Original Article

The Emergence of Oral Cavity Cancer and the Stabilization of Oropharyngeal Cancer: Recent Contrasting Epidemics in the South Korean Population

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BACKGROUND: By analyzing the recent epidemiologic trajectory of head and neck squamous cell carcinoma (HNSCC) in South Korea, we tracked 2 findings that have been reported recently in other countries: the stabilization of human papillomavirus (HPV)-related HNSCC incidence and the acceleration of oral cavity cancer incidence. **METHODS:** We analyzed data from the comprehensive population-based Korean Central Cancer Registry for the period 1999 to 2017. The age-standardized incidence rate (ASR), annual percent change (APC), and relative survival were calculated. **RESULTS:** The ASR of total HNSCC decreased from 1999 to 2017 (APC, −0.2 [95% CI, −0.3 to −0.0]), as did the ASR of HPV-unrelated HNSCC (APC, −0.6 [95% CI, −0.8 to −0.5]); however, the ASR of HPV-related HNSCC increased (APC, 2.9 [95% CI, 2.5 to 3.2]). The rapidly increasing incidence of tonsil squamous cell carcinoma, which was the main subsite of HPV-related HNSCC, stabilized after 2011 (APC pre-2011, 6.8 [95% CI, 5.0 to 8.3]; APC post-2011, 1.6 [95% CI, −2.1 to 5.5]), and the difference was significant (*P* = .017). In contrast, oral cavity cancer incidence demonstrated the only increase among HPV-unrelated subsites, with the increase occurring after 2006 (APC pre-2006, 1.6 [95% CI, 0.3 to 2.8]; APC post-2006, 2.8 [95% CI, 2.2 to 3.5]); the main cause of this change was an increase in the ASR of tongue cancer. **CONCLUSION:** This study demonstrates the recent stabilization of tonsil cancer incidence and the contrasting increase in oral cavity cancer incidence, unlike other HPV-unrelated cancers. These trends require further surveillance and understanding in terms of tumor biology and prevention. ***Cancer* 2021;0:1-10**. *© 2021 American Cancer Society*.

KEYWORDS: epidemiology, human papillomavirus, incidence, oral cavity neoplasms, tongue neoplasms, tonsil neoplasms.

INTRODUCTION

Human papillomavirus (HPV) infection has caused an epidemic increase in the incidence of oropharyngeal cancer—which includes cancers of the tonsil, base of the tongue, soft palate, and pharyngeal wall—in North America, northern European countries, and even Asian countries such as South Korea and Japan.[1-6] Increased oral HPV exposure due to changes in sexual behaviors in individuals born in the 1940s is reported to be responsible for the increase in epidemic head and neck squamous cell carcinomas (HNSCCs) of HPV-related sites.[1-3] However, this increase is changing; a recent study using data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry reported that the exponential increase in oropharyngeal cancer incidence in young White American men has ebbed recently, and the burden of the increase has shifted substantially to elderly White men.[7] A similar stabilization of the incidence of HPV-positive HNSCC was documented in Stockholm, Sweden.[8]

A different trend has been observed in tongue cancer, which is a major subsite of oral cavity cancer. Traditionally, tongue cancer affects older men with a history of exposure to conventional risk factors for HNSCC, such as tobacco use and alcohol consumption. There has been a decline in the number of tobacco-associated oral cavity cancers in countries that parallels decreasing rates of smoking.[9] However, in contrast with the observed overall decline in the incidence of oral squamous cell carcinoma (SCC), recent studies have reported a trend toward an abrupt increase in the number of tongue cancers in younger patients (with a higher increase rate in women) and in individuals with no exposure to traditional risk factors.[10-12] There have been isolated reports suggesting that this atypical population has a poorer prognosis, although the evidence remains inconclusive.[13] Moreover, no significant etiological factors have emerged as causative factors, such as HPV infection in oropharyngeal cancer.[14]

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Although these changes in the epidemiology of oral and oropharyngeal cancer have been documented, the recent trajectory of incidence in Asian countries, such as South Korea, has been unclear. The purpose of this study was to elucidate the overall changes in the incidence of head and neck cancer over the past 2 decades and analyze recent incidence trends thoroughly to determine whether the rapid increase of HPV-attributable cancers has stabilized and whether the incidence of oral tongue cancers has increased more rapidly, particularly in younger populations. To this end, we analyzed data from the Korea Central Cancer Registry (KCCR), which is a comprehensive population-based dataset in South Korea.

MATERIALS AND METHODS

Ethical Consideration

The study protocol was approved by our institutional review board (NCC2020-0178). The requirement for informed consent was waived because the study is a secondary analysis of deidentified data.

Patient and Public Involvement

This study was a statistical epidemiology study using deidentified information. Accordingly, patients and public involvement were not appropriate or possible in our research.

Data Source

The KCCR is a nationwide hospital-based cancer registry that was launched in 1999 by the Ministry of Health and Welfare and collected cancer incidence data from 1999 to 2017. It is estimated that the data acquired by the KCCR covers 98.2% of cancer cases in South Korea,[15] which represents nearly the entire population.

HNSCC was coded according to the version of the *International Classification of Diseases for Oncology* (ICD-O) that was in use at the time of diagnosis. The 3rd edition (ICD-O-3) was used for diagnosis from 1993 onward; data coded according to previous editions were converted to ICD-O-3 codes using predefined and standard mapping algorithms.[16] Disease stage at diagnosis was obtained since 2005 and was classified as localized, regional, distant, or unknown using the SEER staging scheme.[17]

Only malignant cases with morphology codes for squamous cell histology or SCC variants were included in the analysis (ICD-O-3 8032, 8033, 8050-8052, 8070-8078, 8082-8084, 8094, and 8123).

Under the premise that the route of HPV transmission is the oral cavity, cancers arising from the digestive tract (including the larynx) were extracted from all HNSCC cases, and the primary sites were classified as HPV-related or HPV-unrelated based on the classification of a previous study.[18] Cancers of the potentially HPV-associated sites were included in the HPV-related sites based on their anatomical similarity, even though an association with HPV infection has not yet been established. Accordingly, the tonsil (C09.0, C09.1, C09.8, and C09.9), the base of the tongue (C01.9), the soft palate (C05.1 and C05.2), and other oropharynx sites, including the pharyngeal wall (C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, and C10.9), were classified as HPV-related sites, while the oral cavity (C02, C03, C04, C05.0, and C06), the hypopharynx (C12 and C13), and the larynx (C32) were classified as HPV-unrelated sites. The lip (C00), the palate with unclear primary site (C05.8 and C05.9), the salivary glands (C07 and C08), the nasopharynx (C11), the nasal cavity and middle ear (C30), the accessory sinuses (C31), and unspecified HNSCC (C14) were classified as "other" sites.

In addition to the primary site, we collected information regarding sex, age, year of diagnosis, stage at initial diagnosis, and socioeconomic status of the study patients.

Statistical Analysis

Age-standardized incidence rates (ASRs) using the world standard population were calculated with a weighted average of age-specific incidence density, which represents the relative distribution of the standard population and average ASR. To summarize and compare trends of ASR for a specific period, the annual percent changes (APCs) and their 95% CIs were calculated.[19] For the age-stratified analysis on APCs of specific primary sites, patients were classified into the following 3 age groups: 20-39 years, 40-59 years, and ≥60 years.

Relative survival is defined as the ratio of observed survival among the studied cancer cases to the expected survival of a general population with the same sex, age, and year of death, as described previously.[20] In brief, relative survival was estimated by using an excess rate model, in which we assumed that the observed mortality rate was the sum of the expected mortality rate and the excess mortality rate (ie, the mortality rate from cancer). The expected mortality rate was obtained from a report from Statistics Korea.[15] The model of relative survival was fitted on the log cumulative excess hazard scale, which is an extension of

TABLE 1. Total Incident Cases and ASR of HNSCC per 100,000 by Subsite and Sex (1999-2017)

	Total			Men			Women			
Subsite	n	%	ASR	n	%	ASR	n	%	ASR	M/F Ratio
All	54,837	100.0	4.33	45,925	100.0	8.00	8,912	100.0	1.26	6.3
HPV-related	8930	16.3	0.71	7832	17.1	1.34	1098	12.3	0.16	8.4
Base of tongue	1634	3.0	0.13	1401	3.1	0.24	233	2.6	0.03	8.0
Tonsil	5352	9.8	0.43	4649	10.1	0.79	703	7.9	0.11	7.2
Soft palate and pharyngeal wall	1944	3.5	0.15	1782	3.9	0.31	162	1.8	0.02	15.5
HPV-unrelated	38,610	70.4	3.04	32,662	71.1	5.72	5948	66.7	0.84	6.8
Oral cavity	13,281	24.2	1.04	8795	19.2	1.51	4486	50.3	0.64	2.4
Hypopharynx	6182	11.3	0.49	5830	12.7	1.03	352	3.9	0.05	20.6
Larynx	19,147	34.9	1.51	18,037	39.3	3.18	1110	12.5	0.15	21.2
Other subsites	7297	13.3	0.57	5431	11.8	0.93	1866	20.9	0.26	3.6
Lip	607	1.1	0.05	389	0.8	0.07	218	2.4	0.03	2.3
Overlapping palate or unknown	119	0.2	0.01	89	0.2	0.02	30	0.3	0.00	5.1
Salivary gland	626	1.1	0.05	460	1.0	0.08	166	1.9	0.02	4.0
Nasopharynx	2641	4.8	0.21	2051	4.5	0.35	590	6.6	0.09	3.9
Nasal cavity and middle ear	1088	2.0	0.08	769	1.7	0.13	319	3.6	0.04	3.3
Accessory sinuses	1771	3.2	0.14	1263	2.8	0.22	508	5.7	0.07	3.1
Unspecified	445	0.8	0.03	410	0.9	0.07	35	0.4	0.00	14.4

Abbreviations: ASR, age-standardized incidence rate; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; M/F, male/female.

the flexible parametric models for survival analysis. We also estimated the relative excess risk (RER) and its 95% CI to examine the relative impact of patient demographic and clinical characteristics. All statistical tests were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) and Joinpoint version 4.8.0.1 software from the Surveillance Research Program of the US National Cancer Institute.[21] The program selected the best-fitting regression model with the minimum number of joinpoints necessary to fit the data. To classify socioeconomic status, the relative area deprivation based on Carstairs' method was used to represent area-level social disparity.[22] Areal deprivation was categorized into 5 subgroups using quintile distribution. The first quintile of relative deprivation was defined as the wealthiest area among the 5 subgroups, while the fifth quintile represented the poorest area.

RESULTS

A total of 54,837 HNSCC cases were identified for the period 1999 to 2017. Overall, 16.3% (n = 8930; ASR, 0.71 per 100,000) of HNSCC cases were HPV-related (base of the tongue [n = 1634], tonsil [n = 5352], and soft palate and pharyngeal wall [n = 1944]), and 70.4% (n = 38,610; ASR, 3.04) were HPV-unrelated (oral cavity [n = 13,281], hypopharynx [n = 6182], and larynx [n = 19,147]) (Table 1). The annual incidences and ASRs of cancers at each site are summarized in Supporting Tables S1 and S2.

The male/female ratio was 8.4 in HPV-related and 6.8 in HPV-unrelated cancers. Of note, the male/female ratio of oral cavity cancer was relatively low (2.4) in contrast to cancers in the hypopharynx (20.6) and larynx (21.2) (Table 1). Analyzed by sex and age, the incidence of HNSCC in men decreased slightly but significantly (APC, −0.9 [95% CI, −1.1 to −0.7]), whereas it increased significantly in women (APC, 2.0 [95% CI, 1.6 to 2.5]) but decreased in older age groups (50-59 years: APC, −1.1 [95% CI, −1.6 to −0.5]; 60-69 years: APC, −0.9 [95% CI, −1.4 to −0.4]) (Table 2 and Supporting Figs. S1 and S2).

During the entire study period, the incidence of total SCC decreased (APC, −0.2 [95% CI, −0.3 to −0.0], $P = .015$); however, the incidence of HNSCC of HPV-related sites increased (APC, 2.9 [95% CI, 2.5 to 3.2], $P < .001$) (Fig. 1). Among HPV-related HNSCC cases, the incidence of tonsil cancer increased most steeply (APC, 5.0 [95% CI, 3.6 to 6.4]; $P < .001$) compared with other sites. However, the single joinpoint model reflected a more significant change in incidence than the linear model calculating 1999-2017 as a single segment ($P = .007$). The increasing trend of tonsil squamous cell cancer became mild after 2011 (Fig. 2); the APC from 1999 to 2011 was 6.8 (95% CI, 5.0 to 8.3; $P < .001$), whereas the APC after 2011 was 1.6 (95% CI, −2.1 to 5.5; $P = .368$), and the decrease in APC was significant (ΔAPC, −4.9; $P = .017$).

In age-stratified analysis (Fig. 3), the incidence of change in the 20-39 years age group was not significant from 1999 to 2017 (APC, 1.9 [95% CI, −0.9 to 4.9]; $P = .176$). The incidence in the 40-59 years age group showed an increased tendency until 2008 (APC, 8.1 [95% CI, 5.2 to 11.0]; $P < .001$) and then stabilized after 2008

TABLE 2. Trends in HNSCC Incidence Rates by Sex, Age, and Subsite (1999-2017)

	ASR			
	1999	2017	APC	95% CI
Sex				
All	4.43	4.36	–0.2*	–0.3 to –0.0
Men	8.72	7.60	–0.9*	–1.1 to –0.7
Women	1.11	1.52	2.0*	1.6 to 2.5
Age, y				
20-29	0.14	0.37	3.4*	0.9 to 5.9
30-39	0.79	1.31	3.7*	2.6 to 4.8
40-49	3.72	3.45	0.3	–0.2 to 0.9
50-59	13.72	11.62	–1.1*	–1.6 to –0.5
60-69	24.35	22.47	–0.9*	–1.4 to –0.4
≥70	22.31	28.50	1.3*	0.6 to 1.9
Subsite				
HPV-related	0.54	0.89	2.9*	2.5 to 3.2
Base of tongue	0.14	0.14	1.1*	0.4 to 1.9
Tonsil	0.22	0.59	5.0*	3.6 to 6.4
Soft palate & pharyngeal wall	0.18	0.16	–0.9	–1.9 to 0.1
HPV-unrelated	3.22	2.91	–0.6*	–0.8 to –0.5
Oral cavity	0.83	1.22	2.5*	2.1 to 2.8
Hypopharynx	0.52	0.47	–0.9*	–1.4 to –0.3
Larynx	1.87	1.22	–2.6*	–2.9 to –2.6
Others	0.67	0.57	–1.3*	–1.9 to –0.8
Lip	0.05	0.03	–3.7*	–5.2 to –2.2
Overlapping palate or unknown	0.01	0.01	–2.1	–5.0 to 0.8
Salivary gland	0.04	0.04	–0.2	–1.8 to 1.4
Nasopharynx	0.27	0.26	–0.6	–2.9 to 1.7
Nasal cavity and middle ear	0.09	0.10	1.6*	0.1 to 3.1
Accessory sinuses	0.17	0.11	–2.6*	–3.2 to –2.0
Unspecified	0.04	0.02	–2.8*	–4.3 to –1.3

ASR, age-standardized incidence rate; APC, annual percent change; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus.
*P < .05 (linear regression).

(APC, 1.7 [95% CI, −1.0 to 4.5]; P = .191). However, the ≥60 years age group exhibited a consistent increase in incidence rate (APC, 6.2 [95% CI, 5.1 to 7.3]; P < .001).

The incidence of HPV-unrelated SCC decreased during the entire study period (APC, −0.6 [95% CI, −0.8 to −0.5], P < .001) along with a decrease in HNSCC incidence (Fig. 1), but HPV-unrelated cancers showed different patterns of change according to the subsite. Although the incidence of oral cavity cancer increased (APC, 2.5 [95% CI, 2.1 to 2.8]), there was a gradual decrease in the incidence of cancers of the hypopharynx (APC, −0.9 [95% CI, −1.4 to −0.3]) and larynx (APC, −2.6 [95% CI, −2.9 to −2.6]).

The increase in the incidence of oral cavity cancer was steeper after 2006 (APC from 1999 to 2006: 1.6 [95% CI, 0.3 to 2.8]; P = .018 and APC from 2006 to 2017: 2.8 [95% CI, 2.2 to 3.5]; P < .001) (Fig. 4). However, using joinpoint regression, the single joinpoint model did not appear to fit significantly more than the general model (P = .157), and the difference in APC was not statistically significant (ΔAPC, 1.2; P = .078).

A dramatic contrast was observed when tongue cancer was separated from other oral cavity cancer. In tongue cancer (Fig. 5), all age-stratified groups exhibited increasing trends of incidence. In addition, the younger age group exhibited a higher increase in incidence. The annual increase in incidence rate was highest in the 20-39 years age group (APC from 1999 to 2017: 7.7 [95% CI, 6.2 to 9.3]; P < .001) versus the 40-59 years age group (APC from 1999 to 2011: 3.3 [95% CI, 2.0 to 4.6]; P < .001 and APC from 2011 to 2017: 4.6 [95% CI, 0.9 to 8.3]; P = .017), and the lowest rate was noted in the ≥60 years age group (APC from 1999 to 2017: 2.7 [95% CI, 1.8 to 3.5]; P < .001). However, oral cavity cancers other than tongue cancer in the ≥60 years age group only showed a significant increasing trend in the incidence rate from 2004 to 2017 (APC, 2.0 [95% CI, 0.9 to 3.2]; P = .002), and this increasing trend was not significant prior to 2004 (APC, −1.8 [95% CI, −6.3 to 3.0]; P = .431) (Fig. 6). APCs were not significantly changed in the 20-39 years and 40-59 years age groups from 1999 to 2017 (APC, 2.0 [95% CI, −3.4 to 7.7]; P = .461 and APC, 0.4 [95% CI, −0.6 to 1.5]; P = .397, respectively). The change in the incidence of tongue cancer with age was also observed when stratified by sex, but no difference was observed between the sexes (Supporting Table S3).

We checked the 5-year relative survival and associated factors according to survival time since diagnosis during 2007-2017 (Table 3). Women had slightly better survival (RER, 0.93 [95% CI, 0.87 to 0.99]) than men. Survival began to worsen at age 50 years (RER of 50-59 years, 1.27 [95% CI, 1.12 to 1.45]) and decreased sharply at age 70 years [RER of ≥70 years: 2.63 [95% CI, 2.32 to 2.98]). Survival was slightly improved in HNSCC diagnosed during 2012-2017 (RER: 0.86 [95% CI, 0.83 to 0.90]) compared with HNSCC diagnosed during 2006-2011. Patients with HPV-unrelated cancers had poorer survival (RER, 1.35 [95% CI, 1.27 to 1.43]) than those with HPV-related cancers. Patients with advanced stage diseases had worse survival; the survival of patients with regional (RER, 3.63 [95% CI, 3.42 to 3.86]) and distant (RER, 7.86 [95% CI, 7.30 to 8.47]) stages was worse than that of patients with localized stages. After grouping according to deprivation, only group 1 (wealthiest) had better survival.

DISCUSSION

Head and neck cancers—which arise in the oral cavity, oropharynx, nasopharynx, hypopharynx, and

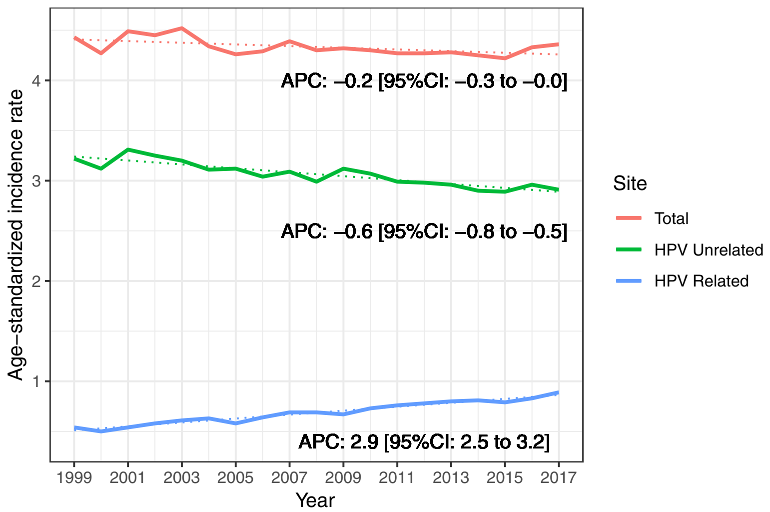

Figure 1. The trends of the age-standardized incidence rate of total head and neck squamous cell carcinoma (HNSCC) and human papillomavirus (HPV)-related and HPV-unrelated HNSCC from 1999 to 2017. APC, annual percent change.

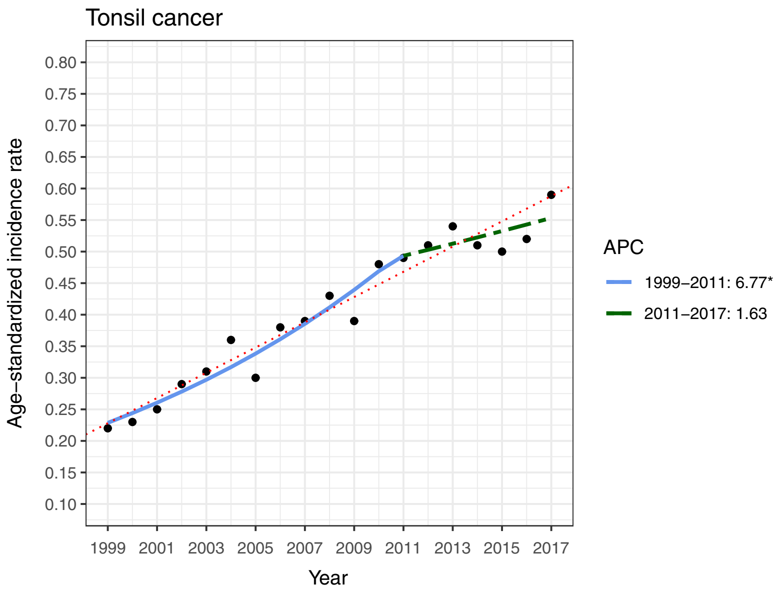

Figure 2. The trends of the age-standardized incidence rate of squamous cell carcinoma of the tonsil. From 1999 to 2011, the incidence increased continuously (annual percent change [APC], 6.8 [95% CI, 5.0 to 8.3]; $^{*}P < .001$), but it stabilized after 2011 (APC, 1.6 [95% CI, −2.1 to 5.5]; $P = .368$).

unspecified pharyngeal wall—represent the 7th most frequent cancer and the 9th leading cause of cancer-related death worldwide,[23] and the majority of cases are SCCs. Using KCCR data from 1999 to 2017, we attempted to trace the trend of the incidence of HNSCC in South Korea.

The incidence of HNSCC increased slightly in women and young individuals (<39 years) but decreased in men and older individuals (>50 years). The male/female ratio was low (2.4) in oral cavity cancer in contrast to "traditional" smoking-related cancers, including cancers of the hypopharynx (20.6) and larynx (21.2). The 5-year relative survival improved slightly but significantly during the period 2012 to 2017 compared with the period 2007 to 2011. The survival of older patients, men, patients with advanced disease, and patients with

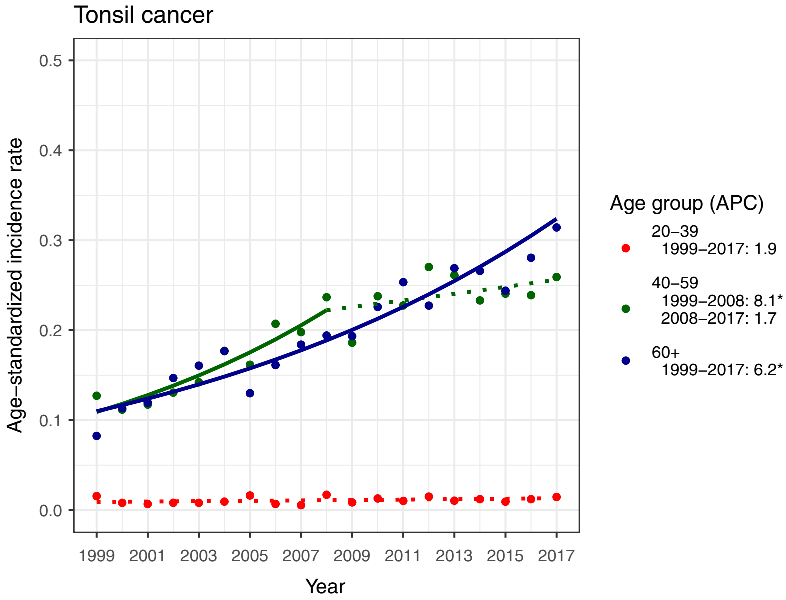

Figure 3. Age-stratified analysis on the trends of age-standardized incidence rates of squamous cell carcinoma of the tonsil. Solid lines indicate statistical significance (**P* < .05), and dotted lines indicate an insignificant result. APC, annual percent change.

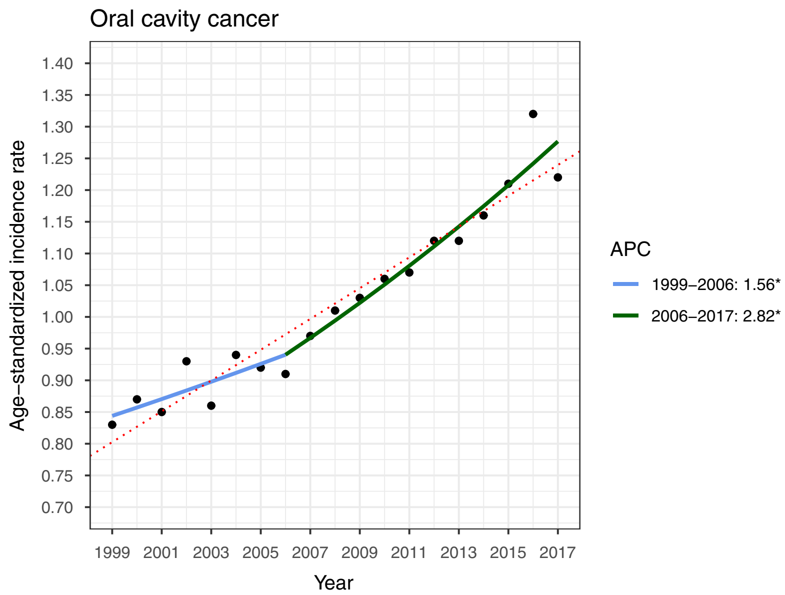

Figure 4. Trends of age-standardized incidence rate of squamous cell carcinoma of the oral cavity. The increase in oral cavity cancer incidence was steeper after 2006 than from 1999 to 2006 (annual percent change [APC] from 1999 to 2006, 1.6 [95% CI, 0.3 to 2.8]; **P* = .018 and APC after 2006, 2.8 [95% CI, 2.2 to 3.5]; *P* < .001).

advanced deprivation was worse than that of their respective comparison groups.

Of note, our population-based trajectory of HNSCC showed 2 interesting features. First, the rapid increase in tonsil SCC, for which HPV infection is known to be the main mechanism of cancer development, stabilized in the period 2012-2017 compared with the period 1999-2012. This finding suggests that the year 2012 was the inflection point of the tonsil SCC epidemic in South Korea. Meanwhile, base of the tongue SCC showed a milder and more gradual increase throughout 1999-2017.

The detailed characteristics of this change in incidence was demonstrated through the age-stratified analysis of tonsil cancer. The incidence in the 20-39 years age

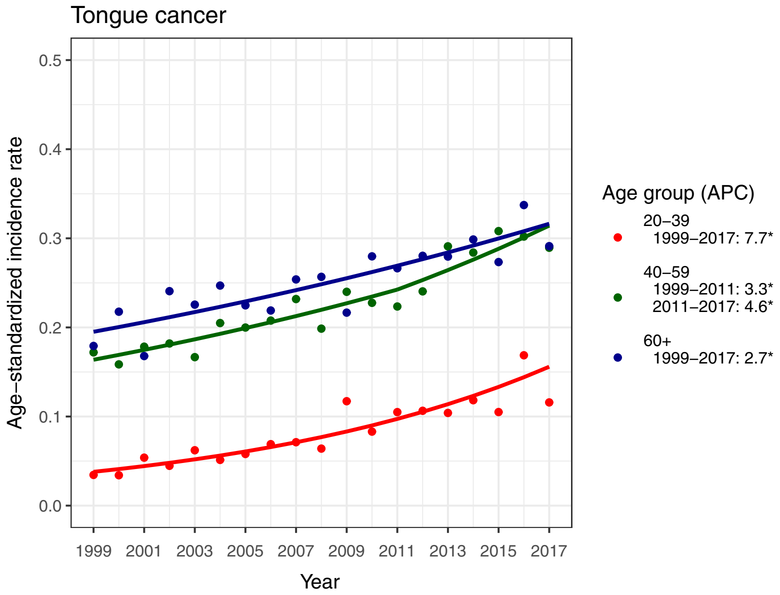

Figure 5. Age-stratified analysis on the trends of age-standardized incidence rates of squamous cell carcinoma of the tongue. Solid lines indicate statistical significance (*$P < .05$).

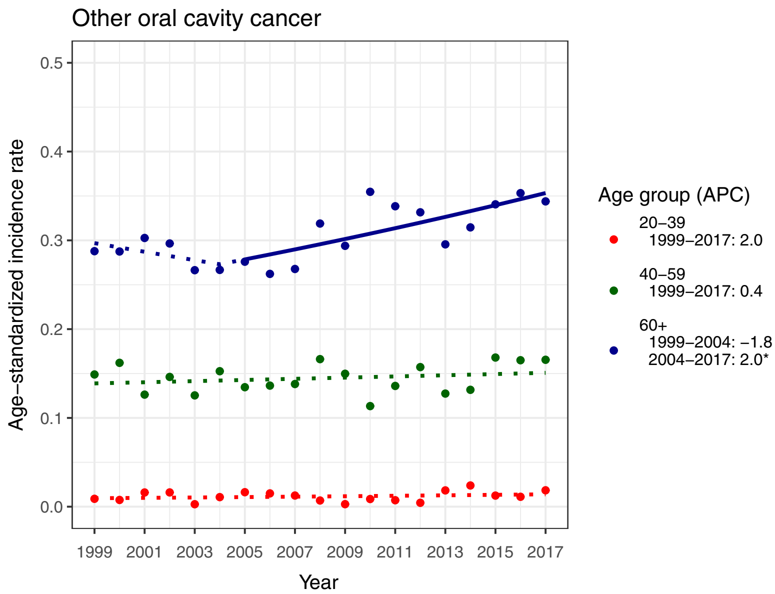

Figure 6. Age-stratified analysis for trends of age-standardized incidence rates of squamous cell carcinoma of the oral cavity other than the tongue. The solid line indicates statistical significance (*$P < .05$), and dotted lines indicate an insignificant result.

group did not exhibit a significant increase or decrease from 1999 to 2017, the 40-59 years and ≥60+ years age groups exhibited comparable changes, and the ≥60 years age group exhibited a continuously increasing trend. However, the incidence in the 40-59 years age group seemed to stabilize after 2008, even though this group exhibited a higher APC than the ≥60 years age group before 2008. Therefore, the disease burden of tonsil cancer may be gradually shifting to patients of older age, a trend that is similar to that reported in the United States.[7]

The substantial attenuation of the increase in oropharyngeal cancer incidence in the recent period has been

TABLE 3. Five-Year Relative Survival and Associated Factors According to Survival Time Since Diagnosis (2006-2017)

				Multivariate Analysis*	
	n	5-Year RSR	95% CI	RER	95% CI
Sex					
Men	27,896	64.9	64.2 to 65.6	1.00	Reference
Women	5851	67.7	66.3 to 69.1	0.94	0.89 to 0.99
Age group					
<40 years	1286	77.1	74.7 to 79.5	1.00	Reference
40-49 years	3336	74.7	73.1 to 76.3	1.05	0.91 to 1.21
50-59 years	8690	71.6	70.5 to 72.7	1.27	1.12 to 1.45
60-69 years	10,118	67.5	66.4 to 68.6	1.49	1.31 to 1.69
≥70 years	10,317	52.5	51.2 to 53.8	2.63	2.32 to 2.98
Year of diagnosis					
2006-2011	15,337	63.5	62.6 to 64.4	1.00	Reference
2012-2017	18,410	67.3	66.3 to 68.2	0.86	0.83 to 0.90
HPV-related site					
Related	5964	66.3	64.9 to 67.7	1.00	Reference
Unrelated	23,628	66.6	65.8 to 67.3	1.35	1.27 to 1.43
Others	4155	57.5	55.7 to 59.3	1.42	1.32 to 1.53
Stage at diagnosis					
Localized	14,263	82.8	81.9 to 83.7	1.00	Reference
Regional	13,952	54.9	53.9 to 55.9	3.63	3.42 to 3.86
Distant	2313	25.2	23.2 to 27.3	7.86	7.30 to 8.47
Unknown	3219	62.7	60.6 to 64.7	2.50	2.30 to 2.73
Socioeconomic status (deprivation index)					
1st (wealthiest)	11,540	70.5	69.5 to 71.6	1.00	Reference
2nd	9471	64.9	63.7 to 66.0	1.22	1.15 to 1.29
3rd	5194	61.7	60.1 to 63.3	1.25	1.18 to 1.34
4th	3622	60.7	58.8 to 62.6	1.26	1.18 to 1.36
5th (poorest)	2909	59.4	57.2 to 61.6	1.27	1.18 to 1.37

Abbreviations: HPV, human papillomavirus; RER, relative excess risk; RSR, relative survival rate.
*Adjusted by sex, age, year of diagnosis, HPV-related site, stage, and deprivation index.

reported only in young White men in the United States or Stockholm.[1,2] To the best of our knowledge, this is the first study to identify the recent stabilization of HPV-related HNSCC epidemics in an Asian population. Given the registry-based nature of our study, additional information on key oropharyngeal cancer risk factors, such as sexual behavior and smoking, was unavailable; therefore, the reasons for this stabilization remain unclear. Further detailed analysis of population-based cohorts (such as a birth cohort) related to sexual behaviors or smoking patterns should be performed to provide a deeper understanding of these trends.

In South Korea, the stabilization of the incidence rate in the 40-59 years age group and the continuous increase in ≥60 years age group may be continued or more emphasized. First, the Korean government launched the HPV National Immunization Program for 12- to 13-year-old girls to prevent cervical cancer in 2016.[24] In a study in the United Kingdom, a female-only vaccination program was significantly associated with reductions in oropharyngeal HPV-16 infection.[25] Second, the smoking rate is gradually declining in South Korea (Supporting Fig. S3),[26,27] and there has been a gradual decrease in traditional smoking-related but HPV-unrelated cancers, such as laryngeal and hypopharyngeal SCC. However, the incidence of oral cavity cancer increased gradually and reached an even higher level than in 2006. For this reason, the increase in oral cavity cancer in South Korea appears to be prominent among HPV-unrelated sites that have traditionally been associated with smoking.

The increase in oral cavity cancers seemed to be steeper in 2006, while typical smoking-related cancers (eg, hypopharyngeal and laryngeal cancers) decreased gradually over the period 1999 to 2017. Interestingly, the changes in the incidence of tongue cancer seemed dramatic compared with other oral cavity cancers in age-stratified analyses. The incidence rates in all ages revealed an increasing trend in tongue cancer; however, only the ≥60 years age group exhibited an increasing trend in other oral cavity cancers after 2004. In addition, APC was confirmed to be statistically steeper in the younger age groups. Data from international cancer registries from 22 countries have shown a worldwide increase in the incidence of oral tongue cancer.[28] In some countries, this increase was more dramatic in women and younger populations (<45 years),[29] even though the majority of nonsmoking and nondrinking young patients are female,[30] suggesting that observations of "young tongue cancer syndrome" may be a real phenomenon. Although tongue cancer incidence increased in both men and women of younger generations and was not prominent in women in the South Korean population, our data are consistent with this worldwide report. Considering that the incidence of HNSCC in women has increased gradually compared with that in men, most of this increase might be attributable to the increase in oral cavity SCC in women. Indeed, the recent increase in the incidence of oral cavity SCC contrasts with the recent stabilization of HPV-related tonsil cancer in the South Korean population.

These findings suggest the possible emergence of new etiological factors driving carcinogenesis in the oral cavity in South Korea. Genetic factors are a possible mechanism,[30] though they have yet to be confirmed as such. The identification of these etiological factors, which might be different from what has been traditionally understood, would help in the understanding, prevention, and treatment of this disease.

This population-based study has several limitations. Our data lack smoking and alcohol status data as well as data on the status of HPV infection. Confounder information is lacking, and there may be missing data. Finally, the study did not include outcomes related to prognosis (such as survival or recurrence) to focus on analyzing changes in the incidence of cancers in specific anatomical sites.

In conclusion, a recent stabilizing incidence of HPV-related tonsil SCC and a contrasting increase in oral cavity SCC have been identified in South Korea. The change in the incidence of oral cavity cancer contrasts with that of traditional smoking-related cancers, such as hypopharyngeal and laryngeal cancers. These trends require further surveillance and understanding in terms of tumor biology as well as prevention strategies.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Yuh-Seog Jung: Study concept and design; data analysis and interpretation; study supervision; writing–original draft; writing–review and editing. **Jungirl Seok:** Data analysis and interpretation; writing–original draft; writing–review and editing. **Seri Hong:** Data acquisition. **Chang Hwan Ryu:** Writing–original draft; writing–review and editing. **Junsun Ryu:** Writing–original draft; writing–review and editing. **Kyu-Won Jung:** Study concept and design; data acquisition; study supervision.

DATA AVAILABILITY

All data processed or analyzed during this study are included within the article text and Supporting Information.

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