

# The prevalence of oropharyngeal carcinoma caused by HPV infections in the U.S.: A review.

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## Abstract

**The incidence and association between human papillomavirus (HPV) infection and oropharyngeal carcinoma has increased in recent years, despite a decline in other causes of oral cancer from smoking and heavy alcohol consumption. HPV infection, particularly serotype 16 (HPV-16), is recognized as a significant player in the onset of HPV positive oral cavity and oropharyngeal carcinoma. The prevalence of HPV positive oropharyngeal carcinoma tends to be generally higher in men, more common in Caucasians and can be attributed to high-risk sexual practices. While the significance of HPV vaccination for oropharyngeal carcinoma prevention is controversial, research supports the possibility that the available vaccine may be effective in reducing the incidence of oral neoplasms caused by HPV. This paper reviews the relationship between HPV and oral cancer prevalence in the United States.**

**Keywords:** Human papillomavirus (HPV), Oropharyngeal carcinoma, Oral cancer, Oral neoplasms, United States.

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## Introduction

Human papillomavirus (HPV) belongs to the large family of viruses, the papovaviridae, and is a small, non-enveloped, capsid virus with circular double-stranded DNA [1]. HPV infection is the most commonly diagnosed sexually transmitted illness (STI) in the United States [2]. HPV infections can lead to condyloma acuminatum, squamous intraepithelial lesions, and anogenital malignancies; including cervical, vaginal, vulval, penile, and anal carcinomas [2]. Studies have shown a strong association between HPV and cervical cancer, independent of other risk factors. Nearly all cases of cervical cancer are attributable to HPV infection, with the HPV-16 strain being the most common, followed by HPV-18, and lower occurrences involving HPV types 31, 33, 45, 52, and 58 [3]. Oral HPV infections are linked to a subset of oropharyngeal carcinomas associated with high-risk HPV type 16 [3].

Globally, oropharyngeal cancers are the sixth most common cancers. Approximately 85,000 cases of oropharyngeal cancers are diagnosed annually, with 12,000 of these cancers occurring in the United States [4]. Oropharyngeal cancers arise where the oral cavity and pharynx merge, including the palatine and lingual tonsils, the posterior one-third of the tongue, the soft palate, and the posterior pharyngeal wall [4]. Although HPV-negative oropharyngeal carcinoma, which is largely attributed to the use of tobacco and alcohol, has declined by approximately fifty percent, the overall incidence of oropharyngeal carcinoma has increased over the last three decades [3]. Recent studies

have shown that 70-80 percent of oropharyngeal carcinoma is attributed to HPV, particularly HPV-16 strain. HPV-positive oropharyngeal carcinoma has predominantly increased among young people, especially males, and white population and, it is associated with sexual behaviors [3]. There has been a significant increase in this cancer among men in developed countries, although the reason remains unclear and there is still little known regarding the epidemiology, determinants of oral HPV infection and the etiological link with oropharyngeal cancer [4]. The purpose of this paper is to examine the prevalence of HPV in the oral mucosa in the United States and its relationship with oral cancer.

## Methodology

An electronic literature search was performed using PubMed, Google Scholar, EBSCOhost, Mendeley and MedLine Plus. The search was limited to peer-reviewed articles published from January 1, 1983 to January 2019. An article was selected if it included keywords such as: human papillomavirus (HPV), human papilloma, oropharyngeal carcinoma, oral cancer, oral neoplasms, and prevalence in the United States. Articles were then reviewed and included based on the applicability to the topic.

## Prevalence of oropharyngeal carcinoma caused by HPV

Studies have shown that despite a gradual decline in the incidence of squamous cell carcinomas in the head and neck region, the incidence of oropharyngeal squamous cell

carcinoma caused by HPV has increased annually [5]. Some studies reported greater than 5% increase in oropharyngeal squamous cell carcinoma linked to HPV annually, from 2000 to 2004 in the USA [6,7]. A recent study reports a prevalence of oral HPV in approximately 11.5% men and 3.2% women in the United States [8]. HPV is a double stranded DNA virus with 120 subtypes which are categorized as either high risk or low risk [6]. HPV causes infections and the high-risk subtypes have been identified as major risk factors for anogenital cancers. In the oropharynx, different HPV subtypes have been identified in normal oropharyngeal mucosa in various degrees, yet these findings remain controversial [9,10]. Oral infections caused by HPV could be benign (warts) or malignant (oropharyngeal carcinoma) and transmission is usually via oral sex, self or instrumental inoculation or by vertical transmission from mother to child [11].

Oropharyngeal carcinoma caused by HPV infection was first described in a report by Syrjanen and colleagues [12]. Other studies have confirmed that high-risk HPV subtypes are implicated in approximately 20-72% of oropharyngeal squamous cell carcinomas of the head and neck region [13-15]. HPV associated oropharyngeal carcinomas are small, poorly differentiated with a basaloid feature and have a higher rate of metastasis from their primary sites (base of the tongue, tonsils, gingiva and oral mucosa) as compared to other causes of oropharyngeal carcinoma [16,17]. High-risk HPV subtypes possess the ability to invade and manipulate the cell's tumor suppression ability; therefore, causing mutations and affecting the cell's growth regulation and cancer formation [15]. The most common high-risk HPV subtype implicated in HPV associated oropharyngeal carcinoma is HPV-16, which has been reported in over 80% of HPV oropharyngeal carcinoma [18,19]. Other studies have identified other high-risk HPV subtypes (HPV-33, HPV-35 and HPV-56) in cases of oropharyngeal carcinoma [16]. In another cohort study, [20] researchers identified other high-risk HPV subtypes, including HPV-31, HPV-52, HPV-18, HPV-33 and HPV-35, as the cause of oropharyngeal carcinoma in 529 samples. Other high-risk HPV subtypes, particularly HPV-16 and HPV-18 are known to cause genital warts. Interestingly, there has been no direct correlation between the incidence of genital warts and oropharyngeal carcinoma caused by HPV.

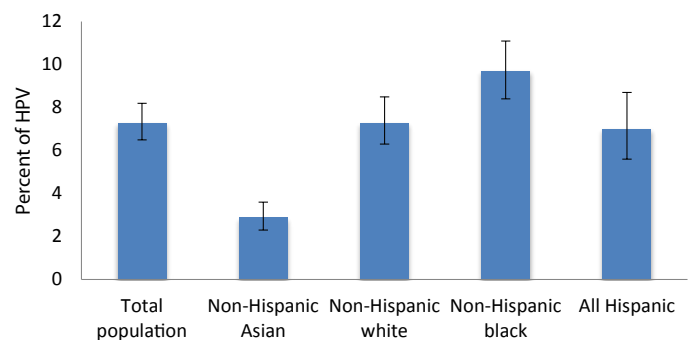
Furthermore, the prevalence of HPV positive oropharyngeal carcinoma tends to be generally higher in men (66%) and lower in women (53%) [4,6]. It is more common in Caucasians and to a lesser degree among non-Hispanic black patients (31%). This can be attributed to the prevalence of high-risk sexual practices, as men who have sex with men are at a higher risk [17,21]. A case-control study shows that a higher number of lifetime vaginal (>26) and oral (>6) sexual partners is associated with an increased risk of oropharyngeal carcinoma caused by HPV [22]. It is important to note that there is less association of tobacco and alcohol consumption with HPV-positive oropharyngeal carcinoma as compared to HPV-negative oropharyngeal carcinoma [16]. Despite this, patients with a history of heavy tobacco use have a worse prognosis than non-tobacco users with HPV associated oropharyngeal carcinoma [23]. Other identified risk factors of HPV associated oropharyngeal carcinoma

include, concurrent genital HPV infection [5], a compromised immune system such as in human immunodeficiency virus (HIV) positive patient's, and men who have sex with men [24].

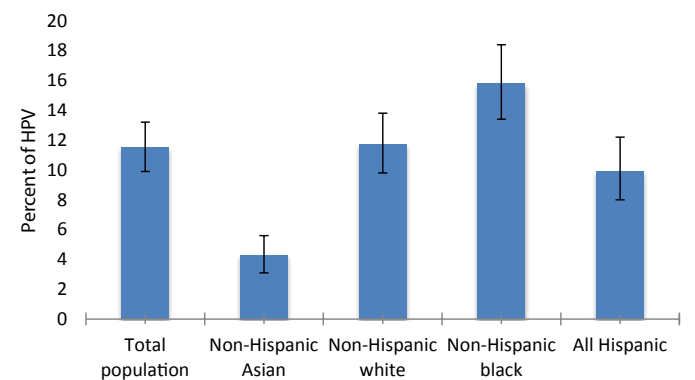
The Centers for Disease Control and Prevention (CDC) published a report in 2017 that showed that the prevalence of any oral HPV in adults (age 18-69) is 7.4%, while the prevalence of high-risk HPV in adults is approximately 4% [25]. This study also showed that the lowest prevalence was observed among non-Hispanic Asian adults and highest among non-Hispanic black adults [25]. In general, men are more affected (7.5%) than women (3.3%), as shown in Figures 1-3 [25].

## Results and Discussion

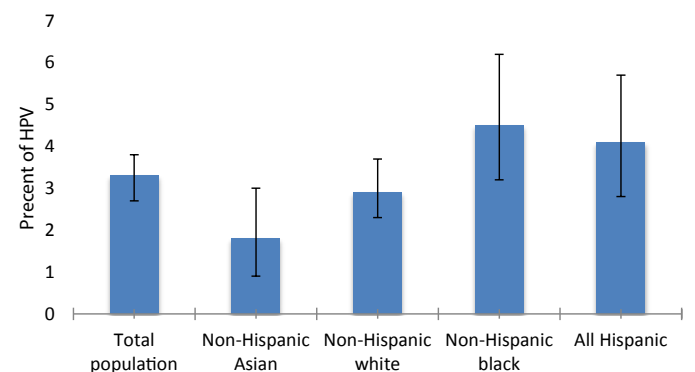
Oropharyngeal carcinoma has been a relatively uncommon cancer; however, its incidence is increasing in epidemic proportion due to a rise in HPV-related carcinoma [26]. Traditionally, oropharyngeal carcinoma has been associated with heavy tobacco use and alcohol consumption [27], but these



**Figure 1.** Prevalence of HPV in men and women.



**Figure 2.** Prevalence of HPV in men.



**Figure 3.** Prevalence of HPV in women.

tobacco and alcohol related oropharyngeal carcinomas are on the decline now [26]. More recent studies show that the majority of oropharyngeal carcinoma is related to HPV, particularly HPV-16 [26]. The incidence of HPV-related oropharyngeal carcinoma is increasing dramatically among middle aged white males, of moderate to upper income class, who have had oral sexual partners [26]. The risk of HPV infection is noted to be higher in people who have had many sexual partners [5]. Additionally, there is a higher prevalence of oropharyngeal cancer in a person who currently has or has had a genital HPV infection [5]. It is projected that in future if urgent preventative measures are not put in place, oropharyngeal carcinoma might eventually be the most common HPV related cancer in the United States, as well as the most common form of cancer arising in the upper aerodigestive tract [26].

The dental community, as well as other health care providers, offers the first line of defense in early detection of oropharyngeal carcinoma through regular oral screening [28]. Presently, the only screening test approved for HPV infection is the cervical Pap smear test [29]. The CDC (2018) does not recommend screening tests for other types of HPV associated cancers [29]. No screening exam exists for the oropharynx equivalent to the cervical Pap smear [26]. The oropharynx proves to be a difficult area to obtain an adequate representative sample due to the large surface area and presence of crypts [26]. Rosenthal and colleagues discussed the use of the Cobas HPV Test on oral rinse rather than cervical specimens [30]. It was found that over ninety percent of oropharyngeal cancer patients tested positive in the study. Therefore, the Cobas HPV Test on oral rinse is specific and potentially sensitive for HPV related oropharyngeal cancer and may serve as a screening test in the future. Kreimer and colleagues found that the presence of HPV-16 E6 antibodies in a patient's serum lead to a higher risk of them developing oropharyngeal carcinoma in the future [31]. Sero-testing for such antibodies may also be implemented as a screening test in the future. According to the National Cancer Institute (2018), there are no formal screening programs currently available for non-cervical HPV related cancers, so universal vaccination could have a consequential public health benefit [32].

There are a variety of vaccines available to prevent HPV, including the Gardasil vaccine which protects against 9 types of HPV. Millions of 11 to 12-year old children in the United States and other developed countries around the world have been vaccinated with the HPV vaccine. Gardasil, Gardasil 9, and Cervarix are the three vaccines approved by the FDA which protect against HPV types 16 and 18; cervical cancer-causing strains (70%) and other HPV strains causing cancer. Gardasil also protects against HPV types 6 and 11, which are the leading cause of genital warts (90%). Gardasil 9 protects against an extra five HPV cancer causing strains [32]. Since the original clinical trials were tailored to cervical cancers, the FDA prohibits the healthcare industry from discussing possible benefits of the vaccines in other locations of the body that HPV is known to infect [28]. In the United States today, the HPV vaccines are approved for the prevention of genital warts, cervical and anal cancers only [26]. Currently available vaccines protect against the HPV types that are associated with oropharyngeal cancer, and therefore, may be used to help prevent oropharyngeal

carcinoma related to HPV in the future [29]. Till date, no clinical trial has been completed to show how HPV related cancer in the oropharynx can be prevented by vaccines, although the vaccines are shown to be effective against similar strains of HPV that cause cancers of the reproductive tract [29]. Research reveals that administration of the HPV vaccine can protect against oral infections caused by HPV virus types responsible for causing oropharyngeal carcinoma [33].

Health care professionals should be aware of the different epidemiologic factors and clinical behaviors associated with HPV related oropharyngeal carcinoma in order to properly screen and diagnose patients [26]. An increase in public awareness for the importance of oral screening may improve early diagnosis, as well [28]. Furthermore, patient knowledge on the available HPV vaccines is vital. As shown, in one pilot study, African American males who have sex with males were favorable to vaccination, but were completely unaware of the approval of the HPV vaccine for use in males, for prevention of anal cancers [34].

## Conclusion

This review confirms that HPV related oropharyngeal cancer has become a growing epidemic amongst a new demographic of individuals, especially men who have high-risk sexual practices. More research is required in the areas of HPV related oropharyngeal carcinoma screening. In addition, vaccine knowledge should be aimed at the general public and designed to help people make informed decisions. Emphasis is needed in the area of currently available vaccines for HPV prevention and their effectiveness in preventing oropharyngeal infection and carcinoma, since the most appropriate way to tackle HPV related oropharyngeal carcinoma is prevention.

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