PEAK

HPV 101: What Dentists Should Know

Dr. Vivien Brown, MDCM, CCFP, FCFP, NCMP
Dr. Pamela Liao, BScHons, MD, CCFP Candidate

Royal College of
Dental Surgeons of Ontario
Ensuring Continued Trust

This PEAK article is a special membership service from RCDSO.
The goal of PEAK (Practice Enhancement and Knowledge) is to provide Ontario dentists with key articles on a wide-range of clinical and non-clinical topics from dental literature around the world.

PLEASE KEEP FOR FUTURE REFERENCE.

Supplement to August/September 2014 issue of Dispatch magazine

HPV 101: What Dentists Should Know

Dr. Vivien Brown, MDCM, CCFP, FCFP, NCMP
Assistant Professor
University of Toronto
Department of Family and Community Medicine

Dr. Pamela Liao, BScHons, MD, CCFP Candidate
University of Toronto
Department of Family and Community Medicine

Abstract

The Human Papillomavirus (HPV) is the most common sexually transmitted infection in Canada. It has been linked as the major causative agent for a variety of cancers affecting the oropharynx, cervix, and anogenital areas. Indeed, HPV-related oropharyngeal cancers are increasing at staggering rates in new risk demographics. One of the major medical breakthroughs this generation will face is the development, and approval, of two vaccines effective at preventing the initial infection. While the technology is at the forefront, patient uptake and adherence lags behind in many demographics. Oral health care providers are experts in counselling patients for preventive health care and can be major stakeholders in education about HPV vaccine.

The New Face of HPV and Oropharyngeal Cancer in Canada

Oral cavity and oropharyngeal cancers (OPC) are among the most common malignancies globally. Head and neck squamous cell carcinoma (HNSCC), the sixth most common malignancy globally, includes the oral cavity, nasopharynx, oropharynx, larynx, and hypopharynx [1]. As such it is an area of concern for both medical and dental care providers.

HPV, the most common sexually transmitted infection in Canada, is the causative agent in approximately 80% of OPC. Notably this profile is different from oral cavity cancers (6% HPV) and other non-HPV associated head and neck cancers (not attributable)[2,3]. The HPV-16 DNA strain has been found in approximately 75% of HPV-cytopositive oral squamous cell carcinoma (SCC) and 90% of HPV-cytopositive oropharyngeal SCC [4]. Those with a history of oral HPV-16 infection have a 15 to 200-fold increase in risk of developing oropharyngeal cancer[5].

While oral cavity cancers have been declining in developed countries with smoking-cessation programs, oropharyngeal cancers (OPC) associated with human papillomavirus have been on the rise dramatically [6]. Consistent with Canadian trends, between 1997-2000, new OPC cases among Ontario men have risen from 3.6 to 5.2 per 100,000 [7].

Historically, public awareness has focused on the relationship between HPV and cervical cancer making it the focus of women's health professionals, but the demographics of who is affected by HPV, and why, is drastically changing. In fact, in the United States it is estimated that HPV-related oropharyngeal cancers will exceed the number of uterine and cervical cancers in the next 15 years [8].

Pathophysiology of HPV Infection and Oncogenic Risk Factors

Human papillomavirus (HPV) is a double-stranded DNA virus that infects the epithelial cells of skin and mucosa. While HPV subtypes 6 and 11 are associated with benign genital warts, subtypes 16 and 18 are oncogenic strains. It is important to note that HPV lesions in the head and neck can be either benign or malignant. Squamous papilloma are caused by HPV subtypes 2, 6, 11, and 57[9]. Similar to their presentation in the anogenital area, these lesions are benign. In the head and neck, they most commonly occur in the hard and soft palate. Importantly, these lesions are not transmissible and recurrence is unlikely, except in HIV positive patients. It is important to educate ourselves, and our patients, about the distinction between benign lesions and the oncogenic ones. The latter are strongly associated with cervical, anal, and oropharyngeal cancers, although further evidence is required. Within the oropharynx, OPCs develop particularly at the palantine and lingual tonsils and base of the tongue[1,2].

While the relationship between HPV and cervical cancer is well established, less is known about risk factors associated with oral HPV infection. Research suggests that the majority of oral HPV

infections clear themselves within a year; however, the natural history of oral HPV lesions is less well understood[10]. Similar to the mechanisms of persistence of infections in cervical HPV, oral HPV infections are aggravated by a history of smoking and HIV infection, likely because of their immunosuppressive effects[11]. Age is another risk factor, which is an unusual pattern compared to other sexually transmitted infections, and some suggest that this may again be related to immunosuppression that happens as part of the aging process (immunosenescence)[11]. While sexual contact is considered to be the main method of HPV transmission, evidence suggests that other forms may include oral contact (i.e. open mouth kissing), autoinoculation, and through the birth canal (vertical transmission)[4,11].

Importantly, history-taking must be tailored to screen for relevant risk factors. While traditional risk factors for oropharyngeal cancers include smoking, alcohol consumption and poor oral health, HPV positive oropharyngeal cancers have a distinct risk factor profile, which is critical for both effective screening but also for prognosis and management[12]. This includes higher number of oral and vaginal sex partners, previous history of genital warts, and early age of sexual debut[13]. Further, in Canada, the average age at diagnosis for OPCs has dropped 3.5 years among both sexes, indicating to care providers the need to be vigilant in screening a broader range of patients[2].

Clinical Screening and Diagnosis – The Oral Pap Test and Future Directions

Currently, visual and tactile examination is the gold standard for surveillance of OPSCC[14]. Kerr and Shah[15] provide an excellent clinical approach to the head, neck, and oral cavity exam, summarized in Table 1.

Currently, investigations are underway for screening tests at the cellular level, much akin to the cervical Pap test, but have yet to demonstrate a reliable means of early detection[17]. While commercial products are available for screening for oral HPV infection, it

Table 1. Approach to Screening Exam for Oropharyngeal HPV Lesions

	KEY POINTS
History	-History of cancer, immunocompromised -HPV exposure/immunization/urogenital disease -Smoking, alcohol, dietary habits -Symptoms – change in swallowing, associated pain, new oral/neck lumps or lesions, changes in speech
Extra-oral Exam	-Inspection and palpation of head, neck, thyroid for asymmetry, colour or skin changes, lymph nodes (enlarged, firm, immobile)
Intra-oral Exam	-Inspection and palpation (where appropriate) of lips, tongue, labial/buccal musocsa, oropharyngeal and retromolar trigone, posterior pharyngeal wall, hard/soft palate
Adjunctive Techniques	*Tissue Auto-fluorescence* (VELscope and Identafi 3000 systems) – emit blue-violet light (400-450nm range) that reveal disruptions in the autoflorescent epithelial tissue layers Toludine Blue Staining – preferentially stains dysplastic and rapidly dividing cells (increased DNA material). Can also be used to monitor SCC post-treatment Both are heavily dependent on clinician experience and have insufficient evidence for routine clinical use at this time[16].

remains unclear what their clinical utility truly is. One of the major limitations is that the majority of OPCs develop in areas that are difficult to assess clinically, such as the tonsillar crypts. Further, the transition from HPV infection to oncogenic disease is dependent on the integration of HPV DNA into the host genome, which is not detected by current tests[18]. Provided the limited data to support its efficacy for screening, clinicians must exercise caution in over-investigating patients with these poorly-validated tests.

There are a number of challenges in developing tests for detecting HPV infection, as well as pre-cancerous and cancerous lesions in the oropharynx. This is particularly true because HPV cannot be cultured in-vitro. While a number of diagnostic tests are under study, including an RNAscope used to directly visualize HPV viral transcripts on tissue samples[19], to date, no specific adjunctive modality has been recommended for screening[16].

Management and Treatment Outcomes

Traditional treatment of oropharyngeal squamous cell carcinomas has included high doses of radiation and chemotherapy, fraught with toxicities for patients. Importantly, the viral basis of HPV-related OPC may result in a dramatic shift in the approach to treatment, with new adjuvant therapies and current investigations underway[19]. For example, one group has shown that topical use of the anti-viral medication cidofovir reduces and clears gingival HPV lesions; however, more extensive research is required[20].

There is some evidence to suggest improved outcomes for those with HPV vs. non-HPV OPC and current investigations are underway to explore the possibility of less aggressive therapy based on OPC subtype[2]. The protein p16, is a surrogate tumor marker over-expressed in over 90% of HPV-HNCSCC[14].

Indeed, HPV status is considered to be the most clinically important indicator of tumor-aggressiveness and overall patient survival[14]. Survival rates for OPC are dramatically different between those with HPV and non-HPV status: 5-year survival is 85% among HPV vs. 45% of non-HPV tumors[5].

HPV Vaccine in Canada

In Canada, there are two approved vaccines for HPV. Gardasil® is a quadrivalent vaccine (HPV-4) effective against HPV 6, 11, 16, 18. Cevarix® is a bivalent (HPV-2) effective against HPV 16 and 18. Both of these vaccines are delivered by intramuscular injection over a three-dose course (Gardasil 0, 2, 6 months and Cevarix 0, 1, 6 months).

In Ontario, Gardasil (HPV-4) is offered through a provincial program to girls in grade 8 (age 13-14). Importantly, while vaccine is approved for use in boys by Health Canada, and recommended by Canada's National Advisory Committee on Immunization (NACI), patients must pay for the vaccine (approx. $300CAD)[21]. In other provinces, the provincial health program pays for the vaccine in both boys and girls.

While their efficacy has been demonstrated for prevention, and not treatment, of cervical and anogenital cancers, HNSCC typically present later in life in 50s and 60s and thus longitudinal data will be required; however, given the overwhelming efficacy in other cancers triggered by a similar etiology, it is reasonable to conclude there can be benefit for patients who are immunized[11].

Although HPV immunization has not yet been shown to prevent HPV infection, and thus malignancy, in the oral cavity, there is good evidence for immunization even in those patients with confirmed HPV-related malignancy. Patients treated for oncogenic cervical HPV lesions have had fewer recurrence after immunization[22]. To date, little is known about the corollary in HPV-related OPC, but this is certainly of great interest.

Table 2. Comparison of HPV Vaccines Available in Canada

	Gardasil (HPV-4)	Cervarix (HPV-2)
HPV Strains Targeted	6, 11, 16, 18	6, 18
Approval in Females	9-26 years (Grade A) 14-26 years – previous abnormal Paps (Grade B) >26 years (Grade A)	>26 years (Grade B)
Approval in Males	Ages 9-26 for anal intraepithelial neoplasia (AIN) grades 1, 2, and 3, anal cancer, and anogenital warts (Grade A) -penile, perianal, perineal intraepithelial neoplasias (Grade B)	Not studied or approved in males
Dose Schedule	0, 2, 6 months	0, 1, 6 months

The NACI is Canada's governmental authority on immunization guidelines and for the most current information we recommend review of their Canada Immunization Guide[23]. A summary of their recommendations for HPV vaccine can be found in Table 2.

Oral and Anogenital Co-Infection

Few studies have directly investigated the relationship between cervical cancer risk in patients with OPC, but one group found that there was a 25-fold increased risk of cervical cancer in those with a history of oropharyngeal squamous cell carcinoma[14], indicating the importance of cross-referral, comprehensive screening, and the value of prevention through immunization.

Oral Health Experts as Advocates for HPV Prevention

A focus group-based study of Oral Health Care Providers (OHCP), including dentists and dental hygienists, demonstrates that while OHCP are generally aware of the relationship between HPV and its oncogenic properties, they feel they require additional knowledge to feel comfortable counselling patients and specific information about screening procedures, their role and expectations[14]. Further, it was identified that OHCP do have experience discussing sensitive topics with patients, such as domestic violence and eating disorders.

Importantly, this phenomenology shows an important area of overlap for primary medical and oral heath care providers. High-risk individuals should be referred for immunization and screening with a medical doctor, and physicians should educate and refer patients at risk for oral health screening. Through combined efforts, health care practitioners can play a major role in prevention and reduction of the burden of oral HPV disease.

In Canada, health care delivery is a team sport. The HPV story shows one way in which an interdisciplinary team is crucial and necessary to not only reducing disease burden, but eliminating it altogether.

References

1. Zandberg DP, Bhargava R, Badin S, Cullen KJ. The role of human papillomavirus in nongenital cancers. CA Cancer J Clin 2013 Jan;63(1):57-81.
2. Johnson-Obaseki S, McDonald JT, Corsten M, Rourke R. Head and neck cancer in Canada: trends 1992 to 2007. Otolaryngol Head Neck Surg 2012 Jul;147(1):74-78.
3. Lingen MW, Xiao W, Schmitt A, Jiang B, Pickard R, Kreinbrink P, et al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol 2013 Jan;49(1):1-8.
4. Feller L, Wood NH, Khammissa RA, Lemmer J. Human papillomavirus-mediated carcinogenesis and HPV-associated oral and oropharyngeal squamous cell carcinoma. Part 2: Human papillomavirus associated oral and oropharyngeal squamous cell carcinoma. Head Face Med 2010 Jul 15;6:15-160X-6-15.
5. Upile T, Jerjes W, Al-Khawalde M, Radhi H, Sudhoff H. Oral sex, cancer and death: sexually transmitted cancers. Head Neck Oncol 2012 Jun 6;4:31.
6. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol 2013 Dec 20;31(36):4550-4559.
7. Cancer Care Ontario. HPV-related oral cancers increasing among Ontario men. 2013; Available at: https://www.cancercare.on.ca/cms/one.aspx?portalId=1377&pageId=101270. Accessed Apr/30, 2014.
8. Mirghani H, Amen F, Moreau F, Guigay J, Ferchiou M, Melkane AE, et al. Human papilloma virus testing in oropharyngeal squamous cell carcinoma: what the clinician should know. Oral Oncol 2014 Jan;50(1):1-9.
9. Jaju PP, Suvarna PV, Desai RS. Squamous papilloma: case report and review of literature. Int J Oral Sci 2010 Dec;2(4):222-225.
10. Kreimer AR, Bhatia RK, Messeguer AL, Gonzalez P, Herrero R, Giuliano AR. Oral human papillomavirus in healthy individuals: a systematic review of the literature. Sex Transm Dis 2010 Jun;37(6):386-391.
11. D'Souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. Prev Med 2011 Oct;53 Suppl 1:S5-S11.
12. Chaturvedi AK. Epidemiology and clinical aspects of HPV in head and neck cancers. Head Neck Pathol 2012 Jul;6 Suppl 1:S16-24.
13. Daley E, Dodd V, Debate R, Vamos C, Wheldon C, Kline N, et al. Prevention of HPV-related oral cancer: assessing dentists' readiness. Public Health 2014 Mar;128(3):231-238.
14. Daley E, DeBate R, Dodd V, Dyer K, Fuhrmann H, Helmy H, et al. Exploring awareness, attitudes, and perceived role among oral health providers regarding HPV-related oral cancers. J Public Health Dent 2011 Spring;71(2):136-142.
15. Kerr AR, Shah SS. Standard examination and adjunctive techniques for detection of oral premalignant and malignant lesions. J Calif Dent Assoc 2013 May;41(5):329-31, 334-42.
16. Rethman MP, Carpenter W, Cohen EE, Epstein J, Evans CA, Flaitz CM, et al. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. Tex Dent J 2012 May;129(5):491-507.
17. Fakhry C, Rosenthal BT, Clark DP, Gillison ML. Associations between oral HPV16 infection and cytopathology: evaluation of an oropharyngeal "pap-test equivalent" in high-risk populations. Cancer Prev Res (Phila) 2011 Sep;4(9):1378-1384.
18. Lingen MW. Can saliva-based HPV tests establish cancer risk and guide patient management? Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010 Sep;110(3):273-274.
19. Mirghani H, Amen F, Moreau F, Guigay J, Ferchiou M, Melkane AE, et al. Human papilloma virus testing in oropharyngeal squamous cell carcinoma: what the clinician should know. Oral Oncol 2014 Jan;50(1):1-9.
20. DeRossi SS, Laudenbach J. The management of oral human papillomavirus with topical cidofovir: a case report. Cutis 2004 Mar;73(3):191-193.
21. Government of Ontario. Publicly Funded Immunization Schedules for Ontario - Aug 2011. 2011; Available at: http://www.health.gov.on.ca/en/public/programs/immunization/docs/schedule.pdf. Accessed Apr/30, 2014.
22. Kang WD, Choi HS, Kim SM. Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)? Gynecol Oncol 2013 Aug;130(2):264-268.
23. National Advisory Committee on Immunization (NACI). Update on Human Papillomavirus (HPV) Vaccines. 2012; Available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php. Accessed Apr/30, 2014.

Royal College of
Dental Surgeons of Ontario

Ensuring Continued Trust

6 Crescent Road
Toronto ON Canada M4W 1T1
T: 416.961.6555 F: 416.961.5814
Toll Free: 800.565.4591 www.rcdso.org

Environmental Stewardship

This magazine is printed on paper certified by the international Forest Stewardship Council as containing 25% post-consumer waste to minimize our environmental footprint. In making the paper, oxygen instead of chlorine was used to bleach the paper. Up to 85% of the paper is made of hardwood sawdust from wood-product manufacturers. The inks used are 100% vegetable-based.

Mixed Sources
Product group from well-managed forests and other controlled sources
www.fsc.org Cert no. SW-COC-002301
© 1996 Forest Stewardship Council
FSC

RAINFOREST ALLIANCE CERTIFIED