



HPV vaccination for prevention of head and neck cancer among men

By Mohamed Toufic El Hussein, PhD, RN, NP and Simreen Dhaliwal

Abstract: *The incidence of human papillomavirus (HPV)-associated head and neck cancer (HNC) has been rapidly increasing in developed countries, with HPV-associated HNC now accounting for 70% of all HNC cases. An increased incidence has been noted particularly among males. The disparities in HPV vaccine uptake rates and the increasing number of individuals with HPV-associated HNC suggest a lack of public awareness of both HPV sequelae and prevention options. This review highlights the importance of prophylactic HPV vaccination for preventing HPV-associated HNC, particularly in males. Current evidence substantiates the need for gender-neutral HPV vaccination programs and reinforces the recommendations made by the CDC. This article raises awareness of the association between HPV and HNC as well as the effectiveness of HPV vaccination in HNC prevention.*

Keywords: 9vHPV, cancer prevention, Gardasil 9, head and neck cancer, HNC, HPV, HPV9, HPV 9-valent vaccine, HPV serotype 16, HPV serotype 18, HPV vaccination, human papillomavirus, human papillomavirus 9-valent vaccine, males, men, oropharyngeal cancer

In 2020, the global burden of head and neck cancer (HNC) was estimated at 700,000 cases and 360,000 deaths, most of which occur in Western countries.¹ Although the incidence of nonviral HNC associated with smoking and alcohol use has steadily decreased over recent decades, the incidence of HNC cases associated with human papillomavirus (HPV) has increased.²⁻⁶ HPV serotypes 16 and 18 are associated with 85% of HPV-related HNC; oropharyngeal cancer is the most common subset, with 62.9% of all cases of oropharyngeal cancer being HPV-positive.^{1,7-12} In many Western countries, HPV-associated oropharyngeal cancer incidence has increased by up to 225% within the last 3 decades, exceeding cervical cancer as the most prevalent HPV-linked cancer.^{6,13-15} Currently, the reason for the drastic increase in incidence of HPV-associated HNC is unknown, although it is hypothesized that it is the result of increasing prevalence of cancer-causing HPV strains.¹⁶

Persistent HPV infection is the primary cause of HNC in many cases. However, because most HPV infections are asymptomatic, they often go untreated

Indications for the HPV vaccine have been expanded to include the prevention of HPV-associated HNC, and national immunization programs across 47 countries include boys in their HPV vaccine recommendations.¹⁰ However, many men refrain from receiving the vaccine due to a lack of health literacy and risk perception. The lack of knowledge identified in numerous studies about HPV vaccination and its benefits deterred many parents of boys from consenting to their children receiving the vaccine at the indicated age.^{13,24} Even among healthcare providers, the correlation between HPV infection and HNC risk in the male population is not widely known. This lack of awareness is often attributed to the strong association of HNC with tobacco and alcohol exposure, as these risk factors were well established a longer time ago; in addition, the extensive marketing of the HPV vaccine as an agent designed specifically for females to prevent cervical cancer significantly contributed to the current misconception. Despite CDC recommendations, many pediatricians only provide the HPV vaccine for boys at the parents' request, according to one study.²

Inadequate healthcare provider communication around and recommendation of the HPV vaccine for males have become a growing concern. HPV vaccination prevents 90% to 100% of chronic HPV infections and covers high-risk serotypes 16 and 18; however, the estimated population-level

effect against these oral infections is only 17% due to the low immunization rates.^{15,25,26} It is critical for NPs and other healthcare providers to be aware of and understand HPV's connection to HNC, to provide strong recommendations for the vaccine, and to further educate the public about the vaccine's role in HNC prevention.

■ HPV 9-valent vaccine

The HPV 9-valent vaccine (9vHPV), or Gardasil 9, protects against infection caused by nine HPV serotypes. Specifically, 9vHPV covers serotypes 6 and 11, which are associated with genital warts, and serotypes 16, 18, 31, 33, 45, 52, and 58, which are associated with head and neck, cervical, vulvar, vaginal, penile, and anal cancers.²⁷ Additionally, the vaccine protects against certain precancerous or dysplastic lesions associated with these nine serotypes.



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for years, potentially resulting in HPV-associated cancer.^{14,17} Vaccination against HPV is considered the primary prevention strategy. More than 90% of oral HPV infections are sexually acquired, and these infections are a primary risk factor for HPV-associated HNC.^{2,18}

Males are at a greater risk of developing HPV-associated HNC. In 2022, 7,500 Canadians were diagnosed with HNC; 5,400 of the total were men. In the US, 71% of all individuals diagnosed with HNC were estimated to be males.^{16,19-21} The disproportionately higher rate in males may be explained by their lower amount of estrogen, possible variation in immune responses against HPV, and higher number of sexual partners.^{3,11} Research also shows that White individuals and those of high socioeconomic status have a higher prevalence of HPV-positive HNC in the US.^{22,23}



All vaccines that provide immunity against HPV contain synthetically manufactured noninfectious virus-like peptides of the major capsid (L1) protein, which mediates cell attachment during infectious HPV entry, of the previously mentioned serotypes. However, 9vHPV has an increased concentration of L1 protein for HPV serotypes 16 and 18, which account for 85% of all HPV-related HNC cases, providing stronger resistance when exposed to these serotypes and eliciting long-lasting neutralizing antibodies.²⁷ Antibodies in the saliva have been found following HPV vaccination, demonstrating the vaccine's ability to protect against oral infections.^{28,29} Notably, the prevalence of oral HPV 16 and 18 infections in the US is reduced by approximately 88.2% in vaccinated versus unvaccinated individuals (0.11% versus 1.61% for all individuals; 0.0% versus 2.13% for men).³⁰⁻³³

HPV vaccines are prophylactic and do not treat HPV-related diseases or prevent their progression.⁶ Due to the extensive latency period between HPV infection and cancer development, the effect of vaccination implementation for HNC is not expected to be seen for decades.³⁴

■ Current policies and guidelines

In 2009, the quadrivalent HPV vaccine was licensed in the US for use in males for prevention of genital warts and later also for the prevention of anal cancer. In 2011, the CDC Advisory Committee on Immunization Practices (ACIP) recommended routine HPV vaccination for males in the US, where routine vaccination of females only had been previously recommended, in recognition of the efficacy of the vaccine in preventing anal cancer and genital warts. Although the ACIP acknowledged the link between HPV infection and development of oropharyngeal cancer, no data was available on the efficacy of the HPV vaccine for prevention of oropharyngeal cancer at the time. 9vHPV was approved by the FDA in 2014; however, its indications did not include HNC prevention. In 2020, the FDA approved indication of 9vHPV for HNC prevention via an accelerated approval pathway based on the vaccine's effectiveness in preventing HPV-related anogenital disease.^{2,35} Continued approval of the vaccine for HNC prevention may be contingent upon clinical benefit demonstrated in a vaccine-efficacy trial.³⁵

The underlying molecular mechanism by which the vaccine is believed to work to prevent HNC has not been found to differ from that by which it works to prevent anogenital disease, for which it was originally developed.^{15,27,30,34} Research on the effectiveness of the vaccine for HPV-associated HNC prevention has been hindered by the challenge of directly demonstrating vaccine efficacy, given factors such as the difficulty of detecting precancers in the oropharynx.³¹ To this end, the US National Cancer Institute and the International Agency for Research on Cancer jointly endorsed the prevention of persistent oral HPV 16 infection as an acceptable endpoint for clinical trials aimed at determining the efficacy of the vaccine in preventing HNC.³¹

In its annual vaccine schedule, the CDC includes HPV vaccination for girls and boys at age 11 or 12 years (or starting as early as age 9 years) in the US. The age recommendation is based on the fact that vaccination is most effective before HPV exposure through sexual activity.^{6,36} A two-dose schedule is recommended for individuals younger than 15 years at initial vaccination, whereas a three-dose schedule

can protect against infection with other strains of HPV to which an individual has not been previously exposed.¹⁵ Therefore, an individual who has previously been infected with an HPV variant could still benefit from vaccination. This further illustrates the efficacy of the HPV vaccine in preventing oral infections in individuals older than age 27 years. The duration of protection with HPV vaccines remains unclear. However, clinical trials of participants who received the quadrivalent HPV vaccine and who have been followed for more than 10 years have shown no evidence of decreased effectiveness.^{15,39}

■ Male population vaccination disparities

Data from 2014 to 2017 showed that only 1 in 11 males in the US had initiated the HPV vaccine and 1 in 30 males had completed all doses.⁸ Other studies have found that only 37.5% of 13- to 17-year-old males and 4% of 19- to 26-year-old males had completed the vaccine series.^{8,40,41} Although many studies unpack the effects of herd immunity for males, the data remain relatively inconclusive, particularly for men who have sex with men, who are at substantially

higher risk for HPV 16 and 18 infection than men who have sex with women.^{10,17,28} Data from Sweden illustrate how catch-up vaccination for males could further reduce HPV prevalence by 17% compared with female-only vaccination.⁴² Males have been found to

be more willing to endorse vaccine acceptance if they are aware of the male-specific HPV-linked health outcomes, such as disproportionate rates of HNC.⁴³ In addition, vaccination of males could also decrease risk of HPV-related cancers in females by decreasing transmission, although this concept is outside of the scope of this article. NPs should use every encounter to educate patients regarding HPV-associated cancers in men such as HNC as well as the primary preventive agent, the HPV vaccine.

■ Vaccination versus natural immunity

The effectiveness of HPV vaccines in eliciting an immune response stands in stark contrast to the seroconversion seen in only a portion of individuals following incident HPV infection.⁴⁴ The high purity of the L1 proteins in the vaccine leads to a sustained and robust antibody response, with antibody titers



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is endorsed for those who are age 15 years or older at initial vaccination.^{17,37} In Canada, 9vHPV is approved for people ages 9 to 45 years for prevention of oropharyngeal cancer and other HNCs caused by HPV, as well as for other indications; providers should refer to relevant resources for more information.^{5,27}

The CDC currently recommends catch-up vaccination for males and females through age 26 years and for specific populations through age 45 years according to their ongoing risk of HPV exposure and shared clinical decision-making.^{6,17,36,38} Although limited data are available on the safety and effectiveness of 9vHPV after age 27 years, recent studies have shown that the immune response to HPV vaccination in men ages 27 to 45 years is comparable to that seen in younger males.^{2,17} Vaccination has been shown to protect against reinfection at different mucosal sites in previously exposed individuals; additionally, vaccination

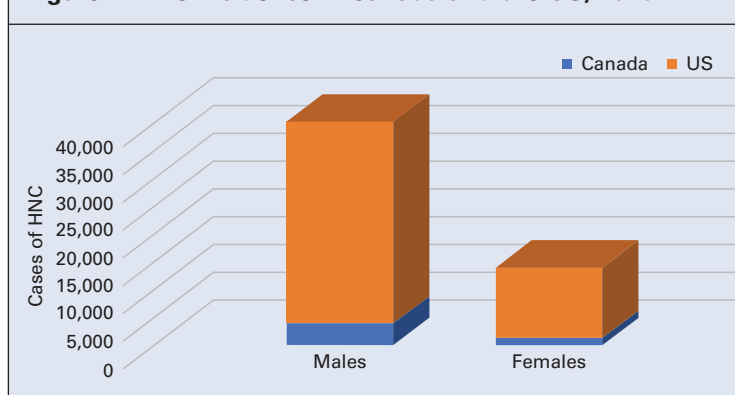
following vaccination exceeding levels seen following natural HPV infection.⁴⁵ One study found that the higher levels of antibodies induced by vaccination were predicted to remain higher than those seen in naturally acquired immunity for more than 30 years after vaccination.⁴⁶ Furthermore, research suggests that protection after infection is limited to individuals with higher levels of naturally acquired antibodies.⁴⁴ Recent findings have shown that antibodies cloned from memory B cells produced naturally through exposure are generally not neutralizing, whereas those obtained through vaccination are.^{44,47} Depending on the type of vaccine, vaccination can generate 10- to 100-fold higher levels of specific neutralizing antibody titers compared with naturally acquired immunity.⁴⁶

Although vaccination against HPV is most effective in individuals who have not been previously exposed to HPV, current evidence demonstrates that vaccination continues to be beneficial in individuals between the ages of 27 and 45 years.⁴⁷ Individuals previously infected with an HPV strain can still benefit from vaccination, as HPV vaccination augments natural HPV immunity by boosting antibody levels and memory B cell numbers.⁴⁷ Finally, naturally acquired antibodies following infection with one HPV serotype do not protect against the virus's other serotypes; therefore, individuals who have been infected but not vaccinated remain at risk of infection with other HPV strains.¹⁵

■ NP practice implications

With HPV-associated oropharyngeal cancer, a subset of HNC, surpassing cervical cancer as the leading HPV-associated cancer in the US, it has become critical to understand the link between HPV and HNC as well as the significance of HPV vaccination for primary prevention. A general lack of awareness or knowledge of noncervical HPV-associated cancers is an identified cause of disparities in vaccination and, resultantly, health outcomes among the male population, with HPV-associated cancer incidence rising in this group.¹⁴ *Figure 1* highlights the increased incidence of HNC among males versus females living in Canada and the US. A questionnaire conducted in Canada regarding counseling practices

Figure 1. HNC incidence in Canada and the US, 2020²⁰



relating to HPV infection revealed that 68% of healthcare providers “never” or “rarely” educated individuals on HPV-associated HNC and that 57% of healthcare providers more often counseled females than males about HPV.¹⁶ Several studies have demonstrated a direct correlation between vaccine recommendations given by healthcare providers and individuals’ vaccination rates. Individuals who received a strong recommendation from a healthcare provider were more likely to perceive an urgency to receive the vaccine, and greater trust in the information they received led to decreased vaccine hesitancy compared with those who received a presumptive recommendation.^{14,24,48} A greater understanding of the risks of HPV and the benefits of vaccination has directly been correlated with individual or parent vaccine acceptance.¹⁴

All individuals are at risk of contracting HPV; therefore, NPs, particularly those in primary care, should work to educate their patients on HPV vaccination as a means of preventing infection and mitigating associated illnesses. A simple way to start a conversation about HPV vaccination is to ask patients about their vaccination status to attempt to trigger their interest in learning more about preventive options. Conversations about sexual safety can also lead to discussions of HPV—and the opportunity to receive a vaccine—specifically. The NP can potentially motivate patients to assume an active role in their health by first commending them for any healthy habits that help them to prevent or improve chronic conditions and then by introducing additional options to maintain health, such as the HPV vaccine for prevention of HPV infection and subsequent cancer development. If a patient

asks an NP about another vaccine, the NP can use the opportunity to discuss HPV vaccination. The NP can highlight the ability of the vaccine to prevent several different types of cancer.

NPs must find the opportunity to talk to all parents/guardians about vaccination for their children wherever appropriate. The NP can initiate a vaccination conversation when a parent/guardian brings a child to a well-child visit or visits the office to receive a refill for a prescription, beginning with, “Did you know that due to COVID-19, many schools stopped or temporarily suspended routine vaccination programs?” Then, further lead the conversation, saying, “Let’s discuss your child’s vaccination status.” It is critical for NPs to know how to start the conversation around vaccination, as the approach can influence the willingness of patients or patients’ parents/guardians to agree to receive a vaccine for themselves or their children.

■ Discussion

A high incidence of HPV-attributed HNC cases can be seen in the US, Canada, and Western Europe.³³ However, no approved screening exists for early detection of HNC, and so the majority of individuals with HNC present with advanced cancer, equating

to report a recommendation for the HPV vaccine from their healthcare provider than males, despite the rapid increase in HPV-related HNC in the male population.²⁶ Health promotion campaigns, provider recommendations, and public policy can serve to create an environment in which misconceptions are sanctioned; oppositely, however, they can serve to promote and publicly disseminate relevant information on the effectiveness of HPV vaccination for both males and females in prevention of associated cancers.

■ Conclusion

Developed countries have been facing a rapid increase in the incidence of HPV-related HNC, particularly in the male population, which has caused increased suffering and a significant burden on the healthcare system. Prophylactic use of 9vHPV is the most effective approach for preventing HPV-associated HNC, as vaccination has been proven to prevent infection with HPV 16 and 18, the serotypes that are most commonly associated with HNC. The CDC and the Canadian government have previously acknowledged the effectiveness of HPV vaccination as a prevention strategy for HPV-associated HNC, with the CDC including HPV vaccination in its guidelines and recommendations for this purpose.


Despite this, as shown by many studies, the general public remains unaware of the link between HPV and HNC; even some healthcare providers, including NPs, are not aware.¹⁴ The vaccine’s success in reducing cervical cancer among cisgender, heterosexual women raises hope that, by adopting a similar strategy of vaccine promotion among males, a reduction in the surging HPV-related HNC incidence could be achieved.

Some therapeutic vaccines for cancer treatment are in phase I of clinical studies, but none have been shown to reverse HPV-associated cancers; prevention therefore remains critical.^{11,21} Although the feminization of HPV-associated cancers has had a significant impact on perception of HPV risk and the importance of vaccination in prevention for males, providing appropriate recommendations and education regarding the benefits of vaccination can reverse misconceptions. Through awareness-raising efforts and patient education, NPs can improve



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to increased patient suffering and burden on the healthcare system.^{2,8,16} Prior to introduction of the HPV vaccine in the US, treatment of HPV-related oropharyngeal cancer cost \$300 million annually.²² Gender-neutral vaccination programs are likely to be cost-effective; the CDC found that the incremental cost per quality-adjusted life year for expanding male vaccination through age 26 years was \$178,000.^{17,22,33} The feminization of the HPV vaccine upon its introduction created a gender bias.^{14,42} Many international epidemiologic studies have established that the lack of HPV vaccination coverage among men of all ages has resulted from the misconception that HPV is only a predominant risk factor for cervical cancer in cisgender, heterosexual women. A cross-sectional survey in the US found that females are more likely

vaccine uptake rates, which will in turn ultimately lead to decreased HNC incidence. 

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