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Head and Neck Cancer (CP Rodriguez, Section Editor)

Epidemiology of Head and Neck Squamous Cell Carcinomas: Impact on Staging and Prevention Strategies

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Opinion statement

The epidemiology of head and neck squamous cell carcinoma (HNSCC) has shifted dramatically over the last 50 years, as smoking-related HNSCCs decrease in incidence while human papillomavirus (HPV)-related cancers rise. The shift in HNSCC risk factors has changed patient demographics, the distribution of affected anatomical subsites, and prognosis of this illness. As such, the medical community has responded by devising novel staging systems and prevention strategies. The medical community will require continued vigilance in reducing HNSCC traditional risks factors for HNSCC, such as cigarette use, and emerging risk like HPV infection.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is diagnosed in over 550,000 patients per year globally and is responsible for over 380,000 deaths [1]. This paper will discuss HNSCC's shifting epidemiology, how the underlying causes of HNSCC affect staging, and possible ways to reduce HNSCC incidence.

Worldwide HNSCC epidemiology

According to the Global Burden of Disease study, lip and oral cavity cancers are the 15th most common cancers worldwide and are in the top 10 in South and Southeast Asia, Tropical Latin America, and Sub-Saharan Africa. The incidence has increased by 36.5% in the past decade [1••, 2]. Larynx cancers are the 20th most common and have increased by 23.1% in the past 10 years and other pharynx cancers are the 24th most common and have increased by 29.9% [1••, 2]. In the USA, HNSCC accounts for approximately 3% of cancers with 63,000 cases per year and 13,000 cancer-related deaths [3•]. Throughout all of the anatomical subtypes, males are more likely to be diagnosed with HNSCC than females at a 2:1 to 4:1 ratio [4, 5]. In some global regions, including areas of France, Hong Kong, India, Central and Eastern Europe, Spain, Italy, and Brazil, the incidence of HNSCC in males is over 20 per 100,000 people [4, 5]. In the USA, the incidence of laryngeal cancer is 50% higher in African American men compared with the rest of the population [6].

The most common risk factors for HNSCC include the use of tobacco products, alcohol, and human papillomavirus (HPV) infection [7, 8]. Smoking tobacco (including cigarettes, cigars, and pipes) increases the risk of HNSCC 5- to 25-fold with a clear dose-relationship between duration and quantity of cigarettes use and cancer incidence [9–12]. Similarly, smokeless tobacco increases the risk of HNSCC, particularly in the oral cavity and oropharynx, by at least 2- to 4-fold [13, 14]. Alcohol independently doubles the risk of HNSCC and the concurrent use with tobacco is thought to be synergistic [9, 15–17]. In the USA, the risk of HNSCC related to alcohol and tobacco products is amplified in African Americans and those with lower socioeconomic status [18•, 19]. High-risk HPV infection, including the HPV-16, 18, 31, and 33 genotypes, is increasingly the cause of oropharyngeal HNSCCs attributing to over 70% of new cases in North American and Europe [20••, 21].

Other risk factors independent of tobacco, alcohol, and HPV have also been found to be important globally. Betel nut chewing, a rising epidemic in Asia, increases the risk of oral/oropharyngeal HNSCC by 2- to 15-fold [22, 23]. Poor oral health including lack of tooth brush use, poor mouth conditions, and lack of mouthwash use are related to 2-fold increased risk of HNSCC [24, 25]. Patients with chronic hepatitis C infection and/or chronic HIV infection and related immunodeficiency are at increased risk of developing HNSCC and may have worse cancer-related outcomes [26, 27, 28•]. Other immune-suppressed patients, particularly those with solid organ transplants, have up to a 3-fold higher incidence of HNSCC [29, 30]. Finally, various genetic polymorphisms contribute to the susceptibility and carcinogenesis of HNSCC and likely interact with the other risk factors [31, 32].

Rise of HPV-positive cancers

Evidence pointing to the human papilloma virus (HPV) as a causative agent for HNSCC emerged during the 1980s and 1990s [21, 33, 34]. It is now well

established that the high-risk subtypes including HPV-16, 18, 31, and 33 play a carcinogenic role by integrating their viral DNA into cells and expressing the E6 and E7 oncogenes [21, 35]. HPV is generally a sexually transmitted disease, though can also be transmitted perinatally [36, 37]. Globally, the HPV virus is responsible for approximately 570,000 total cases of cancer in women and 60,000 cases in men [38•]. Of these, 38,000 HNSCC cases per year are attributed to HPV with most in the oropharyngeal site [38•].

HPV-related oropharyngeal cancers (OPC) have significantly increased in incidence over the past half century. A systematic review analyzing studies for the pathologic presence of an HPV infection showed that the prevalence of HPV from the 1980s to 2000 in OPC was 40.5% and had increased to 72.2% after 2005 [39]. A Surveillance, Epidemiology, and End Results (SEER) study found that the rate of HPV-related cancer has increased by 2.5% per year between 2002 and 2012 [40]. In this study, the SEER Residual Tissue Repositories program examined 271 OPCs from 1984 to 2004 (representing 4% of the SEER OPC population) by polymerase chain reaction (PCR) for 28 HPV types and found that the prevalence of HPV-related tumors increased from 16.3% in 1984–1989 to 72.7% in 2000–2004. When weighted to population changes, this represented a 225% increase from 1988 to 2004 [41]. In a National Cancer Database (NCDB) study of patients diagnosed between 2010 and 2013, 65% of the oropharyngeal cancers were reported as HPV positive [42]. The median age of diagnosis of HPV-related OPC is 59, though the mean age has been rising over time [42, 43]. Patients with HPV-positive OPC are more likely to be male (82%) and white (88%) [42]. Unlike tobacco- and alcohol-related cancers, a higher proportion of patients with HPV-positive cancers have higher socioeconomic status [42].

The patterns found in HPV-related OPCs correlate to the prevalence of oral HPV infections in a general population. As part of their comprehensive investigations, the National Health and Nutrition Examination Survey (NHANES) tests healthy volunteers for the presence of HPV infection by PCR and in situ hybridization (ISH). Between 2009 and 2014, the overall prevalence of oral HPV infection among men and women aged 14–69 was 6.9% [36]. Peak prevalence was among individuals aged 30 to 34 (7.3%) and 60 to 64 (11.4%) [36]. Men have higher prevalence of overall HPV infection than women (approximately 11% vs 3%) and of high-risk HPV infection (approximately 7% vs 1.5%) [36, 44]. These studies also found that oral HPV infection prevalence was increased in those with higher numbers of sexual partners, same-sex partners, concurrent genital infections, cigarette smoking, and current marijuana users [36, 44]. Fortunately, an NHANES study conducted after the introduction of the HPV vaccine found that the prevalence of vaccine-type HPV significantly decreased in both vaccinated and unvaccinated women ages 18–59 between the years 2009–2010 and 2013–2014 [45].

There is a definite heterogeneity of HPV prevalence and cancer-related diagnoses globally. Worldwide, HPV accounts for approximately 30% of oropharyngeal cancers, but much higher rates have been found in more developed countries including nations in Europe, North America, Australia, New Zealand, Japan, and the Republic of Korea where they account for over 40% [38•]. Tumor sampling has found that the proportion of HPV-positive

OPCs differ by continent with 40–60% in North America, 30%–40% in Western Europe, 24% in Eastern Europe, 9% in Asia, and 4% in South America [39, 46–48]. Other sites, such as oral cavity and larynx, also have a small proportion of HPV-positivity in North America and Europe, but not in South America [46]. The HPV 16 genotype accounts for about 82–95% of all cases with HPV 33 being the second most frequent worldwide (0.7% of cases) followed by HPV 18 (0.2% of cases). The genotypes 6, 11, 31, 45, 52, and 58 make up most of the remainder of cases [38•, 39, 47]. Despite their currently low rates of HPV-related OPC in Asian countries, the incidence is trending upwards similarly to North American and Europe [49]. This increasing global trend suggests that it will continue to be extremely important to address preventative measures for HPV-related OPC despite the significantly better prognosis compared with non-HPV OPC [50].

Fall in smoking-related squamous cell carcinoma

Historically, 80–90% of HNSCCs diagnosed in Europe, the USA, and other industrialized countries were attributed to the combination of cigarette smoking and/or alcohol drinking [10, 51, 52]. Tobacco exposure remains the strongest risk factor for developing HNSCC but many industrialized countries have declining rates of cigarette smoking due to successful tobacco control programs [8–12]. In the USA, the prevalence of any cigarette use had declined from nearly 50% in 1965 to approximately 25% in 2015 [53, 54]. Western Europe and the rest of North America have also had declining tobacco use since their peak rates between World War II and the 1980s [55, 56].

Trending with the decline in tobacco use, HNSCCs most commonly associated with smoking are declining in many countries according to population-based registry data. Between the 1980s and early 2000s, oral cavity cancer decreased in China, India, the Philippines, Thailand, Canada, and the USA [2]. Larynx and hypopharynx cancers have also decreased in Finland, Italy, China, India, Singapore, Thailand, Canada, the USA, Costa Rica, and Australia during the same time period [2]. Between 2002 and 2012, the rate of laryngeal cancer in the USA decreased by 1.9% per year [40]. In contrast to the increased rates of HPV-related OPC in the USA, HPV-negative OPC declined by 50% from 1988 to 2004 [41].

Despite these optimistic trends, there is still ample concern over tobacco use and related HNSCCs. In the USA, the Population Assessment of Tobacco and Health (PATH) study found that tobacco use in males, young adults aged 18–24, members of racial minorities, and members of sexual minorities remains higher than their counterparts [54]. Though smoking rates of decreased overall in Western Europe, smoking initiation in early adolescence remains high and has been increasing [57]. In many developing countries, tobacco use is just gaining popularity and reaching its peak with daily cigarette use found in well over 20% of the populations of Eastern and Central Europe, East and Southeast Asia, and Oceania [40, 58]. Compared with alcohol and illicit drug use, smoking continues to have the highest age-standardized related rates of mortality and the highest burden on disability-adjusted life years [58]. Therefore, it

is critical that global efforts to reduce tobacco use remain a priority in public health research and spending.

Changes in staging based on changing epidemiology

The epidemiology of HNSCC has change significantly over the last several decades, with smoking-related cancers decreasing in frequency whereas HPV-positive cancers have become much more common. As this epidemiological shift was occurring, it became clear that HPV-positive and HPV-negative HNSCC vary in outcomes and require different staging systems. For instance, in the seminal analysis of RTOG 0129, the utility of the 7th edition of the America Joint Commission on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) stage was heavily influenced by a subjects smoking history and HPV status. The study clearly demonstrated that non-smokers with HPV-positive oropharynx cancers (OPC) have markedly improved overall survival compared with subjects with HPV-negative, smoking-related tumors [50]. In fact, the AJCC/UICC staging system was poorly predictive of outcomes in HPV-positive OPC [59]. As such, a new staging system for OPC based upon HPV status was required.

To devise new staging systems for OPC cancers based upon HPV status in addition to tumor, node, and metastasis (TNM) status, several groups proposed new staging systems. One consortium called the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) performed a retrospective study of 1907 HPV-positive OPCs largely treated with radiation therapy [20••]. The ICON-S study devised a training cohort based upon patients treated at Princess Margaret Hospital in Toronto and confirmed the findings in a validation cohort comprising six different institutions in three countries. Similarly, a study originating from MD Anderson Cancer Center (MDACC) applied key features of the AJCC/UICC 7th edition staging system for nasopharyngeal cancers, another viral-mediated cancer, to HPV-positive OPC in an attempt to improve the predictive utility of TNM staging [60]. After publication, other groups evaluated the prognostic abilities of each proposed system, finding both were improvements over the AJCC/UICC 7th edition TNM but that ICON-S stratified patients better [61]. Therefore, the ICON-S proposal became the backbone for the AJCC/UICC 8th edition clinical staging system for HPV-positive OPC. For the pathologic staging system of OPC, the AJCC/UICC 8th edition relied heavily upon a 704 patient series of surgically managed patients from five cancer centers [62••].

The UICC/AJCC 8th edition separates OPC into HPV-positive cancers using IHC testing for p16, a surrogate for HPV status. Cancers may be either HPV-positive, HPV-negative, or HPV unknown [63]. For HPV-negative OPCs, the change in staging from the 7th edition to the 8th edition was modest. However, the staging between editions for HPV-positive cancer changed dramatically (Tables 1 and 2). In general, tumors were downstaged in the new edition. For instance, any ipsilateral nodal disease in the neck changed from "N1-N2b" to simply "N1" in the new staging system. Bilateral nodal involvement transitioned from "N2c" to "N2" while neck nodes exceeding 6 cm in size remained "N3." However, N3 cancers now became stage III and only distant

Table 1. TNM changes from AJCC 7th Ed. to 8th Ed for oropharynx cancers (OPC), p16 (+) clinical staging, and p16 (–) staging

	AJCC 7th ed. OPC staging	AJCC 8th ed. P16(+) OPC clinical staging	AJCC 8th ed. P16(–) OPC staging
T-stage	T1: tumor ≤ 2 cm	T1: unchanged	T1: unchanged
	T2: tumor 2–4 cm	T2: unchanged	T2: unchanged
	T3: tumor > 4 cm	T3: unchanged	T3: unchanged
	T4:	T4: consolidates T4a and T4b	T4:
	-T4a: moderately advanced local disease		-T4a: unchanged
	-T4b: very advanced local disease		-T4b: unchanged
N-stage	N0: no LN involvement	N0: unchanged	N0: no LN involvement
	N1: one ipsilateral LN ≤ 3 cm	N1: ≥ 1 ipsilateral LN all ≤ 6 cm	N1: one ipsilateral LN ≤ 3 cm and ENE negative and ENE (–)
	N2:	N2: contralateral or bilateral LNs all ≤ 6 cm	N2:
	-N2a: one ipsilateral LN 3–6 cm		-N2a: one ipsilateral LN 3–6 cm and ENE (–)
	-N2b: ≥ 2 ipsilateral LNs all ≤ 6 cm		-N2b: ≥ 2 ipsilateral LNs all ≤ 6 cm and ENE (–)
	-N2c: bilateral LN all ≤ 6 cm		-N2c: Bilateral LN all ≤6 cm and ENE (–)
	N3: any LN ≥ 6 cm	N3: unchanged	N3:
			-N3a: any LN ≥ 6 cm and ENE (–)
			-N3b: any LN and clinically over ENE (+)
M-stage	M0: no distant metastases M1: distant metastases	Unchanged	Unchanged

LN, lymph node; *ENE*, extranodal extension

Table 2. Changes between 7th ed. oropharynx cancer staging and 8th ed. p16 (+) clinical staging and p16 (–) staging

8th Ed. p16 (+) cTNM Grouping				
	N0	N1	N2	N3
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III
M1	IV	IV	IV	IV

7th Ed. TNM Grouping				
	N0	N1	N2	N3
T1	I	III	IVA	IVB
T2	II	III	IVA	IVB
T3	III	III	IVA	IVB
T4a	IVA	IVA	IVA	IVB
T4b	IVB	IVB	IVB	IVB
M1	IVC	IVC	IVC	IVC

8th Ed. p16 (-) TNM Grouping				
	N0	N1	N2	N3
T1	I	III	IVA	IVB
T2	II	III	IVA	IVB
T3	III	III	IVA	IVB
T4a	IVA	IVA	IVA	IVB
T4b	IVB	IVB	IVB	IVB
M1	IVC	IVC	IVC	IVC

metastatic disease was termed stage IV. The new staging system should greatly assist clinicians and patients alike in determining the prognosis of HPV-positive versus HPV-negative OPC, though the staging has not yet changed recommended therapies.

Whereas the TNM staging of OPC changed significantly with the transition from the AJCC/UICC 7th to 8th editions, the TNM stage groups for other HNSCC cancer subsites were fairly similar between editions with the addition of depth of invasion and extracapsular extension [63]. This reflects HNSCC epidemiology, as HPV-negative cancers reflect the most common HNSCC in the AJJC 7th ed. and earlier. Though there are emerging data that p16-positive HNSCC has a better prognosis than p16-negative HNSCC regardless of anatomical site, these data are not consistent and, therefore, p16 status was not included in the TNM staging of other HNSCC sites [64, 65].

Prevention strategies for HNSCC

Vaccinations in HPV-positive disease

As HPV-positive cancers have dramatically risen in incidence, new strategies are required to decrease the rate of new cases. Fortunately, there is precedence for ways to decrease the incidence HPV-positive malignancies in large populations. Uterine cervical cancer is an HPV-driven malignancy where primary (prevention of initial infection) and secondary (screening for precancerous or easily treated disease) prevention have decreased the incidence dramatically over the last 50 years [66]. In fact, prevention strategies in cervical cancer have decreased the incidence to the point where HPV-positive OPC is the most common HPV-associated cancer in the USA [67]. Lessons, therefore, may be taken from cervical cancer eradication efforts and applied to HPV-positive OPC.

The first strategy is primary prevention, or prevention of the initial HPV infection. Prophylactic vaccinations against high-risk HPV subtypes, such as HPV 16 (the most common cause of HPV-positive HNSCC) and HPV 18, have proven effective in decreasing the incidence of anogenital HPV infections precancerous lesions of the cervical and anus [68–70]. As HPV 16 is the primary driver of HPV-associated OPC, widespread vaccination against HPV 16 may decrease the incidence of HPV-positive OPC. There are preclinical data to support HPV vaccination in HNSCC. In mice vaccinated against HPV were immune to developing oral HPV pseudovirus [71]. Similarly, human subjects treated with an HPV vaccine expressed high levels of HPV-neutralizing antibodies in their saliva [72]. Lastly, a study of women in Costa Rica demonstrated that vaccination against HPV 16/18 was associated with a 93% reduction in the prevalence of oral HPV 16/18 4 years after vaccination. Unfortunately, this study was limited by lack of data on baseline oral HPV infection rates and there are no data on the later incidence of HNSCC in this study cohort [73].

Sadly, prevention vaccine using vaccines may be more challenging in HNSCC than in anogenital cancers. First, until recently, vaccination campaigns have largely been aimed at women. Men comprise the majority of HPV-positive HNSCC patients, yet only a few countries in the world license HPV vaccines for boys or men, and the coverage levels are extremely low

[1••, 74]. The US Food and Drug Administration (FDA) recently expanded the licensing of an HPV 16/18 vaccine to include men age 27–45 in hopes of decreasing overall HPV-positive cancer burden [75]. Second, even in females, the HPV vaccination rates in many developed countries have been generally poor. However, this trend may be changing. In the USA, for example, the rate of receiving any HPV vaccination has increased over 5% per year since 2013 such that over 65.5% of teens in 2017 had received at least one vaccination, though two to three vaccinations are recommended [74]. The vaccination rates are better in the UK and Australia, where full vaccination courses were complete in over 80% of 9-year-old girls [76] and 15-year-old, respectively [77]. Thirdly, the latency between virus exposure and disease development differs in anogenital and oral disease. In anogenital disease, virus infection typically occurs long before oral infection following the onset of sexual activity [78]. Thus, vaccinations given prior to sexual debut may need to confer immunity for longer to prevent oropharyngeal disease. Fortunately, it appears that vaccine-induced HPV immunity may last for more than 8 years for cervical infections, though it is not known if this will translate to oral infections [79]. Lastly, a large portion of the population is already infected with oral HPV and vaccinations may have already come too late. Nevertheless, vaccination against HPV is an exciting strategy for reducing HPV-positive HNSCC.

Risk reduction

Significant efforts have been made to reduce the incidence of smoking-related HNSCC. Historically, more 80% of HNSCCs in developed countries were due to cigarette smoking and alcohol ingestion [10, 51, 52]. Though tobacco exposure remains the strongest risk factor for developing HNSCC, many industrialized countries have seen a marked decreased in cigarette usage due to successful public health campaigns [9–12]. For instance, the cigarette smoking rate has decreased from 50 to 25% in the USA between the 1960s and 2015. As such, the incidence of smoking-related HNSCC had dropped significantly in recent years. Efforts to decrease cigarette usage continue across the globe.

As cigarette-associated HNSCC has decreased, new potential risk factors emerged. E-cigarettes that have vaporizers are novel methods for ingesting tobacco in which a steam or vapor from a liquid containing nicotine and other products is inhaled. This procedure, called vaping, has increased dramatically in recent years. Unfortunately, the increase in vaping raises concerns for increase cigarette use, as young people who use E-cigarettes are more likely to use conventional cigarettes in the future [80]. Some patients use E-cigarettes to try to discontinue cigarettes. Sadly, E-cigarettes are not effective in helping a general population or HNSCC patients achieve cigarette cessation [81, 82]. While the exact role of E-cigarettes in HNSCC development has not been elucidated, E-cigarette vapor can cause DNA damage in cell lines [83]. The FDA has recently tightened E-cigarette regulations, but it is unclear what public health effect this will have on cancer incidence [84].

Lastly, while betel leaf and areca nut chewing is not common in the Western Countries, a combination of betel leaf, tobacco, areca nut, and/or other products known as betel quid is commonly used in Asia [85]. Betel

quid chewing increases the risk of oral/oropharyngeal HNSCC by 2- to 15-fold [22, 23]. Recently, the importance of this risk factor has come to the forefront and efforts are ongoing to research betel quid usage, biological consequences, and public health priorities [86].

Conclusion

HNSCC remains a significant burden on the world, though HNSCC epidemiology has changed significantly in recent years. As cigarette-related HNSCC has decreased in incidence, HPV-driven cancers have increased. The rise of HPV-positive OPC cancers required novel staging systems and greater resources will need to be poured into emerging risks factors to decrease the incidence of HNSCC worldwide.

Compliance With Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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