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ORIGINAL PAPER

Epidemiological trends of oropharyngeal and oral cavity squamous cell carcinomas in Northern New England, 2000–2013

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Abstract

Background This study examines the epidemiological trends of oropharyngeal squamous cell carcinoma (OPSCC) and oral cavity squamous cell carcinoma (OCSCC) in Northern New England.

Methods Data were obtained from the Maine, New Hampshire and Vermont cancer registries. The age-standardized incidence rates (ASIR), age-specific incidence rates, and annual percentage changes (APC) for OPSCC and OCSCC were calculated using Joinpoint regression.

Results The overall ASIR for OPSCC in Northern New England increased by 54.2% from 2000 to 2013 with an increase of 61.5% and 27.3% in men and women, respectively. Overall ASIR for OCSCC, on the other hand, declined throughout 2000 to 2013 by 6% and among men by 11%. In joinpoint analyses, the overall ASIRs for OPSCC significantly increased at an APC of 3.15 from 2000 to 2013, whereas the ASIRs for OCSCC remained stable at an APC of − 0.26. In men, ASIRs for OPSCC significantly increased (APC: 3.46), while that of OCSCC remained stable at an APC of − 0.87. In women, the ASIRs remained stable for both OPSCC and OCSCC at an APC of 1.97 and 0.49, respectively. For patients in the 6th decade of life, the age-specific incidence rates for OPSCC increased significantly at an APC of 3.06, also among those in the 7th and 8th decade with a significant increase at an APC of 4.98 and 3.51 per year, respectively. There were no significant changes in the APC of patients with OCSCC with respect to age group.

Conclusion The overall incidence of OPSCC is increasing in Northern New England, specifically among men. Given the etiological association between OPSCC and HPV, vaccination against HPV should be effectively encouraged among the populace. The efforts on tobacco cessation, abstinence, and alcohol abuse control should be continually expanded in order to bring about a decreasing trend in OCSCC.

Keywords HPV · Oropharynx · Head and neck cancer · Maine · New Hampshire · Vermont

Introduction

Cancers of the head and neck mostly arise from the mucosa lining of the aerodigestive tract including the oral cavity, oropharynx, hypopharynx, nasopharynx, larynx, and paranasal sinuses. Squamous cell carcinoma is by far the most common histological type and grade can vary from well-differentiated to poorly-differentiated. Tobacco use and alcohol consumption are primary risk factors for head and neck cancers [1, 2]. Human papillomavirus (HPV) infection is etiologically linked to oropharyngeal cancers; 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) have been implicated, with HPV 16 being the most common [3–7]. HPV is the most common cause of sexually transmitted infections in the United States [8]. Majority (75%) of sexually active adults will be infected with HPV during their lifetime [9, 10]. HPV is transmitted by direct skin to skin contact, typically through sexual contact with the genitalia, oral cavity, or anus. In the head and neck, HPV have a preference for the specialized reticulated epithelium of the tonsillar crypts (lingual and palatine tonsils). The virus integrates into the host DNA genome,

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which dysregulates the oncopreotiens E6 and E7 [11]. The E6 oncoprotein induces degradation of tumor protein p53 through ubiquitin-mediated proteolysis, while E7 oncoprotein binds and inactivates pRb [11]. Both p53 and pRb function as tumor suppressors. The proportion of oropharyngeal cancers caused by HPV varies widely with different geographical location. In the USA, about 40–80% of oropharyngeal cancers are attributed to HPV, amongst European countries it varies from less than 20–85% in Stockholm, Sweden and in Asian countries such as India it accounts for less than 5% of oropharyngeal cancers [12–14].

In 2012, the International Agency for Research on Cancer estimated that cancers of the oral cavity and oropharynx accounted for 3.7% of all cancers globally [15]. The American Cancer Society estimates that 51,540 new cases of these cancers will occur in the USA in 2018, with a projected death count of 10,030 [16]. When oral cavity and oropharyngeal cancers are grouped, they account for the 8th most common cancers among men in the USA [16]. Oropharyngeal squamous cell carcinoma (OPSCC) are defined as squamous cell carcinoma involving the base of tongue and tonsil (palatine and lingual) and oral cavity squamous cell carcinoma (OCSCC) are defined as squamous cell carcinoma involving the oral lip, anterior 2/3rd of the tongue, gingiva, floor of mouth, hard palate, buccal mucosae, retromolar areas, and vestibules. Of the 15,738 OPSCC cases that are diagnosed yearly in the USA, 80% of the cases are in men [17]. While studies using the Surveillance, Epidemiology, and End Results (SEER) registry have shown an overall decline in the incidence of OCSCC that of OPSCC is on the rise, specifically in men [18, 19]. A study projected that the national incidence rate of OPSCC would surpass that of cervical cancers by 2020 [20].

The incidence trends of OPSCC among men make this disease a public health concern. Recent studies on this topic have utilized the SEER database which does not include cases from the Northern New England states (Maine, New Hampshire, and Vermont). Therefore, we sought to examine the epidemiological trends of OPSCC incidence and compare to the incidence of OCSCC in the Northern New England population from 2000 to 2013.

Methods

This study was approved by the institutional review board of the University of New England, Maine. Data on cases of oral and pharynx cancer between 2000 and 2013 were received from the population-based, Maine, New Hampshire, and Vermont Cancer Registries. These cases were categorized according to the International Classification of Disease for Oncology (ICD-O)-3 for primary site and histology codes and retrieved from the states cancer registries by ICD-O-3 codes.

OPSCC were defined as cases of squamous cell carcinoma (8,050–8,084) diagnosed in the base of tongue (C01.9 and 02.4) and tonsil (C09.0–09.1, 09.8–09.9). Oral cavity squamous cell carcinoma (OCSCC) were defined as cases of squamous cell carcinoma (8,050–8,084, 8,120–8,131) diagnosed in the oral lip (C00.3–00.9), tongue (C02.0–02.3, 02.8, 0.29), gingiva (C03), floor of mouth (C04), palate (C05.0, 05.8, 05.9), and other unspecified parts of mouth (C06; buccal mucosae, retromolar areas and vestibules). The population-based OPSCC and OCSCC data were categorized into 5-year age groups (truncated at < 1 and 85+) to correspond with age categories used in the 2000 US Standard Population and Maine, New Hampshire and Vermont population data for each calendar year (2000–2013). We calculated age-standardized rates per 100,000 (for each 5-year age group and calendar year) based on the 2000 US Standard Population. In addition, we calculated age-specific incidence rates (from < 39 to 80+, within 10-year groups). Joinpoint regression analyses were used to determine the best fit for inflection points (joinpoints) through the annual age-standardized incidence data to identify where significant changes in trend take place. First, we specified the least number of joinpoints (i.e., 0 joinpoints, a straight line) to a maximum number of four to test for model fit on a logarithmic scale. We used the permutation test approach to control the error probability of selecting the wrong model at a certain level. An annual percentage change (APC) in age-standardized incidence rate (ASIR) for each line segment and corresponding 95% confidence interval were estimated. The APC was computed to determine whether a significant difference of zero exists at the alpha < 0.05. APCs were calculated and stratified by sex, age groups and state. In describing trends: *increased* and *decreased* are used only when the APC slope is statistically significant or otherwise described as *stable*. All analyses were performed using joinpoint trend analysis software from Surveillance Research Program of the National Cancer Institute version 4.5.0.1 (Statistical Research and Application Branch).

Results

Table 1 describes the ASIRs for OPSCC and OCSCC, and summarizes the results of the joinpoint analyses by sex and state. The overall ASIRs from OPSCC increased by 54.2% from 2000 to 2013 with an increase of 61.5% and 27.3% in men and women, respectively. New Hampshire had the highest increase in ASIRs for OPSCC among the states in Northern New England throughout the period at 79.9% with a marked increase observed among men at 103.5%. However, New Hampshire had the lowest increase in OPSCC ASIRs

Table 1 ASIRs and APC in of oropharyngeal and oral cavity squamous cell carcinomas in Northern New England from 2000 to 2013

	OPSCC					OCSCC				
	ASIR		ASIR % change	*APC (95% CI)	*p*-value	ASIR		ASIR % Change	*APC (95% CI)	*p*-value
	2000	2013				2000	2013			
Overall	2.71	4.18	54.2	3.15 (2.29–4.00)	**< 0.001**	4.00	3.76	−6.0	−0.26 (−1.39 to 0.88)	0.627
Sex										
Men	4.55	7.35	61.5	3.46 (2.65-4.28)	**< 0.001**	5.37	4.78	−11.0	−0.87 (−2.23 to 0.513)	0.195
Women	0.99	1.26	27.3	1.97 (−0.06 to 4.04)	0.056	2.95	2.95	0.0	0.49 (−1.51 to 2.54)	0.606
State										
Maine										
Both sexes	3.28	4.56	39.0	3.13 (2.41–3.85)	**< 0.001**	3.69	3.63	−1.6	−0.81 (−2.69 to 1.11)	0.374
Men	5.60	7.58	35.4	2.96 (2.13–3.79)	**< 0.001**	5.39	4.72	−12.4	−0.98 (−2.7 to 0.76)	0.242
Women	1.14	1.77	55.3	3.69 (1.51–5.93)	**0.003**	2.41	2.80	16.2	−1.10 (−4.52 to 2.43)	0.505
New Hampshire										
Both sexes	2.24	4.03	79.9	3.09 (0.91–5.33)	**0.009**	4.44	4.21	−5.2	0.71 (−1.69 to 3.18)	0.535
Men	3.69	7.51	103.5	3.89 (1.55–6.29)	**0.003**	5.49	5.11	−6.9	0.37 (−1.77 to 2.56)	0.716
Women	0.84	0.87	3.6	0.36 (−3.25 to 4.09)	0.836	3.67	3.48	−5.2	1.17 (−2.71 to 5.19)	0.529
Vermont										
Both sexes	2.45	3.86	57.6	4.16 (0.66–7.8)	**0.019**	3.93	3.19	−18.8	−1.40 (−3.91 to 1.17)	0.255
				11.69 (4.29–19.62)[a]	**0.005**					
				−1.89 (−6.11 to 2.53)[b]	0.353					
Men	4.09	6.93	69.4	4.87 (1.17–8.69)	**0.009**	5.26	4.29	−18.4	−2.84 (−6.83 to 1.32)	0.161
				12.15 (4.39–20.49)[a]	**0.006**					
				−1.00 (−5.46 to 3.67)[b]	0.633					
Women	0.92	1.02	10.9	0.19 (−4.74 to 5.39)	0.934	2.81	2.28	−18.9	0.88 (−2.41 to 4.27)	0.576

Bold indicates a significant *p*-value ($p < 0.05$)

OPSCC oropharyngeal squamous cell carcinoma (tonsil and base of tongue), *OCSCC* oral cavity squamous cell carcinoma, *ASIR* age-standardized incidence rates, **APC* annual percentage change for period 2000–2013, *CI* confidence interval

[a]2000–2006

[b]2006–2013

among women across the three states at 3.6%. The lowest increase in ASIRs for OPSCC was observed in Maine at 39%. Overall ASIRs for OCSCC, on the other hand, declined throughout 2000–2013 by 6% and among men declined by 11%; no changes were observed among women. The highest decrease in ASIRs for OCSCC was observed in Vermont at 18.8% with similar decrease in both sexes, whereas Maine had the lowest decrease at 1.6%. Interestingly, the only observed increase in ASIRs for OCSCC was seen among women in Maine at 16.2%.

In joinpoint analyses, overall ASIRs for OPSCC increased significantly (APC: 3.15) and among men (APC: 3.46) from 2000 to 2013. Similarly, ASIRs for OPSCC showed upward trends in all three states (APC: Maine, 3.13; New Hampshire, 3.09; Vermont, 4.16) from 2000 to 2013. In Vermont, ASIRs for OPSCC significantly increased at a considerable rate from 2000 to 2006 (APC until 2006: 11.69) and also among men (APC: 12.15) but remained stable thereafter. In contrast, we observed a stable trend in the overall ASIRs for OCSCC (APC: − 0.26), among men (APC: − 0.87), among women (APC: − 0.49) and in Maine, New Hampshire, and Vermont at APCs of − 0.81, 0.71 and − 1.40 respectively (Figs. 1, 2, 3 and 4).

There was a significant increased rate of OPSCC (2000–2013) among patients in the 6th, 7th, and 8th decade of life. For patients in the 6th decade (50–59 years) age group, the age-specific incidence rate increased significantly at an APC of 3.06, while among those in the 7th (60–69 years) and 8th decade (70–79 years), we observed a significant increase of 4.98 and 3.51, respectively. There were no significant changes in the APC of patients diagnosed with OCSCC with respect to age group (Table 2).

Discussion

This study examined the epidemiological trends of OPSCC and OCSCC in Northern New England from 2000 to 2013. The results showed a significant increasing ASIR of OPSCC compared to a stable ASIR of OCSCC observed in Northern New England. Among men, the ASIRs for OPSCC significantly increased, while that of OCSCC remained stable. The ASIRs for OPSCC and OCSCC were stable among women. The recent study by Mourad et al., which used the SEER population database, reported an overall significant increase of OPSCC (HPV-related) at an annual rate of 2.53%, with a significant increase of 2.89% among men and a stable trend of 0.57% among women [19]. The study by Chaturvedi et al. which used the SEER dataset showed a significant decreasing trend in the incidence of OCSCC at an APC of − 1.85 from 1983 to 2004 [18]. The SEER database used in those studies included patients from 12 registries: Connecticut, Hawaii, Iowa, Kentucky, Utah, New Mexico, New Jersey, Michigan, Georgia, Washington, and California, which did

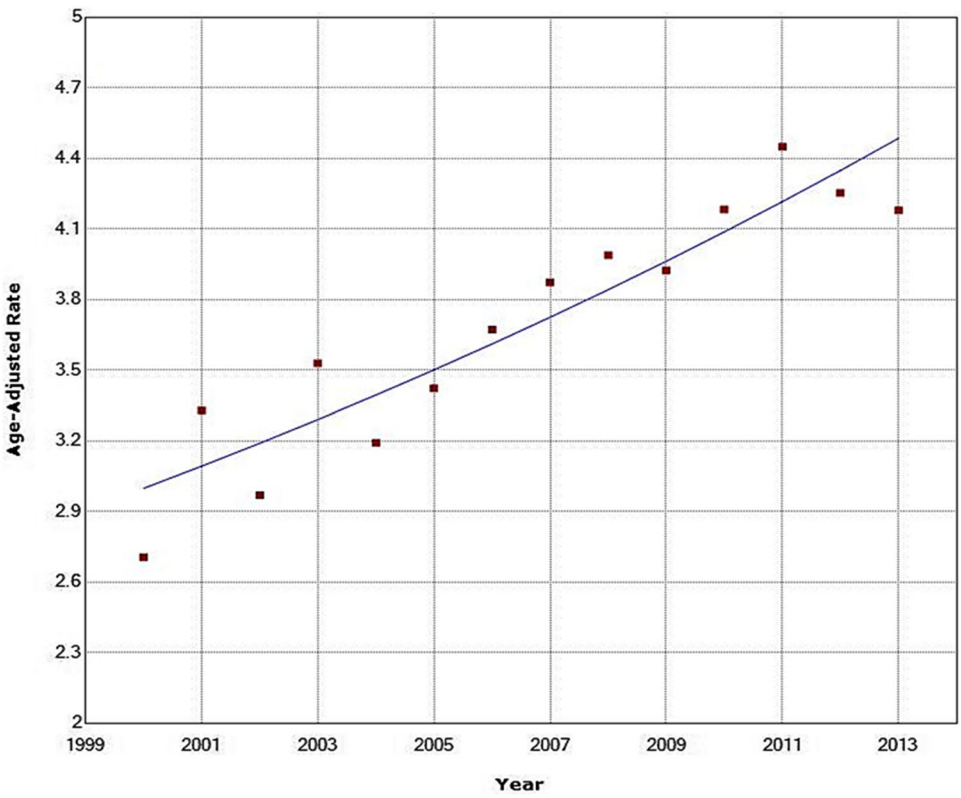

Fig. 1 Overall APC (3.15, $p < 0.001$) of OPSCC (HPV-related) in Northern New England for the period from 2000 to 2013

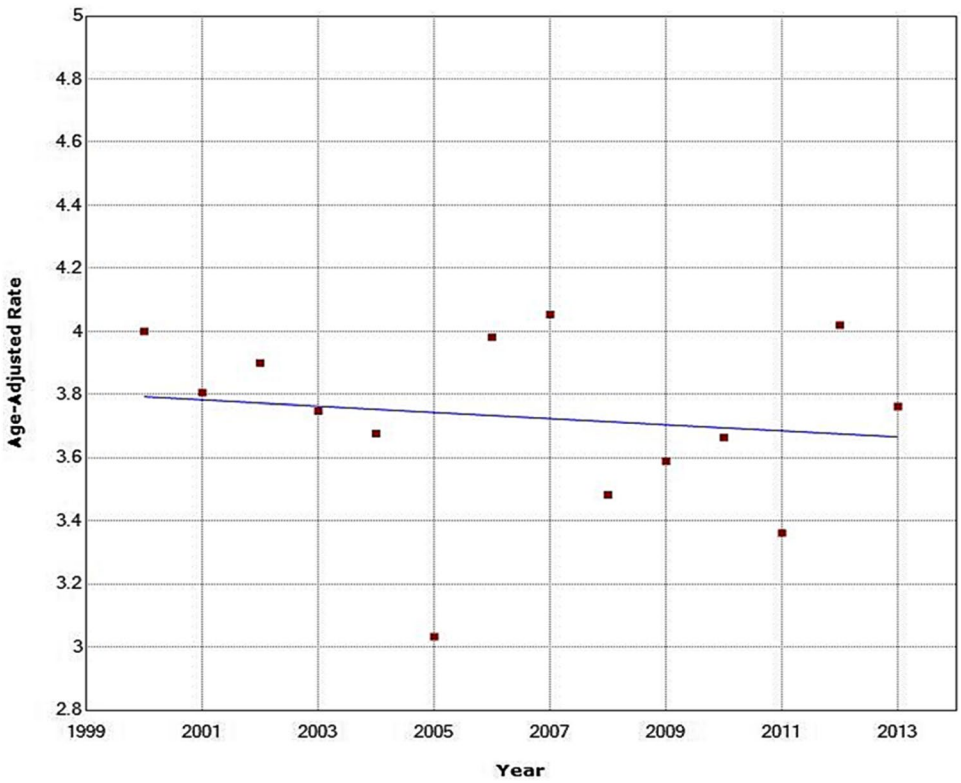

Fig. 2 Overall APC (−0.26, $p=0.627$) of OCSCC in Northern New England for the period from 2000 to 2013

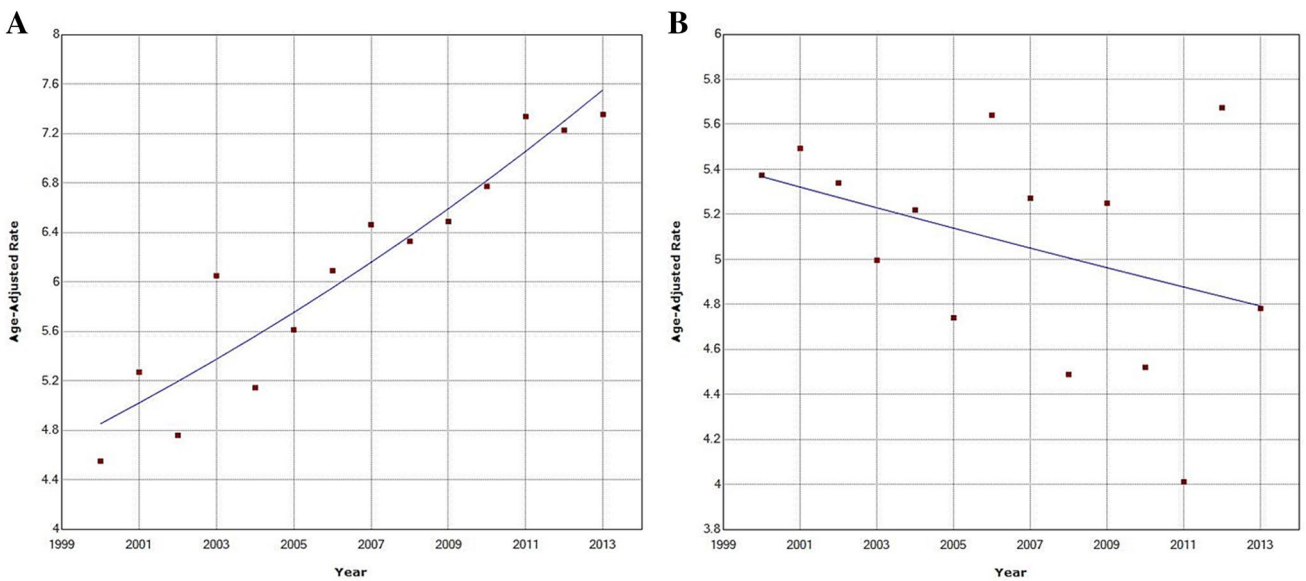

Fig. 3 APCs of OPSCC and OCSCC among males in Northern New England for the period from 2000 to 2013. APC (3.46, $p<0.001$) of OPSCC among males (**a**), APC (−0.87, $p=0.195$) of OCSCC among males (**b**)

not include any of the Northern New England states, based on this we decided to evaluate the epidemiological trends of OPSCC and OCSCC in this region.

Studies from other countries have reported similar observation of a higher annual increasing rate of OPSCC (HPV-related) in men compared to women [21–23]. The study by Forte et al. [21] using the Canadian Cancer Registry of cases diagnosed between 1992 and 2009 identified the APC of OPSCC to be 2.80 in men, compared to 1.80 in women. A Portuguese study by Monteiro et al. [22] showed a significant increasing rate of OPSCC in men at an APC of 3.49, compared to an insignificant APC of 2.02 in females.

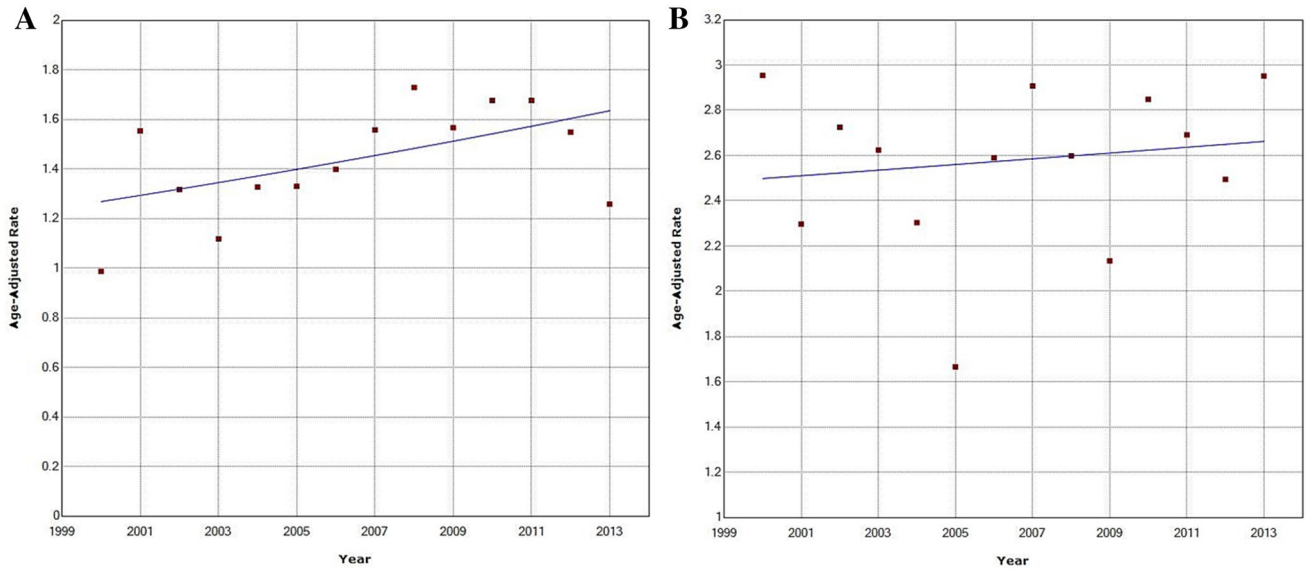

Fig. 4 APCs of OPSCC and OCSCC among females in Northern New England for the period from 2000 to 2013. APC (1.97, $p = 0.056$) of OPSCC among females (**a**), APC (0.49, $p = 0.606$) of OCSCC among females (**b**)

Table 2 ASIRs and APC in oropharyngeal and oral cavity squamous cell carcinomas in Northern New England from 2000 to 2013, by age-group

Age-group	OPSCC				OCSCC			
	ASIR		APC (95% CI)	*p*-value	ASIR		APC (95% CI)	*p*-value
	2000	2013			2000	2013		
0–39	0.24	0.13	−2.66 (−8.07 to 3.07)	0.324	0.32	0.35	3.82 (−2.22 to 10.22)	0.198
40–49	3.24	3.95	2.09 (−0.90 to 5.16)	0.156	3.62	2.19	−2.37 (−6.88 to 2.36)	0.292
50–59	7.24	14.15	3.06 (1.43–4.71)	**0.001**	7.50	5.58	0.17 (−1.86 to 2.24)	0.858
60–69	9.63	15.28	4.98 (3.04–6.96)	**< 0.001**	13.82	12.13	−1.08 (−3.59 to 1.48)	0.373
70–79	10.12	12.50	3.51 (0.21–6.92)	**0.039**	16.52	18.98	−0.38 (−3.58 to 2.93)	0.805
> 80	1.82	7.07	4.97 (−1.59 to 11.97)	0.127	16.41	19.08	0.92 (−1.02 to 2.89)	0.325

Bold indicates a significant *p*-value ($p < 0.05$)

OPSCC oropharyngeal squamous cell carcinoma (tonsil and base of tongue), *OCSCC* oral cavity squamous cell carcinoma, *ASIR* age-standardized incidence rates, *APC* annual percentage change, *CI* confidence interval

A Danish population-based study reported a significant increase in HPV-associated head and neck cancers in men at an annual rate of 4.40%, compared to 4.10% in women between 1978 and 2007 [23]. In contrast, recent studies from other European countries such as Italy, Netherlands, and France have reported a different epidemiological trend with a higher increasing incidence of OPSCC (HPV-related) in women compared to men [24–26]. Similar to our finding in the state of Maine where the annual increasing rate of OPSCC was higher in women (3.69%) compared to men (2.96%), the Italian study reported a significant increase in HPV-related head and neck cancers in women at an annual rate of 2.72%, while the incidence in men remained stable during the same period (1988–2012) [24]. The Dutch study identified a significant increase in OPSCC in women at an annual rate of 2.40%, compared to 1.90% in men between 1989 and 2008 [26]. The French study identified the APC of HPV-related head and neck cancers to be 1.90 in women, compared to −3.50 in men for the period between 2005 and 2012 [25].

Differences in the age-standardized incidence trends of OCSCC observed between men and women have been reported from countries such as Italy and Portugal [22, 24]. The Italian study reported a significant increase in OCSCC in females at an annual rate of 2.15%, while the incidence in males significantly decreased at an annual rate of 1.77% during the same period (1988–2012) [24]. The Portuguese study by Monteiro et al. showed a significant increase in the

rate of OCSCC among women at an APC of 4.34, compared to an insignificant APC of 1.30 in men [22]. Similar findings were observed in our study where among men, the trend of OCSCC decreased while that of women increased, although both were non-significant. The explanation for these findings may be attributed to the decrease in tobacco and alcohol consumption among men and uptake of these social habits among certain birth cohorts in women.

The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention reported in 2016 that only 37.5% of adolescent males and 49.5% of adolescent females have completed their recommended HPV vaccination in the United States [27]. However, it is important to note that HPV vaccination rate in New England is the highest in the United States with 49.3% among adolescent males and 61% among their female counterparts [27]. This vaccination program is based on the recommendations of healthcare providers. Several reasons have been attributed to this variation in HPV vaccination coverage between male and female adolescents such as parents' poor awareness and healthcare providers practice that favor recommending the vaccination to girls more than boys [28–31]. The first HPV vaccine (GARDASIL®) was approved by the FDA in June 2006 for use in females and in October 2009 for use in males, 9 through 26 years of age for the prevention of HPV-related diseases. Recently, the FDA approved the use of HPV 9-valent vaccine, recombinant (GARDASIL 9®) to include individuals 27 through 45 years of age. This policy is to account for newly infected middle-aged adults as recent studies have shown that a large proportion of HPV infections in middle-aged individuals are due to newly acquired infections, rather than recrudesce [32, 33].

As oral healthcare providers, we typically see our patients more frequently compared to our medical counterparts giving us that unique advantage in educating our patients on the need to be vaccinated against HPV. However, recent studies have identified a deficit in knowledge and the lack of expertise in communicating the link between HPV and oropharyngeal cancer with patients among oral healthcare providers [34, 35]. The American Dental Association Council on Scientific Affairs motivates oral healthcare providers to educate themselves and their patients on the association between HPV and oropharyngeal cancer [36].

There has been enormous progress in the control of conventional cigarette smoking since the landmark 1964 Surgeon General's report on "Smoking and Health." In 2014, the Surgeon General's report indicated that tobacco control had more than halved the smoking rates in the US since 1964 [37]. The prevalence of conventional cigarette smoking has declined from 42% of the adult US population in 1965 to 18% of the adult US population in 2012 [37]. However, a recent Surgeon General's report published in 2016 noticed a trend of electronic cigarette use rapidly growing among US youths and young adults [38]. Electronic cigarettes are now the most commonly used form of tobacco among US youths, from 2011 to 2015 the use of electronic cigarette increased by 900% among high school students, making this a major public health concern [38]. Teenagers who use electronic cigarettes (30.7%) are more likely to use combustible tobacco products (cigarettes, cigars and hookahs) compared to non-users (8.1%), within 6 months of commencement [39]. The last two decades have seen an increase in the total per capita alcohol consumption in the US among individuals 14 years of age and above from 2.15 gallons in 1995 to 2.32 gallons in 2014 (the latest year with published data by the National Institute on Alcohol Abuse and Alcoholism) [40]. There is a strong association between smoking and drinking habits and a close relationship in the use of these two substances together [41–43].

The limitation of this study is the lack of molecular confirmation on the HPV status of oropharyngeal cancer cases in the cancer registries. Nonetheless, based on previous studies showing that squamous carcinomas from the tonsil and base of tongue are frequently etiologically related to HPV, it was deemed that squamous carcinomas from these oropharyngeal sites were HPV-related OPSCC. It is also important to consider that the number of diagnosed cases of OPSCC and OCSCC are subject to bias as screening, accuracy and consistency of diagnosis of these cancers changes over the course of time. Since awareness of these cancers has been increasing, providers may have become more proactive at screening for them which may have had the effect of artificially inflating the number of incident cases diagnosed over a period of time.

In conclusion, our study showed that the overall ASIR of OPSCC increased, specifically among males, while the ASIR of OCSCC showed a stable trend between 2000 and 2013, in Northern New England. Vaccination against HPV should be frequently communicated to patients, in order to combat the growing incidence of OPSCC. The efforts on tobacco cessation, abstinence, and alcohol abuse control should be continually expanded in order to bring about a decreasing trend in OCSCC.

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Compliance with ethical standards

Conflict of interest All authors declare that there are no financial conflicts associated with this study.

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