National Collaborating Centre for Infectious Diseases

Centre de collaboration nationale des maladies infectieuses

Purple Paper

HPV Infections and Head and Neck Cancers

Paul Masotti, PhD, and Janice Linton, BA, MLS

1. Introduction

Human papillomavirus (HPV) is considered to be the most frequently diagnosed sexually transmitted disease in the world (1-11). According to the Centers for Disease Control and Prevention (CDC), HPV accounts for 71.6% of new sexually transmitted infections (STIs) representing 14.1 million of the 19.7 million new STIs each year in the United States (11.) The body's immune system usually limits the duration of each HPV infection to one to two years (4,5,7,9,11-15). However, infection may persist in as many as 5–10% of affected people. If the infections are caused by high-risk HPV types (e.g., HPV 16), the risk of developing precancerous lesions and cancer is increased two to 13 times, in a process that takes ten to 20 years or longer (4,7,16).

HPV is the aetiological cause of genital warts and respiratory papillomatosis (warty growths in the upper airway). It also causes head and neck and anogenital (cervical, vaginal, vulval, penile and anal) cancers (4,7,9,12,17-19). Head and neck cancers include cancers of the oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract and nasopharynx (20). Overall head and neck cancer rates have been steadily decreasing over the past decades as a result of reduced use of tobacco (12,21-28) These cancers typically occur later in life, from age 60 to age 80. However, oropharyngeal cancers, such as those at the base of the tongue and involving the tonsils are now increasing, especially among younger cohorts. Most are HPV positive (3,5,16,29,30) and the oncogenic HPV type 16 is found in over 90% of the HPV-associated cancers (18,31,32). HPV-positive cancers are frequently observed in people at earlier ages and without the traditional risk factors for head and neck cancers such as tobacco or alcohol use (5,19). These rates have been steadily increasing with the highest rates observed in males (3,5,10,12,18,23,25,27,28,30,32-38). If these trends continue, HPV-related oropharyngeal cancer could exceed cervical cancers within a decade (29).

Frequently reported risk factors for oral HPV infection include: the number of sex partners, the number of oral sex (oral-genital) partners, tobacco use, excessive alcohol, and poor oral hygiene. The CDC reports that 80% of sexually active people, aged 14–44 years, have had oral sex with a partner (9, see also 13,18) Although this may be one of the main risk factors, evidence also suggests that the number of open-mouth kissing partners is also a risk factor for oral HPV infection (12,13,37,38).

2. Epidemiology

Head and neck cancers represent more than 3% of all new cancers worldwide (18,19,22). One positive outcome from public-health programs has been that head and neck (laryngeal, hypopharyngeal, and oral cavity) cancer rates have been declining since the late 1980s (40). This is attributed primarily to a decreased used of tobacco (5,21,22,24,26-28). However, during this same time period, oropharyngeal cancer rates initially remained constant and then began to rise (22,41,42). This increase continues. For example, in a Toronto study of 6,085 head and neck cancer patients the proportion of all head and neck cancers classified as orophyaryngeal cancers increased from 23.3% to 31.2% between 2000 and 2010 (30).

HPV and Oropharyngeal Cancer Rates

It is now estimated that 70–90% of oropharyngeal cancers are caused by HPV (5,19,31,38,42). For example, Lin reported that 90% of oropharyngeal patients in one study were HPV-positive, and other studies have reported similar high rates (38,43). Two high-risk variants, HPV 16 and HPV 18, are likely associated with approximately 90–95% of all oropharyngeal cancers (6,7,12,19,28,31,32,35, 44,45). Higher prevalence of HPV 16 has been noted in studies of younger patients (under age 40) diagnosed with oropharyngeal cancer (46,47).

Worldwide reported rates vary but also show increases in the past two decades. For example, between 1982 and 2008, Australian incidence of oropharyngeal cancer increased from 2.83 to 3.97/100,000 among men and from 0.79 to 1.01/100,000 among women, representing average annual increases of 1.2% and 0.8%, respectively (28). A similar trend was observed in Spain for which increases of 2.39% in men and 1.52% in women occurred between 1991 and 2001 (22). Rates in Canada and the United States have demonstrated similar increases (3,26). In a Canadian study on cancer incidence and socioeconomic status, Hwang et al. reported that incidence was the highest in the lowest income group, but that the largest increase in incidence between 1992 and 2007 was among those in the highest-income quintile (26).

HPV-positive oropharyngeal tumours are most frequent at the base of the tongue and in the tonsillar region (5,7,9). Annual increases in incidence of 2.1% (tongue) and 3.9% (tonsils) have been observed (19) and rates in men are *three to four times higher* than in women (1,2,5,7,13,18,22,28,48). For example, studies in Europe have indicated head and neck cancer incidence rates of 16/100,000 in men versus 3.3/100,000 in women (22). These results parallel sex differences in oral HPV infection prevalence rates seen (e.g. 10.5% in men and 3.6% in women) that have been reported in large sample studies (13).

Oral HPV Infection

Prevalence and incidence of oral HPV infection vary by geographic location and sub-population. However, several large sample studies have reported results that are similar. Kreimer et al. conducted a systematic review of 18 studies from 11 countries (Spain, Canada, USA, Brazil, UK, Japan, Greece, South Africa, Tobago, Sardinia and Finland) that were completed between 1997 and 2009. The studies included both males and females (N=4,581 in all studies) and Kreimer reported an overall prevalence of 4.5% (16). In more recent studies, Gillison et al. reported an overall prevalence of 6.9% in a cross-sectional study of 5,579 men and women aged 14 to 69 (49). Rates in men were higher, at 10.1%, versus 3.6% in women. Of the 6.9% with HPV infections, 3.7% were positive for one of 18 high-risk HPV types. In another study, Pickard reported a prevalence of 2.4% among 1,000 male and female college students (8,13). In addition, Edelstein et al. found a 7.5% prevalence in male university students (50). In these studies, HPV 16 was the most common high-risk HPV variant. Gillison et al. and Kreimer et al. reported high-risk HPV prevalence rates of 1% and 1.3% in their respective studies (16,49).

HPV Variants and Disease

There are over 100 known types of HPV, and they are classified into two types: a) low risk and b) high-risk or oncogenic (cancer causing). Fifteen or more are classified as oncogenic (3,7,12,36,39).

As noted earlier, of the oncogenic HPVs, research indicates that HPV 16 accounts for about 90% of all HPV-positive oropharyngeal cancer; whereas HPV 16, 18 and 33 combined account for about 98% of HPV-positive oropharyngeal cancers (6,7,12,19,28,31,33,35, 44,45).

3. Natural History

The natural history of HPV from infection to oropharyngeal cancer is not well researched, and much of what is known comes from research on HPV-related cervical cancer. More needs to be known about the probability of infection under different conditions; incidence in different populations; duration of infections; and factors associated with persistent infections versus increased ability to clear the infections.

HPV viruses are double-stranded DNA viruses. They replicate in the squamous epithelia in areas such as the cervix, anus and tonsils (7,51). The HPV infections occur in the keratinocytes of the skin or in the mucous membranes. After infection, the viruses use the host cell's DNA replication mechanisms to produce viral genetic fragments at the supra-basal layer of the epithelium (7). It is these HPV oncoproteins, primarily E6 and E7, that are considered to cause cancer by suppressing or eliminating natural tumour suppressors in the body (e.g. p53 and pRb)(4,5,12,33,45). HPV-positive tumours are distinctly different from HPV-negative tumours (which are often caused by tobacco use) and demonstrate a different aetiology and clinical pathological characteristics (12,19,23,30,32,38). HPV-related oropharyngeal tumours typically present as T1/T2 tumours and with advanced disease in the neck (N2/N3). They are frequently mistaken for cysts (5).

Some evidence indicates that oral HPV infections likely clear within one to two years in most people (3-5,10,12-15). However, infections may persist in as many as 5–10% of patients. If the infections are caused by high-risk HPV 16 or 18, there is an increased risk of developing precancerous lesions in a process that takes 10 to 20 years or longer (5,7). Signs and symptoms of oropharyngeal cancer may include persistent sore throat, earaches, hoarseness, enlarged lymph nodes, pain when swallowing, and unexplained weight loss. However, some people may not have these signs or symptoms (9).

Risk Factors

In the literature on head and neck cancer, tobacco use and heavy alcohol consumption are almost always indicated as main or classical risk factors for oral cavity and oropharyngeal cancers (5,12,13,19, 22,31,33,48). However, oropharyngeal cancer rates have been rising among people without those classical risk factors, and some studies have not found significant associations between smoking and drinking alcohol and risk (5,19). For example, in an Australian study, 28.6% of the HPV-positive cases were "never smokers" (32) The risk associated with HPV is further illustrated by Anantharaman et al., who reported that HPV 16 seropositivity was associated with a significantly increased risk of oropharyngeal cancer (OR 8.6, 95% CI 5.21-14.2)(35). Similar results (e.g., OR 5.39, 95% CI 3.25-8.94) have been found in other studies (8).

Given this and other recent evidence, the most important risk factors for all HPV-positive oropharyngeal cancer appear to be oncogenic HPV infections (particularly HPV 16) and sexual activity, where earlier age of first sex and multiple partners were associated with increased risk (2,6,7,12,13,16, 20,22,27,28,31-33,35,44,45,48,52). Kreimer et al., for example, found that detection of prevalent HPV infection in oral exfoliated cells increased the odds of oropharyngeal cancer more than 13-fold. And in the study by Gillison et al. of 5,579 adult males and females, the prevalence of HPV infection was higher among males, at 10.1%, than among females, at 3.6%. Among males and females with 20 or more sex partners, vaginal and oral infection rates, at 20%, were almost three times higher than the overall rate of 6.9% (16,49).

Additional evidence suggests that open-mouthed kissing may also be a risk factor (8,9,13,20,27,52). For example, a recent study of university students by Pickard et al. found that open-mouth kissing (i.e., five or more kissing partners and no other sexual

activities) was associated with a much higher risk of oral cancer than alcohol use (8).

4. Screening, Treatment, Outcomes, Vaccine

Screening

Detection of HPV is usually done using one or more of the following methods: a) HPV DNA testing, b) HPV RNA testing to look for E6 or E7 oncoprotein expression, c) immunohistochemistry to detect p16 expression (p16 protein functions as a tumour suppressor and is over-expressed in HPV cancers), or d) a real-time polymerase chain reaction (PCR) to measure HPV viral load (4,5,12,20,35,38). Routine screening for HPV has been recommended for oropharyngeal cancers as an important component of staging and to identify the best course of treatment (53-56).

However, screening is generally not routinely conducted in dental or primary care offices because of a lack of standardized government-approved tests (9).

Oropharyngeal Cancer Treatment and Outcomes

Typical treatment is combined radiation therapy and chemotherapy and may include surgery (7,20). Patients diagnosed with HPV-positive oropharyngeal cancers have a better prognosis and treatment outcomes compared to HPV-negative cancers attributed to tobacco or alcohol use (3,21,22,30,32, 34,36,38). For example, in a Johns Hopkins study, three-year survival rates for HPV-positive patients were 93% and at five years were 89%. Those free of cancer at five years had an 8.6% chance of recurrence at 10 years. This is better than HPV-negative cases, with 50% recurrence rates, most of which occur two to four years after therapy (38). Other studies have reported three-year survival rates of 87% in HPV-positive oropharyngeal cancer, cases compared to 57% in HPV-negative patients (5). However, there is some evidence that survival rates among HPV-positive cases are still negatively affected by smoking (38,44).

The recognition that HPV-positive tumours are aetiologically distinct and have a better prognosis than HPV-negative tumours has led to the suggestion that treatment for each type could differ. Bose et al. suggest that treatment for HPV-positive patients could be reduced in intensity, as do Gildener-Leapman et al. Additionally, HPV-positive patients may be candidates for immunotherapies such as those directed towards E6 and E7 oncoproteins (21,39,57). These approaches represent a shift from the standard anatomically specific approaches such as surgery and radiotherapy (21).

Vaccines

Two HPV vaccines, Cervarix and Gardasil, are known to prevent the same HPV variants that are associated with oropharyngeal cancers (HPV 16 and HPV 18). Until recently, HPV vaccination programs in most countries focused on girls and women and the prevention of cervical cancer. However, increasingly it is being suggested that there is the need for more comprehensive vaccination programs that include both males and females (1,3,7,9,16,27,29,30,48,58-60). This is based on the recognition that both sexes share the burden associated with HPV and that the vaccines will likely prevent other HPV-related diseases. For example, the CDC in the United States has suggested that the available HPV vaccines may prevent oropharyngeal cancer (9). In support of the CDC's position, it has been estimated that 33% to 72% of oropharyngeal cancers could be prevented through the elimination of HPV with an effective vaccination program (2).

The quadrivalent HPV vaccine (Gardasil) provides protection against HPV types 6, 11, 16 and 18, whereas the bivalent HPV vaccine (Cervarix) protects against the high-risk oncogenic types 16 and 18 (6,59,61). The CDC recommends the HPV vaccine for 11- to 12-year-old girls, and the quadrivalent vaccine, Gardasil, for 11- to 12-year-old boys. The vaccines can be given starting at nine years of age. Other examples of medical organizations that have recommended the need for

vaccination programs to include both males and females are: Canada's National Advisory Committee on Immunization; the European Medicines Agency; CDC (US); American Academy of Pediatrics (AAP); and advisory bodies in Australia (7,11,62).

It has been argued that previous economic evaluations underestimated the future prevalence of HPV, and thus the benefits of comprehensive vaccination programs (29). Crosignani et al. (2013) reviewed studies on the natural history of HPV infection in women and men including analyses of clinical effectiveness and economic efficacy of HPV vaccination. They concluded that the evidence supports HPV vaccination programs for both males and females. When non-cervical diseases, such as oropharyngeal cancer, were considered in the analysis, the cost per quality-adjusted life year (QALY) decreased significantly (7). This conclusion was supported by Elbasha et al., who found that vaccination programs that included boys would be beneficial in reducing head and neck cancers in men, and would also be cost-effective (59). This study and others have shown that cost-effectiveness of vaccines in males increases *substantially* if vaccine uptake in females is low (63,64). Lower awareness and less promotion of vaccination for males have resulted in low uptake in that population to date. Stupiansky noted that there is general acceptability of HPV vaccination among men, parents of boys, and health care providers (1).

5. Discussion – Implications for Public Health

Head and neck cancers represent more than 3% of all cancers worldwide (18,19,23). Although the overall rates of head and neck cancer have been declining, significant increases in HPV-related oropharyngeal cancer have occurred in the past two decades, with clear evidence that rates are three to four times higher in males. These cancers are the result of oral HPV infections that are likely sexually transmitted. There is evidence of a globally emerging HPV-related oropharyngeal epidemic that will likely worsen in the coming decade (54,65).

Public health leaders and policy makers must acknowledge this growing problem. There is a need for increased public-health messaging about HPV transmission and prevention and screening for oropharyngeal cancer, especially in younger men who are unaware of the risks and opportunities for prevention (28). Enhanced screening would contribute to the evaluation of vaccine effectiveness for the prevention of oropharyngeal cancers (66), and furthermore the CDC has indicated the vaccines would likely prevent oropharyngeal cancer (9).

Policy makers and health care providers should therefore promote more comprehensive vaccination programs that include both males and females to provide an enhanced, more equitable cancer prevention program for sexually transmitted diseases and related cancers (67-70).

Additionally, the opportunities for public health to have an impact in this area include the following activities: a) development of a standardized screening test for oral HPV infection, b) routine screening for oral HPV infections in primary care and dental offices (3,7,36,37) c) development of a self-administered screening test (36), d) increased public health surveillance of oral HPV infections, and e) evaluations of vaccination programs for older people. Implications for both treatment and research are based upon the different aetiologies of HPV-positive and HPV-negative oropharyngeal cancers, and the evidence of better treatment outcomes achievable for HPV-positive patients (23,28,71-74). The research suggests HPV-positive patients could be treated differently from HPV-negative patients, and that these groups should be managed separately for future clinical studies (22,35,75).

Oropharyngeal cancer incidence has been on the rise, and there are sufficient indications that this trend will continue. In the field of public health, HPV vaccines are beginning to reduce the prevalence of

sexually transmitted HPV infections. There are ten to 20 years between the time of HPV infection and the development of oropharyngeal cancer. There are therefore many opportunities to effectively prevent, detect and treat a disease whose true impact on adults during their most productive years has not yet been fully realized.

References

1. Stupiansky NW, Alexander AB, Zimet GD. Human papillomavirus vaccine and men: What are the obstacles and challenges? *Curr Opin Infect Dis*. 2012;25(1):86-91.

2. Colón-López V, Ortiz AP, Palefsky J. Burden of human papillomavirus infection and related comorbidities in men: Implications for research, disease prevention and health promotion among Hispanic men. *P R Health Sci J*. 2010;29(3):232-240.

3. Azvolinsky A. Concerned about HPV-related cancer rise, researchers advocate boosting HPV vaccination rates. *J Natl Cancer Inst*. 2013;105(18):1335-1336.

4. Palefsky J, Cranston R. Virology of human papillomavirus infections and the link to cancer. In: Dezube B, ed. *UpToDate.* Waltham, MA: UpToDate; 2013. Accessed December 7, 2013.

5. Haddad R. Human papillomavirus-associated head and neck cancer. In: Brockstein B, ed. *UpToDate.* Waltham, MA: UpToDate; 2013. Accessed December 7, 2013.

6. Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. *Lancet Infectious Diseases*. 2006;6(1):21-31.

7. Crosignani P, De Stefani A, Fara GM, et al. Towards the eradication of HPV infection through universal specific vaccination. *BMC Public Health*. 2013;13(1).

8. Pickard RK, Xiao W, Broutian TR, He X, Gillison ML. The prevalence and incidence of oral human papillomavirus infection among young men and women, aged 18-30 years. *Sex Transm Dis*. 2012;39(7):559-566.

9. Centers for Disease Control and Prevention. Human papillomavirus (HPV) and oropharyngeal cancer – CDC. http://www.cdc.gov/std/HPV/STDFact-HPVandOralCancer.htm. Updated 2013. Accessed December 28, 2013.

10. Schlecht NF, Rojas M, Lorde-Rollins E, et al. Burden of cervical, anal, and oral HPV in an inner-city pre-vaccine adolescent population. *Journal of Urban Health*. 2013;90(1):141-146.

11. Centers for Disease Control and Prevention. Incidence, prevalence, and cost of sexually transmitted infections in the United States. http://www.cdc.gov/std/stats/STI-Estimates-Fact-Sheet-Feb-2013.pdf. Updated 2013. Accessed December 28, 2013.

12. Chung CH, Bagheri A, D'Souza G. Epidemiology of oral human papillomavirus infection. *Oral Oncol*. 2013.

13. Gillison ML, Castellsagué X, Chaturvedi A, et al. Eurogin roadmap: Comparative epidemiology of HPV infection and associated cancers of the head and neck and cervix. *International Journal of Cancer*. 2013;134(3):497-507.

14. Kreimer AR, Chaturvedi AK. HPV-associated oropharyngeal cancers – are they preventable? *Cancer Prevention Research*. 2011;4(9):1346-1349.

15. Kreimer AR, Pierce Campbell CM, Lin HY, et al. Incidence and clearance of oral human papillomavirus infection in men: The HIM cohort study. *The Lancet*. 2013;382(9895):877-887.

16. Kreimer AR, Bhatia RK, Messeguer AL, González P, Herrero R, Giuliano AR. Oral human papillomavirus in healthy individuals: A systematic review of the literature. *Sex Transm Dis*. 2010;37(6):386-391.

17. Centers for Disease Control and Prevention. HPV vaccine information for clinicians – fact sheet. http://www.cdc.gov/sTd/hpv/STDFact-HPV-vaccine-hcp.htm. Updated 2013. Accessed December 28, 2013.

18. Mannarini L, Kratochvil V, Calabrese L, et al. Human papilloma virus (HPV) in head and neck region: Review of literature. *Acta Otorhinolaryngologica Italica*. 2009;29(3):119-126.

19. Mayeaux EJ, Khan MJ. Nongenital human papillomavirus disease. *Obstet Gynecol Clin North Am*. 2013;40(2):317-337.

20. Ramqvist T, Dalianis T. Oropharyngeal cancer epidemic and human papillomavirus. *Emerging Infectious Diseases*. 2010;16(11):1671-1677.

21. Bose P, Brockton NT, Dort JC. Head and neck cancer: From anatomy to biology. *International Journal of Cancer*. 2013;133(9):2013-2023.

22. De Souza DLB, De Camargo Cancela M, Pérez MMB, Curado M-P. Trends in the incidence of oral cavity and oropharyngeal cancers in Spain. *Head and Neck*. 2012;34(5):649-654.

23. De Souza DLB, Curado MP, Bernal MM, Jerez-Roig J, Boffetta P. Mortality trends and prediction of HPV-related cancers in Brazil. *European Journal of Cancer Prevention*. 2013;22(4):380-387.

24. Cerezo L, de la Torre A, Hervás A, et al. Oropharyngeal cancer related to human papilloma virus: Incidence and prognosis in Madrid, Spain. *Clinical and Translational Oncology*. 2013:1-6.

25. Jégu J, Binder-Foucard F, Borel C, Velten M. Trends over three decades of the risk of second primary cancer among patients with head and neck cancer. *Oral Oncol*. 2013;49(1):9-14.

26. Hwang E, Johnson-Obaseki S, McDonald JT, Connell C, Corsten M. Incidence of head and neck cancer and socioeconomic status in Canada from 1992 to 2007. *Oral Oncol*. 2013;49(11):1072-1076.

27. Brisson M, Drolet M, Malagón T. Inequalities in human papillomavirus (HPV)-associated cancers: Implications for the success of HPV vaccination. *J Natl Cancer Inst*. 2013;105(3):158-161.

28. Ariyawardana A, Johnson NW. Trends of lip, oral cavity and oropharyngeal cancers in Australia 1982-2008: Overall good news but with rising rates in the oropharynx. *BMC Cancer*. 2013;13.

29. Schache AG, Simcock R, Gilbert DC, Shaw RJ. Changing face of HPV- related cancer in the UK. *BMJ (Online)*. 2011;343(7828).

30. Habbous S, Chu KP, Qiu X, et al. The changing incidence of human papillomavirus-associated oropharyngeal cancer using multiple imputation from 2000 to 2010 at a comprehensive cancer centre. *Cancer Epidemiology*. 2013;37(6):820-829.

31. Dietz A, Wichmann G. Head and neck cancer: Effective prevention in youth and predictive diagnostics for personalised treatment strategies according to biological differences. *EPMA Journal*. 2011;2(2):241-249.

32. Hong AM, Martin A, Chatfield M, et al. Human papillomavirus, smoking status and outcomes in tonsillar squamous cell carcinoma. *International Journal of Cancer*. 2013;132(12):2748-2754.

33. Bahl A, Kumar P, Dar L, et al. Prevalence and trends of human papillomavirus in oropharyngeal cancer in a predominantly North Indian population. *Head and Neck*. 2013.

34. Baxi SS, Shuman AG, Corner GW, et al. Sharing a diagnosis of HPV-related head and neck cancer: The emotions, the confusion, and what patients want to know. *Head and Neck*. 2013;35(11):1534-1541.

35. Anantharaman D, Gheit T, Waterboer T, et al. Human papillomavirus infections and upper aero-digestive tract cancers: The ARCAGE study. *J Natl Cancer Inst*. 2013;105(8):536-545.

36. Cubie HA, Cuschieri K. Understanding HPV tests and their appropriate applications. *Cytopathology*. 2013;24(5):289-308.

37. Gupta B, Ariyawardana A, Johnson NW. Oral cancer in India continues in epidemic proportions: Evidence base and policy initiatives. *Int Dent J*. 2013;63(1):12-25.

38. Lin BM, Wang H, D'Souza G, et al. Long-term prognosis and risk factors among patients with HPV-associated oropharyngeal squamous cell carcinoma. *Cancer*. 2013;119(19):3462-3471.

39. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: A virus-related cancer epidemic. *The Lancet Oncology*. 2010;11(8):781-789.

40. Sturgis EM, Ang KK. The epidemic of HVP-associated oropharyngeal cancer is here: Is it time to change our treatment paradigms? *JNCCN Journal of the National Comprehensive Cancer Network*. 2011;9(6):665-673.

41. Sturgis EM, Dahlstrom KR. HPV vaccination. inaccurate assumptions about oropharyngeal cancer. *BMJ*. 2009;339.

42. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *Journal of Clinical Oncology*. 2011;29(32):4294-4301.

43. González-Ramírez I, Irigoyen-Camacho ME, Ramírez-Amador V, et al. Association between age and high-risk human papilloma virus in Mexican oral cancer patients. *Oral Dis*. 2013;19(8):796-804.

44. Maxwell JH, Kumar B, Feng FY, et al. Tobacco use in human papillomavirus-positive advanced oropharynx cancer patients related to increased risk of distant metastases and tumor recurrence. *Clinical Cancer Research*. 2010;16(4):1226-1235.

45. Mork J, Lie AK, Glattre E, et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2001;344(15):1125-1131.

46. Van Monsjou HS, Van Velthuysen MLF, Van Den Brekel MWM, Jordanova ES, Melief CJM, Balm AJM. Human papillomavirus status in young patients with head and neck squamous cell carcinoma. *International Journal of Cancer*. 2012;130(8):1806-1812.

47. Kaminagakura E, Villa LL, Andreoli MA, et al. High-risk human papillomavirus in oral squamous cell carcinoma of young patients. *International Journal of Cancer*. 2012;130(8):1726-1732.

48. Wu X, Watson M, Wilson R, Saraiya M, Cleveland JL, Markowitz L. Human papillomavirus-associated cancers – United States, 2004-2008. *Morb Mortal Weekly Rep*. 2012;61(15):258-261.

49. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009-2010. *JAMA: the journal of the American Medical Association*. 2012;307(7):693-703.

50. Edelstein ZR, Schwartz SM, Hawes S, et al. Rates and determinants of oral human papillomavirus infection in young men. *Sex Transm Dis*. 2012;39(11):860-867.

51. Johannsen E, Lambert PF. Epigenetics of human papillomaviruses. *Virology*. 2013;445(1-2):205-212.

52. D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *J Infect Dis*. 2009;199(9):1263-1269.

53. Mirghani H, Amen F, Moreau F, et al. Human papilloma virus testing in oropharyngeal squamous cell carcinoma: What the clinician should know. *Oral Oncol*. 2014;50(1):1-9.

54. Panwar A, Batra R, Lydiatt WM, Ganti AK. Human papilloma virus-positive oropharyngeal squamous cell carcinoma: A growing epidemic. *Cancer Treat Rev*. 2014;40(2):215-219.

55. Klozar J, Tachezy R, Rotnáglová E, Košlabová E, Saláková M, Hamšíková E. Human papillomavirus in head and neck tumors: Epidemiological, molecular and clinical aspects. *Wiener Medizinische Wochenschrift*. 2010;160(11-12):305-309.

56. Olthof NC, Straetmans JMJAA, Snoeck R, Ramaekers FCS, Kremer B, Speel E-M. Next-generation treatment strategies for human papillomavirus-related head and neck squamous cell carcinoma: Where do we go? *Rev Med Virol*. 2012;22(2):88-105.

57. Gildener-Leapman N, Ferris RL, Bauman JE. Promising systemic immunotherapies in head and neck squamous cell carcinoma. *Oral Oncol*. 2013;49(12):1089-1096.

58. Partridge JM, Hughes JP, Feng Q, et al. Genital human papillomavirus infection in men: Incidence and risk factors in a cohort of university students. *J Infect Dis*. 2007;196(8):1128-1136.

59. Elbasha EH, Dasbach EJ. Impact of vaccinating boys and men against HPV in the united states. *Vaccine*. 2010;28(42):6858-6867.

60. Shearer BD. *HPV vaccination: Understanding the impact of HPV disease.* Winnipeg, Man.: National Collaborating Centre for Infectious Diseases; 2011. http://www.nccid.ca/files/Purple_Paper_Note_mauve/PP_34_EN.pdf;. Accessed December 10 2013.

61. Centers for Disease Control and Prevention. 2011 sexually transmitted diseases surveillance. http://www.cdc.gov/sTd/stats11/other.htm#hpv. Updated 2013. Accessed December 28, 2013.

62. Public Health Agency of Canada. National Advisory Committee on Immunization (NACI): Update on human papillomavirus (HPV) vaccines. *Canada Communicable Disease Report*. 2012;37 (ACS-7).

63. D'Souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. *Prev Med*. 2011;53(SUPPL. 1):S5-S11.

64. Brisson M, Van de Velde N, Boily M. Economic evaluation of human papillomavirus vaccination in developed countries. *Public Health Genomics*. 2009;12(5-6):343-351.

65. Nichols AC, Palma DA, Dhaliwal SS, et al. The epidemic of human papillomavirus and oropharyngeal cancer in a Canadian population. *Current Oncology*. 2013;20(4):212-219.

66. Grulich AE, Jin F, Conway EL, Stein AN, Hocking J. Cancers attributable to human papillomavirus infection. *Sexual Health*. 2010;7(3):244-252.

67. Osazuwa-Peters N. Human papillomavirus (HPV), HPV-associated oropharyngeal cancer, and HPV vaccine in the United States – do we need a broader vaccine policy? *Vaccine*. 2013;31(47):5500-5505.

68. Lenzi A, Mirone V, Gentile V, et al. Rome consensus conference – statement; human papilloma virus diseases in males. *BMC Public Health*. 2013;13(1).

69. Marty R, Roze S, Bresse X, Largeron N, Smith-Palmer J. Estimating the clinical benefits of vaccinating boys and girls against HPV-related diseases in Europe. *BMC Cancer*. 2013;13.

70. Jemal A, Simard EP, Dorell C, et al. Annual report to the nation on the status of cancer, 1975-2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. *J Natl Cancer Inst*. 2013;105(3):175-201.

71. O'Rorke MA, Ellison MV, Murray LJ, Moran M, James J, Anderson LA. Human papillomavirus related head and neck cancer survival: A systematic review and meta-analysis. *Oral Oncol*. 2012;48(12):1191-1201.

72. Rainsbury JW, Ahmed W, Williams HK, Roberts S, Paleri V, Mehanna H. Prognostic biomarkers of survival in oropharyngeal squamous cell carcinoma: Systematic review and meta-analysis. *Head and Neck*. 2013;35(7):1048-1055.

73. Bosch FX, Broker TR, Forman D, et al. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine*. 2013;31(SUPPL.8):11-131.

74. Ankola AA, Smith RV, Burk RD, Prystowsky MB, Sarta C, Schlecht NF. Comorbidity, human papillomavirus infection and head and neck cancer survival in an ethnically diverse population. *Oral Oncol*. 2013;49(9):911-917.

75. Quon H, Cohen MA, Montone KT, et al. Transoral robotic surgery and adjuvant therapy for oropharyngeal carcinomas and the influence of p16INK4a on treatment outcomes. *Laryngoscope*. 2013;123(3):635-640.

Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada through funding for the National Collaborating Centre for Infectious Diseases (NCCID). The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.

NCCID Project No. 167