2001 were overall 2 times higher than rates of pharyngeal tongue SCC (Fig. 2). The incidence of oral tongue SCC among non-whites ages 20–44 years decreased from 0.61 per 100,000 in 1973 to 0.13 per 100,000 in 2001. However, the APC could not be computed for the entire time period because the rate was 0 in 1982 (data not shown). When computing the APC for the 1973–1981 and the 1983–2001 time periods, it was found to be not significantly different from 0 during either time period, indicating no evidence of trend change over time for oral tongue SCC among nonwhites. The APC could only be computed from 1974 to 2001 for tonsil SCC among young nonwhites because the incidence rate in 1973 was 0, and it was found to not significantly differ from 0.

Relative Survival

The 5-year relative survival was overall higher among younger adults ages 20–44 years for both oral tongue and tonsil SCC (64% and 63%, respectively) compared with adults age ≥ 45 years (51% and 43%, respectively) (Table 3). The 5-year relative survival was also higher for adults with tonsil SCC in either age group compared with adults with SCC affecting other pharyngeal sites.

TABLE 3
Five-Year RS by Age Group and Site for Oral and Pharyngeal SCC Cases Reported to the SEER Program, 1973–2001

Site	20–44 yrs		≥ 45 yrs	
	No.	5-yr RS	No.	5-yr RS
Oral cavity				
Oral tongue	816	0.64	5937	0.51
Lip	657	0.96	7268	0.95
FOM/other	610	0.56	12894	0.51
Pharynx				
Tonsil	519	0.63	5494	0.43
Base of tongue	355	0.47	4609	0.39
Other	289	0.36	8130	0.27

SCC: squamous cell carcinoma; SEER: Surveillance, Epidemiology and End Results program; RS: relative survival; FOM: floor of mouth.

TABLE 4
Tongue and Tonsil SCC Reported to the SEER Program, 1973–2001: Distribution by Stage at Diagnosis and Age

Site	Stage at diagnosis		
	Localized No. (%) ^b	Spread ^a No. (%) ^b	Unstaged No. (%) ^b
Oral tongue			
20–44 yrs	537 (62)	275 (32)	59 (7)
≥ 45 yrs	4047 (56)	2618 (36)	551 (8)
Base of tongue			
20–44 yrs	67 (18)	296 (77)	19 (5)
≥ 45 yrs	1062 (19)	4296 (76)	299 (5)
Tonsil			
20–44 yrs	75 (14)	462 (83)	17 (3)
≥ 45 yrs	1194 (18)	4961 (76)	407 (6)

SCC: squamous cell carcinoma; SEER: Surveillance, Epidemiology and End Results program.

^a Metastasis to regional lymph nodes or to a distant site.

^b Row percentage (may not add to 100% because of rounding).

Stage at Diagnosis

Among younger adults, the proportion of tongue SCC diagnosed at a localized stage (48%) was similar to that of SCC that had metastasized (46%), whereas greater than one-half of the tongue SCC among older adults had already metastasized at the time of diagnosis (Table 4). With respect to tonsil SCC, the majority of lesions had metastasized to a regional or distant site at time of diagnosis in both younger and older adults (83% and 76%, respectively).

DISCUSSION

Of 33,864 cases of SCC affecting the oral cavity reported to the SEER program between 1973 and 2001, 7% occurred among younger adults (ages 20–44 years). Similarly, of 23,460 cases of SCC affecting the

pharynx, 5% occurred in the younger age group. Despite an overall decrease in the age-adjusted incidence rate of SCC of the oral cavity and pharynx among adults of all ages during that time period, there was a significant increase in the incidence of SCC of the oral tongue, base of tongue, and tonsil in younger whites ages 20–44 years. This increase was in contrast to SCC rates in all other oral cavity and pharyngeal sites, which either decreased or stayed constant over time. The incidence rate of tongue and tonsil SCC among younger nonwhites also was constant over time. This underlines the importance of exploring not only site-specific trends but also age-specific cancer trends, and of examining these trends in relation to race, to capture changes that may occur in some subgroups but not in others. The significant changes for site-specific cancer incidence among younger whites would have been missed if all groups were combined in the analyses. The increased trend in incidence rate of tongue and tonsil SCC in younger adults is unlikely to be due to improved reporting because the increase was not seen in other age groups nor for SCC affecting oral and pharyngeal sites other than the tongue and tonsil. We purposely explored oral tongue SCC separately from base of tongue SCC because the latter site is part of Waldeyer's ring, and would be expected to have more similarities with tonsil SCC with respect to trends over time. Nevertheless, we found that both oral tongue and base of tongue SCC incidence increased over time. Furthermore, the increase in oral tongue SCC in a younger age group is consistent with the increase reported in the Scandinavian tumor registry, which includes 95% of all cancers diagnosed in Denmark, Sweden, Norway, and Finland from 1960 to 1994.⁸ That analysis also focused on oral tongue as a separate entity from base of tongue.

Although an increase in tongue carcinoma in younger populations has been reported in the literature worldwide,^{2–8} the current report is among the first to document an increased incidence rate in tonsil SCC in younger adults. There is an intriguing similarity between tongue and tonsil SCC with respect to the increased incidence rate as opposed to SCC in all other oral and pharyngeal sites. The etiologic basis of this increase of SCC incidence in two contiguous sites is not known. However, the strong association between tonsil SCC and HPV infection, mainly HPV-16 and HPV-18, is now well recognized, from studies conducted in different countries, and well reported.^{9–14} Furthermore, some studies have suggested a better prognosis and increased relative survival among patients who had HPV-related tonsil SCC.^{19,20} A favorable prognosis among patients with HPV-16 DNA-positive oral SCC was also demonstrated by in-

investigators in Washington state who studied survival among 254 patients with such cancers.²¹ Question now arise regarding the possible association between the increased incidence rate of tongue SCC in younger adults and HPV infection, especially because HPV infection has also been reported as having increased in some younger populations in the past 30 years.^{22,23} The role of HPV infection in carcinogenesis has been demonstrated in tissues other than oral mucosa. For example, high-risk HPV including types 16 and 18 are the causative agents of SCC of the uterine cervix. Cervical carcinomas arise via HPV-E6 and HPV-E7-mediated disruption of p53 pathways and deregulation of the retinoblastoma gene.²⁴ HPV is also known to be involved in the development of a subset of mucosal carcinomas in the head and neck particularly those arising in the tonsil. The mechanism for this is also believed to be mediated by HPV-E6 and HPV-E7 oncoproteins although recent expression analysis of p53 and other cell cycle proteins at this site suggests that the mechanism may differ from that occurring in the uterine cervix.²⁴ The possible association between HPV infection and oral cavity SCC has been explored by many investigators. However, these studies have yielded varying results. Some investigators have found no evidence of HPV DNA by polymerase chain reaction technique in oral SCC,²⁵ whereas others found oral SCC lesions to be HPV DNA positive but found the same proportion of HPV DNA-positive normal oral mucosa biopsy specimens.²⁶ A large multicenter case-control study of 1415 cases with carcinoma of the oral cavity, 255 with carcinoma of the oropharynx, and 1732 controls was conducted across 9 countries in 5 continents by investigators from the International Agency for Research on Cancer.²⁷ In that study, the odds of detecting antibodies against HPV-16 L1 and/or E6 or E7 were significantly higher among cases with oral cavity carcinoma than among controls (for L1, the odds ratio [OR] was 1.5, 95% confidence interval [95% CI], 1.1–2.1; for HPV-E6 or HPV-E7, the OR was 2.9, 95% CI, 1.7–4.8). However, Herrero et al.²⁷ found a higher prevalence of HPV DNA in biopsy specimens of carcinoma of the oropharynx (18.3%) than in carcinoma of the oral cavity (3.9%). Similarly, Gillison et al.¹³ detected HPV genomic DNA in 12% of 84 biopsy specimens collected from oral cavity carcinoma versus 57% among 60 specimens of carcinoma of the oropharynx. In another recent study, conducted in Sweden, HPV was detected in 40% of 25 base of tongue SCC cases but in only 2.3% of 85 mobile tongue SCC cases.²⁸

The prevalence of HPV infection has probably been increasing in industrialized countries over the past 30 years as demonstrated by an increase in HPV

seroprevalence in a population-based study of pregnant women in Sweden.²² This increase can probably be explained, in part, by a change in sexual behaviors and an increase in the number of sexual partners. Kreimer et al.²⁹ found that the OR of oral HPV infection, detected by isolating HPV DNA from oral rinses among HIV-positive and HIV-negative adults, was higher in participants who reported > 1 oral sex partner in the previous year (OR = 12.8; 95% CI, 3.1–53).²⁹ In a study of oral carcinoma risk in relation to sexual history and evidence of HPV infection, other investigators found that the risk of oral carcinoma increased significantly with decreasing age at first intercourse, increasing number of sexual partners, and a history of genital warts.³⁰ However, these authors used the SEER grouping that comprises SCC of the tongue, gum, floor of mouth, and “other/unspecified part of the mouth, tonsils, or oropharynx.” They did not report the percentage of cases that were solely in the oral cavity, so it is unclear whether the association they uncovered pertained more to sites in the oral cavity or in the pharynx.

The increased use of marijuana in industrialized countries in the past 20–30 years may be another potential risk factor that may be associated with the recent increase in tongue and tonsil SCC in young adults. A study of 173 head and neck carcinoma cases at Memorial Sloan-Kettering Cancer Center from 1992 to 1994 and 176 controls revealed that the OR of ever using marijuana was 2.6 (95%CI, 1.1–6.6) in cases compared with controls after adjusting for age, gender, race, education, heavy alcohol use, and cigarette smoking.³¹ However, the controls had been recruited among blood donor centers, which may have biased the results because blood donors are probably less likely to use recreational drugs. Another study conducted in Washington State among 407 cases of oral SCC compared with controls recruited by random-digit dialing found no association between marijuana use and risk of oral SCC.³² The study was not limited to younger patients. However, age was one of the covariates included in the multivariate analysis. A comprehensive literature review of possible risk factors of oral carcinoma among young adults was conducted by Llewelyn et al.³³ It revealed that only few studies had reported a high proportion of heavy smoking and alcohol consumption among younger patients with oral carcinoma whereas the majority of studies found no such association. The Llewelyn et al. review uncovered the paucity of research examining risk factors for oral carcinoma among younger populations.

The increase in tongue and tonsil SCC among young adults demonstrated by the current analysis, and the consistency of some of these results in previ-

ously published studies (i.e., the tongue SCC increase), underscores the need for further research to identify which risk factors may explain this phenomenon. A multicenter, case-control study would be the design of choice because tongue and tonsil SCC remain rare among younger adults.

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