The Journal of Laryngology & Otology (2010), ***124***, *941–944.*

doi:10.1017/S0022215110001179

Review Article

Oncogenic impact of human papilloma virus in head and neck cancer

C B Heffernan, J P O'Neill, C Timon

Abstract

There is considerable debate within the literature about the significance of human papilloma virus in head and neck squamous cell carcinoma, and its potential influence on the prevention, diagnosis, grading, treatment and prognosis of these cancers. Cigarette smoking and alcohol consumption have traditionally been cited as the main risk factors for head and neck cancers. However, human papilloma virus, normally associated with cervical and other genital carcinomas, has emerged as a possible key aetiological factor in head and neck squamous cell carcinoma, especially oropharyngeal cancers. These cancers pose a significant financial burden on health resources and are increasing in incidence. The recent introduction of vaccines targeted against human papilloma virus types 16 and 18, to prevent cervical cancer, has highlighted the need for ongoing research into the importance of human papilloma virus in head and neck squamous cell carcinoma.

Key words: Human Papilloma Virus; Head And Neck Neoplasms; Pharynx Neoplasms; Squamous Carcinoma

Introduction

Head and neck squamous cell carcinoma (SCC) is a relatively common malignancy, accounting for 5 per cent of all newly diagnosed cancer cases internationally. Despite significant improvements in treatment modalities, the overall survival rate for patients with head and neck SCC has essentially remained stationary, with an average five year survival rate of approximately 50 per cent.[1] Environmental risk factors such as tobacco and alcohol abuse play a well defined and important role in the pathogenesis of head and neck SCC.

Evidence is accumulating which suggests that human papilloma virus (HPV) types 16 and 18 may be aetiological agents in up to one-quarter of head and neck SCC cases, being particularly implicated in SCC of the oropharynx.[2] Oropharyngeal SCC is associated with a significant financial burden to the health service; in 2003, it cost US health services US$38.1 million.[3]

Human papilloma virus 16 and 18 prevalence is highest in the oropharyngeal subtype of head and neck SCC (being 35.6–38 per cent).[2,4] In such HPV-positive oropharyngeal carcinomas, HPV 16 is present in approximately 80 per cent while HPV 18 is present in only 3 per cent.[2] From the best available data, the prevalence of HPV in the oral mucosa of healthy adults is much less, being estimated at 5 to 11 per cent.[5] The incidence of oropharyngeal carcinoma is increasing in a younger age group in developed countries, patients less likely to have strong tobacco or alcohol histories, and this makes the HPV association more important.[4,6] Of particular relevance is the fact that HPV has been found to be the most significant positive prognostic factor in patients with oropharyngeal tumours, with a 60–80 per cent reduction in the risk of death if HPV is identified in the tumour cells.[7]

Pathophysiology and carcinogenesis

Human papilloma virus is a small, non-enveloped, oncogenic DNA virus with more than 120 identified genotypes. 'Low risk' types (e.g. HPV 6 and 11) are associated with benign proliferative growths, such as common plantar and genital warts, and have been identified in respiratory papillomatosis. Human papilloma virus types 16 and 18, considered 'high risk' genotypes, have been found in the host DNA of patients with cervical cancer.[3,8] These HPV types are also the most common genotypes identified in head and neck SCC, with HPV 16 identified in approximately 90 per cent of oropharyngeal SCC specimens. Human papilloma virus 16 has six global variants: European, North American, Asian American, Asian, African one and African two.[9] Human papilloma virus is an obligatory intracellular organism which infects epithelial tissue initially by

From The Royal Victoria Eye and Ear Hospital, Adelaide Road, Dublin, Ireland.
Accepted for publication: 23 February 2010. First published online 2 June 2010.

mucosal damage, followed by transportation of the viral genome to the host's intracellular genome. It is believed that the HPV DNA fragments E6 and E7 bind to and inactivate the tumour suppressors p53 and pRb.[10] This results in defects in apoptosis, DNA repair mechanisms and cell cycle regulation.

In a systematic review of 5046 head and neck SCC cases from 26 different countries, it was noted that the prevalence of HPV was 25.9 per cent in all resection specimens. The prevalence of HPV was 35.6 per cent in oropharyngeal SCC, 23.5 per cent in oral SCC and 24 per cent in laryngeal SCC. The specific HPV 16 genotype was present in 86.7 per cent of HPV-positive oropharyngeal SCC, as compared with 68.2 per cent of oral SCC and 69.2 per cent of laryngeal SCC.[2]

The two possible pathways of HPV transmission to the head and neck mucosa comprise oral–genital contact and perinatal transmission.[11]

There are a number of reasons cited for the predilection of HPV for both oral and cervical mucosa. The oral cavity and uterine cavity are easily accessible for infection. The squamous epithelium in these sites is derived embryologically from endoderm and is susceptible to metaplasia. Cytokines produced by nearby lymphoid tissue may influence HPV transcription and cellular transformation. Finally, the mucosa in these sites contain crypts lined with a reticulated epithelium, which may facilitate viral access to basal cells.[12]

Studies show HPV infection to be associated with an increased risk (up to three times) of head and neck SCC, independent of exposure to alcohol or tobacco. Patient demographics shown to be significantly associated with increased detection of HPV in head and neck SCC includes male gender, minimal tobacco and alcohol consumption, and a history of oro-genital sex.[13,14]

Gillison *et al.* conducted a case–control study to identify independent risk factors for head and neck SCC in a HPV-positive and a HPV-negative group.[15] They noted that an increased number of oral sexual partners and increased frequency of marijuana use were associated with HPV positivity. On the other hand, HPV-negative patients were noted to have a strong history of poor oral hygiene and alcohol and tobacco use. This suggests that patients who are exposed to HPV are probably exposed to many different potential risk factors, and thus make up a unique patient cohort.

Previous studies had suggested that HPV-positive cancer has a better response to treatment and also a better survival advantage. Fakhry *et al.* conducted a prospective study of 96 patients with stage III–IV head and neck SCC, to determine whether there was a difference between HPV-positive and HPV-negative cancers.[7] They noted that patients who were HPV-positive were more likely to be Caucasian, have a <20 pack year smoking history, be diagnosed with tonsillar carcinoma, have basaloid, poorly differentiated SCC, and have a higher Eastern Cooperative Oncology Group performance status. The response rate to induction chemotherapy was 82 per cent in HPV-positive tumours, versus 55 per cent in HPV-negative tumours. The response to chemo-radiotherapy was 84 per cent in HPV-positive tumours, versus 57 per cent in HPV-negative tumours. The survival rate for HPV-negative cancer patients was 90 per cent at one year and 62 per cent at two years; by comparison, the survival rate for HPV-positive cancer patients was 97 per cent at one year and 95 per cent at two years. After performing statistical analysis, these authors concluded HPV status was independently associated with mortality risk, and that patients with HPV-positive tumours had a 64 per cent lower risk of death and a 73 per cent lower risk of progression, compared with patients with HPV-negative tumours.

Virus identification

There is significant research being done in the area of HPV detection in oral specimens. Stratifying patients by HPV status may be necessary if the optimal treatment differs for these groups. Oral HPV does not produce as strong a result with polymerase chain reaction technology as do cervical specimens, and therefore a slightly different approach may be needed, compared with Papanicolaou smear collection.[16] Research to date suggests that exfoliated superficial cells obtained by use of a mouth wash probably constitute the most suitable sample specimen. This method is non-invasive and yields large numbers of cells. Polymerase chain reaction technology currently produces the highest rates of HPV identification.[11,17]

Potential vaccination

The body mounts an immune response against HPV by initially recruiting T-lymphocytes (cluster of differentiation 4+ glycoprotein), which attract and activate B-lymphocytes, which ultimately produce antibodies against the HPV capsid proteins. However, these capsid proteins are not expressed in large numbers, so a vaccine which targeted non-structural proteins would be more efficacious. The E6 and E7 HPV DNA fragments are involved in the induction and maintenance of cellular transformation, and allow uncontrolled cell growth and possible malignant transformation. These proteins might be a more suitable target for an immunotherapeutic vaccine. Vaccines could be both therapeutic and prophylactic.[18]

The vaccines currently licensed for use in pre-adolescent girls target HPV 16 and 18. Human papilloma virus 16 occurs in approximately 90 per cent of oropharyngeal cancers, whereas HPV 16 and 18 combined occur in approximately 75 per cent of cervical cancers. Oropharyngeal cancers are more prevalent in young males, who also may contribute significantly to the spread of genital HPV.

Human papilloma virus is the most common sexually transmitted infection worldwide, and is often asymptomatic. It is believed that the risk of HPV transmission is associated with the number of oral sex or open mouth kissing partners.[19] The prevalence of oral sex is thought to be increasing in all age groups, but most especially adolescents, who perceive it to be less risky. Therefore, it is hoped that these

https://doi.org/10.1017/S0022215110001179 Published online by Cambridge University Press

vaccinations might be offered to all pre-adolescent children, both male and female. This would presumably have a large impact on the future incidence of genital and oropharyngeal carcinomas, which generally affect young, otherwise healthy individuals.[20]

The ideal vaccine to prevent HPV infection would probably consist of virus-like proteins. These proteins are formed by a capsid protein, L1, which spontaneously forms empty capsids. A prophylactic vaccine needs to produce long-lasting antibodies that work at an immunoglobulin (Ig) A mucosal and IgG systemic level. This would not be sufficient to treat established infection or neoplasia, as it would not stimulate a strong enough immune response. A therapeutic vaccine would be more efficacious if aimed at the E6 and E7 DNA fragments, which are fundamental to neoplastic transformation.[18,21,22] Ideally, of course, a combined multivalent vaccination with therapeutic and prophylactic elements would be most useful.[18]

At present, there are two prophylactic HPV vaccines available: the bivalent Cervarix® vaccine (Merck) and the quadrivalent Gardasil® vaccine (GlaxoSmithKline). Gardasil has been approved by the US Food and Drug Administration. Gardasil protects against HPV 6, 11, 16 and 18. Merck, which initially produced the vaccine, conducted a randomised, double-blinded, placebo-controlled trial to determine Gardasil's efficacy. This had to be abandoned on ethical grounds, and the vaccine was subsequently offered to the placebo group. Both vaccines are composed of the L1 capsid protein and produce neutralising antibodies. Both vaccines need to be administered on three occasions over a six-month period. Early vaccination confers 90–100 per cent protection against HPV infection. Further studies are still needed to determine if long term protection is afforded. It is estimated that it would cost the Irish government €9.7 million to vaccinate all 12-year-old girls in Ireland; a national vaccination scheme is currently on hold due to financial difficulties in the Irish health service.

At Johns Hopkins University, the otolaryngologist and head and neck surgeon Sara Pai has been investigating the benefits of vaccinating patients with oropharyngeal cancers, including cancers of the tonsils, soft palate, posterior pharynx and tongue base. Dr Pai and colleagues have developed a vaccine for HPV-related head and neck cancers, with a clinical trial expected in the summer of 2009. Unlike the preventive HPV vaccine for cervical cancer, Pai's vaccine would be available to women and men with HPV who are already being treated for head and neck cancer.

Conclusion

Human papilloma virus is emerging as a significant risk factor for head and neck SCC, particularly tumours involving the oropharynx. The increasing incidence of oropharyngeal carcinoma in younger patients with an insignificant tobacco or alcohol history and a potentially good prognosis has created interest in the prevention and possible treatment modalities for this oncogenic virus. Although identified in healthy oral mucosa, HPV is more common in specimens from patients with known oropharyngeal SCC, and is a positive prognostic factor in these cancers.[23,24] The role of vaccination for established disease is the focus of continued interest in the international oncology community.

References

1 Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and Neck Cancer. *N Engl J Med* 1993;**328**:184–94
2 Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:467–75
3 Hu D, Goldie SJ. The economic burden of noncervical human papillomavirus disease in the United States. *Am J Obstet Gynecol* 2008;**198**;487–8
4 Mineta H, Ogino T, Amano HM, Ohkawa Y, Araki K, Takebayashi S *et al*. Human papilloma virus (HPV) type 16 and 18 detected in head and neck squamous cell carcinoma. *Anticancer Res* 1998;**18**:4765–8
5 Franceschi S, Munoz N, Bosch XF, Snijders PJ, Walboomers JM. Human papillomavirus and cancers of the upper aerodigestive tract: a review of epidemiological and experimental evidence. *Cancer Epidemiol Biomarkers Prev* 1995;**5**: 567–75
6 Syrjanen S. HPV infections and tonsillar carcinoma. *J Clin Pathol* 2004;**57**:449–55
7 Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H *et al*. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst* 2008;**100**:261–9
8 Campisi G, Giovannelli L. Controversies surrounding human papilloma virus infection, head & neck vs oral cancer, implications for prophylaxis and treatment. *Head Neck Oncol* 2009;**1**:8
9 Yamada T, Manos MM, Peto J, Greer CE, Munoz N, Bosch FX *et al*. Human papillomavirus type 16 sequence variation in cervical cancers: a worldwide perspective. *J Virol* 1997; **71**:2463–72
10 Slebos RJ, Yi Y, Ely K, Carter J, Evjen A, Zhang X *et al*. Gene expression differences associated with human papillomavirus status in head and neck squamous cell carcinoma. *Clin Cancer Res* 2006;**12**:701–9
11 Chaudhary A, Singh M, Sundaram S, Mehrotra R. Role of human papillomavirus and its detection in potentially malignant and malignant head and neck lesions: updated review. *Head Neck Oncol* 2009;**1**:22
12 Hafkamp HC, Speel EJ, Haesevoets A, Bot FJ, Dinjens WN, Ramaekers FC, Hopman AH, Manni JJ. A subset of head and neck squamous cell carcinomas exhibits integration of HPV 16/18 DNA and overexpression of p16 and p53 in the absence of mutations in p53 exons 5-8. *Int J Cancer* 2003;**107**:394–400
13 Mork J, Lie AK, Glattre E, Hallmans G, Jellum E, Koskela P, Møller B, Pukkala E, Schiller JT, Youngman L, Lehtinen M, Dillner J. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2001;**344**:1125–31
14 Ringstrom E, Peters E, Hasegawa M, Posner M, Liu M, Kelsey KT. Human papillomavirus type 16 and squamous cell carcinoma of the head and neck. *Clin Cancer Res* 2002;**8**:3187–92
15 Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst* 2008;**100**:407–20
16 Giovannelli L, Campisi G, Lama A, Giambalvo O, Osborn J, Margiotta V *et al*. Human papillomavirus DNA in oral mucosal lesions. *J Infect Dis* 2002;**185**:833–6
17 Ha PK, Pai SI, Westra WH, Gillison ML, Tong BC, Sidransky D *et al*. Real-time quantitative PCR demonstrates low prevalence of human papillomavirus type 16

https://doi.org/10.1017/S0022215110001179 Published online by Cambridge University Press

in premalignant and malignant lesions of the oral cavity. *Clin Cancer Res* 2002;**8**:1203–9
18 Devaraj K, Gillison ML, Wu TC. Development of HPV vaccines for HPV-associated head and neck squamous cell carcinoma. *Crit Rev Oral Biol Med* 2003;**14**: 345–62
19 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**: 1263–9
20 Gillison ML. Human papillomavirus-related diseases: oropharynx cancers and potential implications for adolescent HPV vaccination. *J Adolesc Health* 2008;**43**(suppl 1): S52–60
21 Yan J, Reichenbach DK, Corbitt N, Hokey DA, Ramanathan MP, McKinney KA *et al*. Induction of antitumor immunity in vivo following delivery of a novel HPV-16 DNA vaccine encoding an E6/E7 fusion antigen. *Vaccine* 2009;**27**:431–40
22 Lee DW, Anderson ME, Wu S, Lee JH. Development of an adenoviral vaccine against E6 and E7 oncoproteins to prevent growth of human papillomavirus-positive cancer. *Arch Otolaryngol Head Neck Surg* 2008;**134**:1316–23
23 Klozar J, Kratochvil V, Salakova M, Smahelova J, Vesela E, Hamsikova E *et al*. HPV status and regional metastasis in the prognosis of oral and oropharyngeal cancer. *Eur Arch Otorhinolaryngol* 2008;**265**:S75–82
24 Mendenhall WM, Logan HL. Human papillomavirus and head and neck cancer. *Am J Clin Oncol* 2009 Jul 31. [Epub ahead of print]

Address for correspondence:
Ms Colleen Heffernan,
172 Viewmount Park,
Waterford, Ireland.

E-mail: Heffernan_colleen@hotmail.com

Ms C Heffernan takes responsibility for the integrity of the content of the paper.
Competing interests: None declared