



Published in final edited form as:

*J Surg Oncol.* 2021 November ; 124(6): 920–922. doi:10.1002/jso.26687.

## Epidemiology and incidence of HPV-related cancers of the head and neck

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### Abstract

Globally, 4.5% of cancers are due to HPV. In the U.S., 80 million people are infected with HPV, and the incidence of HPV oropharyngeal cancer has surpassed HPV cervical cancer. The highest burden of oropharyngeal cancer is seen in middle aged and increasingly older white men. HPV vaccination promises to change the epidemiology of this disease, but HPV vaccination rates remain too low today to reduce disease transmission.

### Keywords

HPV etiology; HPV incidence; HPV-related oropharyngeal cancer; HPV vaccine

### Introduction

Human papilloma virus (HPV) is the most common sexually transmitted infection in the United States and around the world. Although most people clear infections, oncogenic HPV types can remain latent and go on to cause cancer years later. Globally, the greatest burden of HPV-related cancers is cervical cancer, especially in low-income countries. However, in the United States and other high-income countries, head and neck cancer has now surpassed cervical cancer as the most common HPV related malignancy. This review provides a current update on the epidemiology of HPV-related cancers, the prevalence of HPV infection, the incidence of HPV-related cancers and recent changes in incidence in oropharyngeal cancer in the United States, and the potential and challenges of using the HPV vaccine to alleviate the burden of HPV-related cancers.

### Varieties of HPV viruses, and their relation to carcinogenesis

HPV includes a family of DNA viruses that infect basal epithelial cells and are divided into low- and high-risk types. Low-risk HPV types, also called non-oncogenic, commonly cause genital warts and respiratory tract papillomas and have been associated with low-grade

abnormalities within cervical cells. The most common HPV low-risk, non-oncogenic types around the world are HPV types 6 and 11. High-risk, oncogenic HPV types are highly associated with cancer of the cervix, oropharynx, anus, vagina, vulva, and penis. The most common high-risk HPV types are 16 and 18, but also include the less prevalent 31, 33, 45, 52, and 58 types. Over 95% of cervical cancer cases are associated with high risk HPV, while over 90% of anal cancer, 70% of vaginal and vulvar cancer, 60% of oropharyngeal cancer, and 60% of penile cancer cases are associated with high risk HPV.

## HPV infection prevalence, US and global variations

Over 80 million Americans were estimated to be infected with an HPV type in 2018, with over 14 million new infections that year. Genital HPV infection prevalence among women between the ages of 18 and 59 is estimated at 43% in the US and around 45% among men in a similar age range.

Oral HPV infection occurs through oral sex, or contact between the mouth and anogenital region. Fewer infections are caused by open-mouth kissing. Prevalence of oral HPV is estimated to be 7% among US adults between the ages of 18 and 69, with 4% having HPV high-risk types. There are differences in oral HPV infection prevalence between populations. Oral HPV infection prevalence for both high- and low-risk types is highest (9.7%) among non-Hispanic Black adults in the US, compared with 2.9% among non-Hispanic Asians, 7% among Hispanics, and 7.3% among non-Hispanic White adults. Oral HPV infection prevalence is also higher among males (11.5%) vs females (3.3%) in the US.

Globally, it is estimated that over 630 million people are infected with HPV, with an even distribution between men and women. HPV genital and oral infection shows significant geographic variations with the highest rates found in Oceania and Africa followed by Europe, the Americas, and Asia.

Most HPV infections are cleared. However, HPV type 16 has the lowest clearance rate of any of the HPV types.<sup>1</sup> Oncogenic HPV types can persist in the oral cavity for years. The latency period between infection and subsequent development of head and neck cancer has been estimated to be between 10 and 30 years.<sup>2</sup>

## HPV cancer incidence trends, US and global variations

While tobacco and alcohol were historically the main drivers of head and neck cancers, in the past several decades, the proportion of head and neck cancers attributable to HPV has increased dramatically both in the US and globally. There is significant heterogeneity in the proportion of head and neck cancers attributable to HPV according to head and neck anatomic subsite, geographic region, and time period. The oropharynx subsite is the most common site of head and neck cancer attributable to HPV. It is believed that the crypts and irregular surface of the tonsils and lymphoid tissue in the base of tongue create a favorable environment for HPV infection to persist. While much less common, oral cavity and larynx subsites have also seen an increase in cancers attributable to HPV.

Globally, 4.5% of all cancers, or 630,000 new cancer cases per year are attributable to HPV, accounting for 8.6% of cancer cases in women and 0.8% in men. The majority of these cases are cervical cancers in India and sub-Saharan Africa. Worldwide estimates of head and neck cancers attributable to HPV vary depending on the countries studied and the methods for making these estimates. For example, use of large cancer registries with many thousands of patients are cost-effective in making estimates and readily available, but the accuracy of reported HPV status of the tumors may not be high. The alternative is smaller studies with hundreds of patients where tumors are re-processed and analyzed for HPV. While these are more expensive, the numerator and denominator are more accurate. In one study that performed rigorous testing for HPV, the proportion attributable to HPV by subsite was 18% for oropharyngeal cancers, 3% for oral cavity cancers, and 1% for laryngeal cancers.<sup>3</sup> Another recent study using cases mainly from Europe and South America attributed 22.4% of oropharyngeal, 4.4% of oral cavity, and 3.5% of laryngeal cancers to HPV.<sup>4</sup>

Higher-income countries have higher proportions of head and neck cancers attributable to HPV. This may be due to different social norms and sexual activities. In the United States, where the greatest number of studies have been performed, approximately 70% of all oropharyngeal cancers are attributable to HPV,<sup>5, 6</sup> a much higher proportion than seen worldwide. The overall incidence of HPV-related oropharyngeal cancers was estimated to be 4.8 in 100,000 in 2013–2014, compared with the incidence of HPV-related non-oropharyngeal head and neck cancers of 0.62 per 100,000.<sup>7</sup>

In the United States, the incidence of HPV-related oropharyngeal cancer differs not only by sex but also by age and race. Through 2015 in the United States, the incidence in White men of all ages increased more than any other subgroup, to greater than 18 per 100,000 people. In contrast, the incidence in Hispanic and Black men was 6 and 4 in 100,000, respectively. In White women, the incidence in 2015 was almost 4 per 100,000.<sup>8</sup> In contrast, the incidence in Hispanic and Black women was approximately 2 per 100,000.

For the past decade, most literature has described the highest incidence of HPV-related oropharyngeal cancers in the United States in younger White men. However, projecting to 2030, the incidence in older cohorts of White men and women—those born before 1955—is expected to increase faster than other age cohorts. In White men aged 65–74, the incidence is estimated to be more than 70 in 100,000 by 2030, while the incidence of White women of the same age bracket is estimated to be more than 10 in 100,000.<sup>8</sup>

The incidence of HPV oropharyngeal cancers continues to steadily increase, in part due to the trends seen in unvaccinated White men. Already due to this cohort of individuals, the number of HPV-related oropharyngeal cancers has surpassed the number of HPV-related cervical cancers. A recent article examined the expected incidence of HPV-related oropharyngeal cancers through 2045 accounting for vaccination rates, and found that while the incidence may decrease in younger individuals who have either been vaccinated or benefit from herd immunity, the incidence in older adults aged 70–83 is expected to increase from 16.8 to 29.0 per 100,000 population.<sup>9</sup> In summary, the next decades will see a further increase in incidence compared to today, with a shift to an older population.

## HPV vaccination

The HPV vaccine has the potential to significantly reduce HPV-related cancers; already HPV vaccination has led to a profound reduction in the global incidence of cervical cancer. While this downward trend in incidence has not yet been seen for oropharynx cancer, some early data on the effect of the vaccine is promising. While vaccinated individuals are protected from infection, a recent study also showed the powerful effect of herd immunity on the oral infection rates in unvaccinated individuals: Over the time period from 2009 to 2016, unvaccinated men saw a decrease in oncogenic HPV prevalence by 38%.<sup>10</sup>

Significant reduction in genital HPV infection and HPV related cancers have also been seen within the vaccinated population. In a recent systematic review and meta-analysis that included data from over 60 million individuals, published in *Lancet*, Drolet et al found a substantial reduction in HPV genital infection among vaccinated men and women. In some populations, the authors found a decrease of over 80% in high risk HPV genital infection among vaccinated individuals. The findings also included a remarkable reduction in CIN (Cervical intraepithelial neoplasia) 2+ among vaccinated women and anogenital warts in men and women.<sup>11</sup>

In 2020 the FDA, using the evidence presented here as a surrogate to predict clinical benefit in preventing HPV associated Oropharyngeal cancer, approved the use of the HPV vaccine specifically for the prevention of HPV related head and neck cancer.<sup>12</sup> However, despite efforts to increase vaccine uptake, HPV vaccination rates remain below levels adequate to reduce disease transmission and eliminate disparities. Current HPV vaccination completion rates in the US are far below the Healthy People 2030 objective of having 80% of 13- to 15-year-old adolescents receive two or three doses of the HPV vaccine as recommended. In 2018, 51% of adolescents were up to date with the HPV vaccine series, and 68% had received more than one dose. Although HPV vaccination rates improved, the increases among all adolescents that year were modest compared with prior years and occurred mostly in males. In 2019, 54% of adolescents were up to date with the HPV vaccine series and 71% had received more than one dose, a small increase from 2018.

In 2020, the coronavirus disease 2019 (COVID-19) pandemic changed the way that providers offered routine and essential services. The Vaccines for Children (VFC Program) reported a decrease in vaccine orders, including the HPV vaccine, in mid-March when a national emergency was declared.<sup>13</sup> The COVID-19 pandemic has negatively affected childhood immunization rates, and there is significant concern that long-term effects may reverse gains made in HPV vaccination coverage. Disparities also exist in HPV vaccination rates in the US. Although studies show higher HPV vaccine initiation among racial and ethnic minority adolescents, Black and Hispanic patients were less likely than White patients to follow up with series completion.

## Conclusion

HPV infections are common worldwide, leading to a significant burden of HPV-related cancers. In high-income countries including the United States, the burden is greatest for

head and neck oropharyngeal cancers, with differences across sex, race, and age. Although HPV vaccination has the potential to dramatically change the incidence of disease, we will need to overcome entrenched barriers to vaccine uptake for this potential to be realized.

### Disclosure Statement:

The authors report no affiliations or conflicts of interest relevant to this material. Research reported in this publication was supported in part by the Cancer Center Support Grant of the National Institutes of Health/National Cancer Institute under award number P30CA008748.

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**Synopsis:**

This report examines the epidemiology and changing incidence of HPV-related head and neck cancers, specifically oropharyngeal cancers. The importance of the HPV vaccine in mediating HPV-related cancers is discussed.

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