

Human papillomavirus: a cause of some head and neck cancers?

Establishing a causal link between HPV and certain head and neck cancers would have implications for prognosis, prevention and therapy

More than half a million cases of squamous cell carcinoma (SCC) of head and neck mucosa are diagnosed each year, making it the eighth most common malignancy globally.¹ The highest incidence has been observed in developed countries like Australia, where there were 853 new cases in 2001, accounting for 3.8% of all cancers in men and 1.9% of all cancers in women.² Tobacco and alcohol consumption are accepted as the two major risk factors for head and neck cancer,³ and micronutrient deficiencies, genetic factors and poor oral hygiene are also suspected of playing a role.⁴

Over recent years, both epidemiological and experimental evidence has implicated oncogenic human papillomavirus (HPV) in the development of a subset of head and neck cancers.⁵⁻⁷ This evidence has been strongly supported by a recent large case-control study coordinated by the International Agency for Research on Cancer (IARC).⁸ The study, involving centres in nine countries (including the Royal Prince Alfred Hospital in Sydney), concluded that HPV plays an aetiological role in many oropharyngeal cancers and possibly in a small group of cancers of the oral cavity. In all studies, the association has been strongest in the tonsil, where HPV DNA positivity rates frequently exceed 50%. HPV type 16, predominant in cervical cancers, is overwhelmingly the most common type.⁸⁻¹⁰

The critical issue now is to confirm that the association of HPV with these cancers is causal, as is clearly the case with cervical cancer. This may have implications for prognosis, treatment and prevention. Both the mutagens in tobacco smoke and alcohol and the HPV oncogenes E6 and E7 are known to disrupt the two major pathways controlling the cell cycle — those involving the tumour suppressors p53 and pRb (the retinoblastoma protein). Experimental evidence supporting a causal role has come from reports that the HPV genome is found localised to only the primary tumour cells and their metastases, at similar copy numbers to those reported in other HPV-associated malignancies, including those of the cervix.^{9,10} Demonstration (by reverse transcription/polymerase chain reaction assays) that E6 and E7 are active in the cancer cell has also been of key importance in establishing an aetiological role.⁷ Integration of HPV DNA into the host chromosome, which frequently heralds malignant conversion in cervical lesions, has also been observed, although there are indications that the proportion of head and neck cancers carrying the virus in non-integrated form in the cell nucleus may be higher than in the cervix.¹⁰ Seroreactivity against the viral capsid proteins and oncogenes has also been associated with an increased risk of cancer.⁸

Molecular analyses of p53 and of cellular proteins in the pRb pathway (including cyclin D1, a positive regulator, and p16, a negative regulator of the cell cycle) have suggested that HPV-positive head and neck cancers are a biologically distinct group. HPV-positive cancers are generally characterised by loss of expression of pRb and cyclin D1 and overexpression of p16

Glossary

Viral oncogenes. DNA sequences in the viral genome that code for a protein capable of setting the cell on a course to malignant transformation.

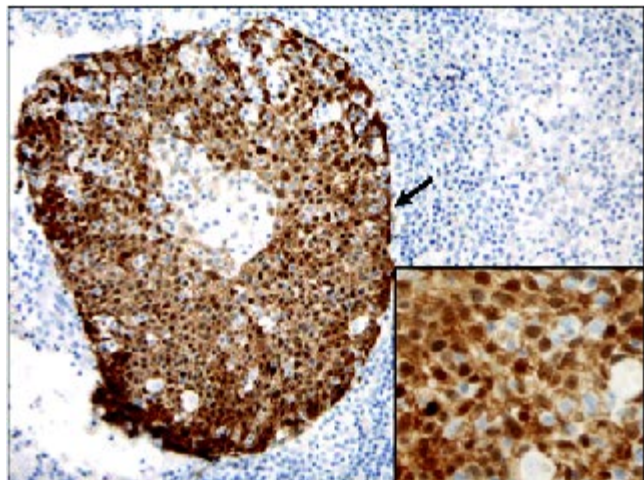
Tumour suppressors. Classes of proteins that protect the cell against malignant transformation (eg, by monitoring the integrity of the cell or by preventing unscheduled cell cycling).

following inactivation of pRb by the viral E7 oncoprotein.^{6,11} In contrast, HPV-negative tumours consistently show overexpression of pRb and cyclin D1 and loss of p16. Mutations in the p53 gene appear to be much more common in HPV-negative cancers than in HPV-positive cancers. In HPV-positive cancers, p53 inactivation is achieved by interaction with the viral oncoprotein E6. Nonetheless, HPV and p53 mutations appear to coexist in at least a proportion of head and neck cancers.

The recent IARC study,⁸ like other, smaller surveys, shows that HPV-positive head and neck cancers are more common in patients who do not smoke or chew tobacco,^{8,12} but HPV infection and tobacco consumption together are associated with an increased risk (whether the effect is additive or synergistic is not known). Several studies have reported a clustering of HPV-positive cancers in younger age groups,¹³ but the association with age remains controversial. HPV has statistical associations with a history of multiple sexual partners, the practice of giving oral sex and a history of genital warts, suggesting sexual transmission, although conclusive data are lacking.^{8,12} A lower rate of oral exposure to HPV because of cultural or social attitudes relating to sexual practices (notably orogenital contact) may help explain the lack of HPV DNA in a recent small series of tonsillar cancers from Chinese patients.¹⁴

What are the practical implications of an aetiological role for HPV in head and neck cancer in the clinical setting? The prognosis for head and neck cancer has not improved appreciably over the past two decades, despite a better understanding of the biology of invasive tumours, advances in surgery and the increased use of combined-modality treatment. Clinical staging is the primary guide to treatment modality, but provides a limited guide to outcome. There have been general expectations that genetic analysis is “the way of the future” in terms of identifying markers for prevention, therapy and prognosis. Attempts to find prognostic cellular markers in head and neck cancers have been disappointing, but including HPV status as a variable in the data analysis may yield more rewarding results. There are real prospects that HPV itself may provide a new generation of prognostic markers. Surveys have consistently linked HPV-positive cancers with a more favourable clinical outcome than HPV-negative cancers. The risk of recurrence or death from the disease associated with HPV status is independ-

Upregulation of p16 as a marker of HPV-mediated transformation in tonsillar cancer cells



Strong, diffuse staining for p16 is shown in a high proportion of tumour cells (arrow). A close-up view of tumour cells (inset, x 400) shows staining throughout the nucleus and cytoplasm.

ent of established prognostic factors, including tumour stage and lymph-node metastasis.^{6,10,11} The apparently better prognosis for patients with HPV-positive cancers may reflect the inability of the viral E6 protein to fully inactivate p53 and/or the adverse effect of radiation and other toxic agents on the ability of E6 to interfere with p53 and other host proteins, so that the cancers are more susceptible to therapy. Screening of head and neck cancers for HPV 16 and/or raised p16 as a marker of HPV-related transformation (Box) may identify a new group of patients (those with HPV-negative tumours) who would benefit from closer-than-usual follow-up or additional therapy. However, large-scale prospective studies will be needed to establish the cost-effectiveness of this approach.

Internationally, HPV DNA testing is gaining acceptance as an adjunct to cytology in cervical cancer screening programs. Early diagnosis is still the best predictor of good outcome in head and neck cancer. The possible public health benefits of cytological screening and/or detection of HPV DNA in cells collected from the oral cavity by dentists or general practitioners await evaluation. Such studies will need to include details of how and when specimens are taken and cost-benefit analyses.

Both in Australia and overseas, clinical trials are under way to test HPV vaccines (developed from viral capsids generated in the laboratory) for prevention of cervical cancer. The demonstrated efficacy of an HPV 16 vaccine in preventing persistent infection in the female genital tract¹⁵ has raised expectations that such vaccines may eventually reduce the incidence of head and neck cancer. However, the potential of vaccine programs designed for the genital tract to reduce the incidence of HPV infection in the head and neck is still to be evaluated. Specific randomised controlled trials to address the prevention of persistent oral HPV infections may need to be considered. Therapeutic vaccines

based on the viral oncogenes E6 and E7 remain at the experimental stage, but may eventually prove a valuable addition to surgical, radiation and chemotherapeutic approaches to managing advanced disease.

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