

## Changing patterns of tonsillar squamous cell carcinoma in the United States

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### Abstract

**Objective:** Tonsillar squamous cell carcinoma (SCC) may differ etiologically from other oral cancers. The aim of this study was to provide a detailed description of the incidence patterns of tonsillar SCC in the United States.

**Methods:** Population-based incidence data from the Connecticut Tumor Registry (period 1945–1994) and from the SEER program (period 1973–1995) were used to calculate age-standardized (US 1970) and age-specific incidence rates and confidence intervals (CIs). Linear regression was used to evaluate trends.

**Results:** The incidence of tonsillar SCC increased fourfold among white women in Connecticut during 1945–1994 but remained rather constant in white men. During 1973–1995, incidence rates per million person-years were considerably higher in blacks (31.6; 95% CI: 29.0–34.4 in men, and 9.6; 95% CI: 8.3–10.9 in women) than whites (14.8; 95% CI: 14.3–15.3 in men, and 6.1; 95% CI: 5.8–6.4 in women). Men, but not women, who were younger than 60 years experienced significant annual increases in tonsillar SCC incidence during 1973–1995 (2.7% in blacks and 1.9% in whites). No similar increases occurred for oral SCC at non-tonsillar sites.

**Conclusion:** Incidence rates of tonsillar SCC vary considerably by sex, race and time in a way that cannot be explained by changes in tonsillectomy practices alone. Changes in environmental risk factors, including changes in smoking patterns and an increase in oral human papillomavirus infections, may have contributed.

### Introduction

Tonsillar squamous cell carcinomas (SCCs) represent approximately 15–20% of all intraoral and oropharyngeal SCCs in the United States. However, although time trends in overall incidence of oral and pharyngeal cancer have been studied in several settings [1–5], no population-based incidence study has reported incidence data for tonsillar SCCs specifically. Such data are of interest, since tonsillar SCCs may differ etiologically from other oral and pharyngeal cancers. Recent studies suggest that a substantial proportion of tonsillar SCCs may be caused by human papillomaviruses (HPVs) [6–8]. We studied long-term incidence data from the Connecticut Tumor Registry and more recent data from the Surveillance, Epidemiology, and End Results (SEER) program for this cancer. Comparable time trends for the group of all other intraoral and oropharyngeal SCCs were studied to assess if patterns observed for tonsillar SCCs were specific.

### Materials and methods

The Connecticut Tumor Registry provided cancer incidence data for the period 1945–1994. This registry covers the entire state of Connecticut (population in 1994: 3.3 millions) [9]. The SEER program has collected cancer incidence data from designated population-based cancer registries in various areas of the United States since 1973 (population covered in 1994: 36 millions). This population, currently approximately 14% of the US population, is believed to be representative of the entire nation [10]. We used SEER data for the period 1973–1995 from nine locations: San Francisco–Oakland, Detroit, Atlanta, Seattle, Connecticut, Iowa, New Mexico, Utah, and Hawaii.

The tonsillar cancers studied were those invasive cancers (behavior code 3) with topography codes C090–C099 and histology codes 8050–8076, 8094, or 8120–8124, according to the *International Classification of Diseases for Oncology*,

second edition (ICD-O2) [11]. The group of SCCs at other intraoral and oropharyngeal sites (referred to as "other oral" SCCs in the following) fulfilled identical histologic criteria and were identified under ICD-O2 topography codes C019–C069 and C100–C109. Cancers that were entered under earlier ICD versions were automatically converted to conform to the ICD-O2 coding system.

Analyses were done separately for men and women and for black and white people. Using Connecticut data we calculated age-standardized (US 1970) incidence rates in 5-year periods for tonsillar SCCs. Since changing diagnostic practices over time could influence long-term trends in histologically determined tonsillar SCCs, we also examined data for all tonsillar cancers regardless of histology. Using SEER data we calculated age-standardized (US 1970) incidence rates (in 3-year intervals 1973–1993 and for 1994–1995). Age-specific incidence rates in 10-year age categories were calculated for three periods (1973–1980, 1981–1988, and 1989–1995) to examine time patterns in separate age groups. Estimated annual percent change in the incidence and tests for linear trend were performed using linear regression by the method of least squares.

We examined whether patients with tonsillar SCC differed with respect to marital status from control patients who had invasive adenocarcinoma (histology codes 8140–8381) of the colon (topography codes C180–C189) or stomach (topography codes C160–C169). These comparison groups were chosen because marital status was not expected to be related to these cancers. Using multivariate logistic regression with ever married persons as the reference category, we compared the odds of belonging to other marital status categories among tonsillar SCC patients and each of the two control groups. Adjustment was made for potential confounding by age (10-year age groups) and race (white, black, other, unknown). When the 95% confidence intervals (CI) excluded unity or *p*-values were < 0.05 (two-sided), differences were considered statistically significant.

## Results

### *Connecticut Tumor Registry*

During the period 1945–1994 a total of 1679 tonsillar cancers in white persons (1223 men, 456 women) were recorded. The majority (85%) were histologically verified SCCs, and observed trends were similar whether histologically unspecified cancers were considered or not. Among white men the age-standardized incidence of histologically verified tonsillar SCC per million

person-years was generally stable, being 12.9 (95% CI: 9.5–17.4) in 1945–1949 and 16.4 (95% CI: 13.7–19.6) in 1990–1994. Among white women the incidence per million person-years rose fourfold, from 1.5 (95% CI: 0.6–3.4) in 1945–1949 to 6.0 (95% CI: 4.5–8.0) in 1990–1994 (Table 1). Numbers of tonsillar cancers among non-white people were small (110 men, 42 women). Although incidence rates were unstable in this category, they were consistently higher than in whites (not shown).

### *SEER cancer registries*

In the period 1973–1995, tonsillar SCCs were more common in blacks than whites and in men than women. Within ethnic groups, however, tonsillar SCCs constituted rather similar proportions of all intraoral and oropharyngeal SCCs in men and women, namely 17% and 15% in white men and women, respectively, vs. 22% and 23% in black men and women, respectively. Median age at diagnosis was 55 years in both black men and women, 61 years in white men, and 63 years in white women. A total of 5329 patients (3634 men, 1695 women) developed tonsillar SCC during 1973–1995. Among black men the average annual age-standardized incidence per million person-years during this period was 31.6 (95% CI: 29.0–34.4) vs. 14.8 (95% CI: 14.3–15.3) in white men. The corresponding figure in black women was 9.6 (95% CI: 8.3–10.9) vs. 6.1 (95% CI: 5.8–6.4) in white women (Table 1). The overall 1½–2-fold higher incidence of tonsillar SCC in black compared to white people was due to considerably higher rates among black women younger than 60 years and among black men younger than 70 years (Figure 1).

Figures 2a and 2b show the age-standardized incidence of tonsillar SCCs and other oral SCCs for people below and above the age of 60 years. While tonsillar SCC incidence remained fairly constant among persons aged 60 years or more, the incidence of other oral SCCs increased in black men. Among men younger than 60 years the incidence of tonsillar SCC increased significantly in both whites (1.9% per year) and blacks (2.7% per year) (*p*-trend < 0.05 in each group). No similar increases occurred for other oral SCCs in this young age group. In contrast, the incidence of tonsillar SCC among women younger than 60 years decreased among both whites (–1.7% per year) and blacks (–4.1% per year), although this decline was statistically significant only in white women.

As shown in Figure 3, the incidence per million person-years of tonsillar SCC in white populations increased gradually over the period 1973–1995 among

Table 1. Numbers and incidence rates of tonsillar squamous cell carcinoma, Connecticut, 1945–1994, and SEER registries, United States, 1973–1995

	No. men	Incidence per million <sup>a</sup> (95% CI)	No. women	Incidence per million <sup>a</sup> (95% CI)
<b>Whites</b>				
<i>Connecticut</i>				
1945–1949	53	12.9 (9.5–17.4)	7	1.5 (0.6–3.4)
1950–1954	69	14.0 (10.9–18.1)	9	1.6 (0.7–3.3)
1955–1959	90	17.6 (14.0–21.9)	11	1.7 (0.9–3.3)
1960–1964	106	17.6 (14.4–21.5)	24	3.5 (2.2–5.3)
1965–1969	122	18.8 (15.6–22.7)	37	4.9 (3.4–6.8)
1970–1974	124	18.8 (15.6–22.5)	47	5.7 (4.2–7.6)
1975–1979	131	18.3 (15.3–21.8)	48	5.5 (4.0–7.4)
1980–1984	122	16.4 (13.6–19.7)	63	6.7 (5.1–8.7)
1985–1989	118	15.1 (12.5–18.3)	63	6.6 (5.0–8.7)
1990–1994	129	16.4 (13.7–19.6)	58	6.0 (4.5–8.0)
1945–1994	1064	16.6 (15.6–17.6)	367	4.8 (4.3–5.3)
<i>SEER</i>				
1973–1980	916	14.4 (13.5–15.4)	481	6.4 (5.9–7.1)
1981–1988	1012	14.4 (13.5–15.3)	491	5.8 (5.3–6.4)
1989–1995	1042	15.5 (14.6–16.5)	461	5.8 (5.3–6.4)
1973–1995	2970	14.8 (14.3–15.3)	1433	6.1 (5.8–6.4)
<i>By registry</i>				
Atlanta	181	15.8 (13.5–18.4)	83	5.9 (4.7–7.4)
Connecticut	576	16.6 (15.3–18.0)	265	6.3 (5.6–7.2)
Detroit	592	17.3 (15.9–18.8)	252	6.1 (5.4–7.0)
Hawaii	79	27.4 (21.6–34.5)	36	13.4 (9.3–18.8)
Iowa	369	11.4 (10.2–12.6)	156	4.0 (3.4–4.7)
New Mexico	109	8.5 (6.9–10.2)	49	3.4 (2.5–4.5)
San Francisco–Oakland	576	19.2 (17.6–20.8)	347	9.8 (8.8–11.0)
Seattle	394	13.7 (12.4–15.1)	219	6.8 (5.9–7.8)
Utah	94	7.5 (6.1–9.2)	26	1.8 (1.2–2.7)
<b>Blacks</b>				
<i>SEER</i>				
1973–1980	142	26.6 (22.3–31.7)	67	10.4 (8.1–13.3)
1981–1988	229	36.0 (31.4–41.1)	76	9.8 (7.7–12.3)
1989–1995	205	31.5 (27.2–36.3)	71	8.7 (6.8–11.0)
1973–1995	576	31.6 (29.0–34.4)	214	9.6 (8.3–10.9)

SEER, Surveillance, Epidemiology, and End Results; CI, confidence interval.

<sup>a</sup> Incidence rates are age-standardized to the US 1970 population.

young men. This applied to men in age groups 30–39 years [from 1.3 (95% CI: 0.7–2.3) in 1973–1980 to 3.0 (95% CI: 2.1–4.2) in 1989–1995], 40–49 years [from 11.2 (95% CI: 8.8–13.9) to 18.7 (95% CI: 16.1–21.7)], and 50–59 years [from 40.3 (95% CI: 35.8–45.3) to 47.6 (95% CI: 42.3–53.5)]. No similar pattern was seen among young women. In contrast, the age-specific incidence among women increased only among those who were 70–79 years [from 18.9 (95% CI: 14.8–23.8) to 25.5 (95% CI: 21.1–30.6)] and those who were 80 years or older [from 4.8 (95% CI: 2.3–8.9) to 14.3 (95% CI: 10.2–19.5)].

Considerable geographic variation in tonsillar SCC incidence was present within the white US population.

Although based on relatively small numbers, highest age-standardized incidence rates per million person-years were in Hawaii [27.4 (95% CI: 21.6–34.5) in men, and 13.4 (95% CI: 9.3–18.8) in women] and lowest rates were in Utah [7.5 (95% CI: 6.1–9.2) in men, and 1.8 (95% CI: 1.2–2.7) in women] (Table 1). The contribution of tonsillar SCCs to the total incidence of all intraoral and oropharyngeal SCCs was also higher among young Hawaii whites than elsewhere. The ratio of standardized incidence rates of tonsillar SCC to other oral SCCs was 0.30 among <60-year-old white men in Hawaii, as compared to 0.13 in Utah. Corresponding ratios for young white women were 0.33 in Hawaii and 0.15 in Utah. Based on data

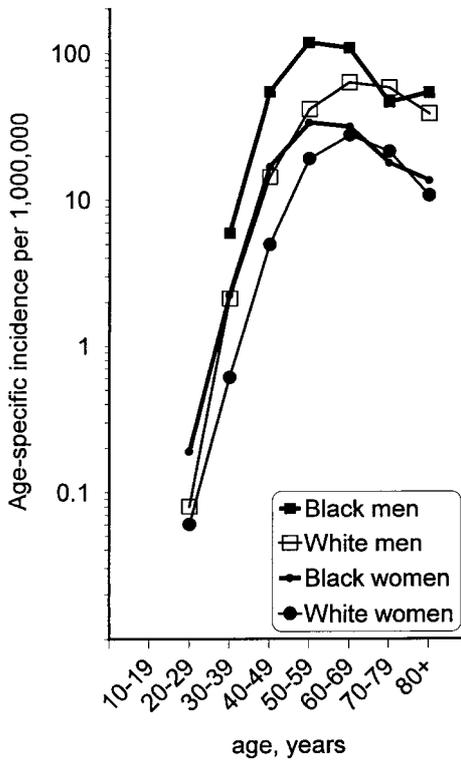


Fig. 1. Age-specific incidence rates (SEER registries) of tonsillar SCC per million person-years (average for the period 1973–1995) among blacks and whites.

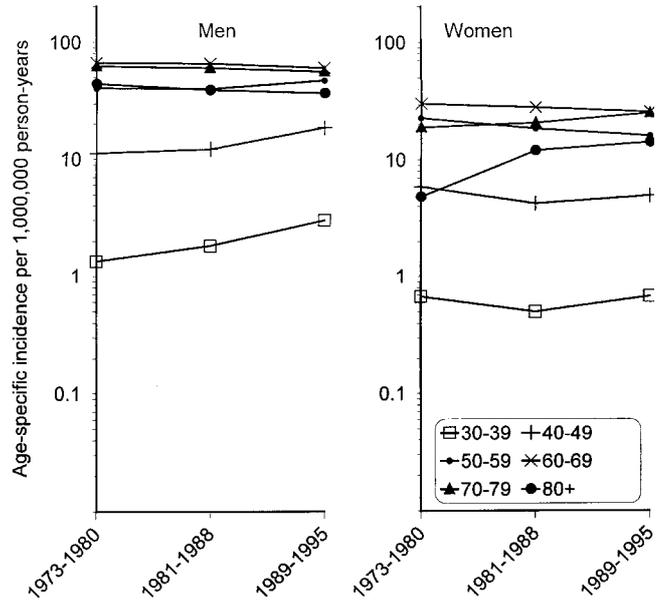


Fig. 3. Age-specific incidence rates (SEER registries) of tonsillar SCC per million person-years for the periods 1973–1980, 1981–1988, and 1989–1995 among white men and women in age groups 30–39, 40–49, 50–59, 60–69, 70–79, and 80+ years.

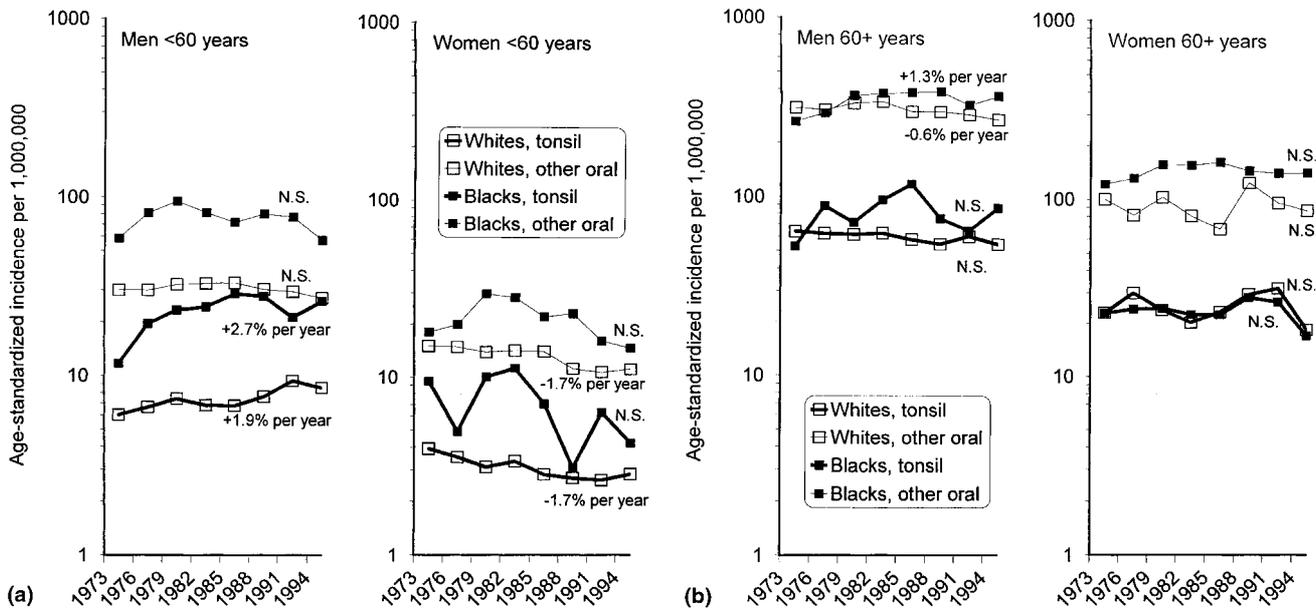


Fig. 2. Age-standardized (US 1970) incidence rates (SEER registries) of tonsillar SCC and other oral SCCs per million person-years for periods 1973–1975, 1976–1978, 1979–1981, 1982–1984, 1985–1987, 1988–1990, 1991–1993, and 1994–1995 among blacks and whites, by age younger than 60 years (a) and age 60 years or older (b). Percentages indicate statistically significant ( $p < 0.05$ ) annual changes in incidence based on data for the entire period 1973–1995. N.S. indicates that the particular annual change was not statistically significant.

Table 2. Marital status among patients with tonsillar squamous cell carcinoma and patients with adenocarcinoma of the colon or stomach. Odds ratios and 95% confidence intervals, SEER registries, United States, 1973–1995

	Tonsillar SCC vs. colon adenocarcinoma OR <sup>a</sup> (95% CI)	Tonsillar SCC vs. stomach adenocarcinoma OR <sup>a</sup> (95% CI)
<i>Men</i>		
Married	1 (referent)	1 (referent)
Never married	1.9 (1.7–2.1)	1.9 (1.7–2.1)
Separated	2.8 (2.2–3.4)	2.2 (1.7–2.8)
Divorced	3.3 (2.9–3.7)	2.7 (2.4–3.0)
Widowed	1.6 (1.4–1.9)	1.5 (1.3–1.7)
<i>Women</i>		
Married	1 (referent)	1 (referent)
Never married	1.2 (1.03–1.5)	1.2 (1.0–1.5)
Separated	1.3 (0.97–1.7)	1.0 (0.7–1.3)
Divorced	2.1 (1.8–2.5)	2.0 (1.6–2.4)
Widowed	1.4 (1.2–1.6)	1.3 (1.1–1.5)

SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

<sup>a</sup> Odds ratios are adjusted for age (<40, 40–49, 50–59, 60–69, 70–79, 80+ years) and race (white, black, other, unknown). Patients with unknown marital status (5% of 5329 patients with tonsillar squamous cell carcinoma, 3% of 151,352 patients with adenocarcinoma of the colon, and 3% of 33,811 patients with adenocarcinoma of the stomach) were not included.

from all nine SEER registries, the overall incidence ratio among <60-year-old whites was 0.24 for each gender.

After adjusting for age and ethnic group, men, and to a lesser extent women, with tonsillar SCC were significantly more likely than patients with colon or stomach cancers to have remained unmarried or to have a history of broken marriage (Table 2).

## Discussion

This is the first study describing long-term incidence patterns for tonsillar SCC. Previous reports on the incidence of cancers of the oral cavity and pharynx included tonsillar cancers in the larger group of pharyngeal cancers [1–5]. Thereby, patterns specific for tonsillar SCC were obscured.

Our main findings include a markedly higher incidence of tonsillar SCC among blacks than whites and changes in rates in different population groups that suggest changes in environmental risk factors. Among women a four-fold increase occurred over the past half-century and among young men there was a recent upward trend, which was not paralleled by increases in SCCs at non-tonsillar sites.

Foremost among the trivial explanations must be the impact of changes in rates of tonsillectomy (with or without adenoidectomy). Unfortunately, we have been unable to identify good long-term data about changes in the frequency of this procedure. In 1970, however, tonsillectomy rates in the United States were estimated to be approximately 5 per 1000 persons, with 76% occurring in children <15 years old, and only 3% occurring in adults 30 years or older [12]. Assuming the 1970 tonsillectomy rate applied in all previous years, we estimate that, as of 1970, about 15% of the United States population would have had a tonsillectomy by the age of 30 years. Removal of these people from the population at risk of developing tonsillar cancer would increase pre-1970 tonsillar cancer rates by 18%. We estimate that to explain the four-fold increase we observed in women, the rate of tonsillectomy should have been 75% in women during the 1940s, a figure that we consider implausibly high.

As noted, there are marked differences in the trends between demographic groups. While rates of tonsillar SCC in women increased significantly, corresponding rates in men over the same period were relatively stable. Tonsillectomy rates in women have been reported to be slightly higher than in men [12, 13]. However, to explain the difference between trends in men and women would have required that women have five-fold higher tonsillectomy rates than men, which also seems implausible. We were unable to identify detailed data in which to evaluate tonsillectomy rates in blacks vs. whites over the years studied, but at least in the early years they were probably lower in blacks, because blacks had less access to the health care system. Thus, part of the one-and-a-half to two-fold higher rates of tonsillar cancer among blacks could be due to lower tonsillectomy rates. Between 1970 and 1990 the frequency of tonsillectomy dropped 70–80% in both sexes after taking outpatient tonsillectomies into consideration [14]. However, while tonsillar cancer rates increased in young men, they decreased in young women.

Overall, the higher frequency of tonsillectomy in previous decades may have led to underestimates of the incidence of tonsillar cancers during the early years of this study. As a consequence, the magnitude of upward trends may be overestimated. However, it is unlikely that changing tonsillectomy rates alone would explain trends of the magnitude we observed and the differences seen in recent decades among young men and women. Assuming, therefore, that these trends are real, our data suggest that the types and/or the prevalence of risk factors for tonsillar SCC in the population have changed.

In Western countries, tobacco and alcohol are the only well-established exogenous causal factors involved in SCCs of the oral cavity and oropharynx [15]. The influence of these factors has not been specifically addressed for tonsillar SCC. The four-fold increase among women might be explained, in part, by the increase in smoking that took place after World War II [16]. Plausibly, the moderate increase among men in Connecticut during the first part of this study might also be related to smoking, and the subsequent decline could have been due to decreasing smoking rates. If so, this would be in accordance with the view that smoking exerts at least one of its carcinogenic effects at a rather late stage in the cancerous process [15].

Studies have demonstrated DNA from cancer-associated types of HPV in varying proportions of oral and pharyngeal cancers. Most studies report HPV-positivity in 10–20% of such cancers [6, 17–24]. A consistent observation has been that tonsillar SCCs are more often HPV-positive than cancers at other oral sites [6, 18, 20, 23–25]. The recent observation that HPV-positivity in tonsillar SCCs correlates closely with both histopathologic features (poor keratinization) and either decreased or over-expressed cell cycle regulatory components (pRb and cyclin D1) suggests that HPV-associated tonsillar SCC may constitute a separate etiologic entity [23, 26]. The particular excess of tonsillar SCCs seen after initial HPV-associated anogenital malignancies supports this idea [8].

A limitation of the present study is that we have no information on HPV status or other risk factors, such as tobacco smoking and alcohol consumption, at the individual level. Consequently, we are unable to separate trends for HPV-associated and HPV-unrelated tonsillar SCCs. However, considering the presumed late stage promoter effect of smoking in oral carcinogenesis [15], we note that the recent increase in tonsillar SCC incidence among young men occurred in spite of the ongoing decrease in the prevalence of current smokers in the United States [27]. Therefore, other factors than smoking may be involved at a late stage in the cancerous process.

We speculate that immune suppression could be one such factor, since other HPV-associated cancers occur in excess among immunosuppressed patients [28–30]. Case reports of transplant patients developing tonsillar SCC at young ages [31, 32] are compatible with this idea. To the extent unmarried status is a proxy for male homosexuality, HIV/AIDS-related immunosuppression could have contributed to the recent increase among young men. Alternatively, the higher prevalence of tobacco smokers [33], the higher consumption of alcohol

[34], and the higher numbers of partners of the opposite sex [35] (and thus the risk of HPV-acquisition) in currently unmarried persons might account for the observed association with marital status.

In summary, a marked increase in the incidence of tonsillar SCC has taken place over the past half-century among white women. While declining tonsillectomy rates have resulted in an increase in the population at risk, the observed changes in incidence of tonsillar SCC cannot be explained by this alone. Young women are now experiencing decreasing incidence rates of tonsillar SCC, whereas a significant recent increase has taken place among men younger than 60 years. Etiologic studies are needed to explain these diverging trends in men and women, as well as the marked differences in incidence between blacks and whites.

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