

HPV-RELATED CANCERS

KEY POINTS

- High-risk human papillomavirus (hrHPV) plays a significant role in lower genital tract precancers and cancers: nearly 100% of cervical cancers, ~90% of vaginal cancers, ~80% of anal cancers, ~50% of penile cancers, and ~40% of vulval cancers.¹
- HPV 16 and 18 are associated with a higher risk of progression to precancerous lesions than infection with other high-risk HPV types. Therefore, it is important to identify these two genotypes of hrHPV to support management.
- *Cervical cancer:*
 - o Most people with a cervix who are infected with hrHPV will not develop cervical cancer and hrHPV infection will resolve spontaneously in many.
 - o Anyone with a cervix who has ever been sexually active should receive cervical cancer screening, including women with female partners and gender diverse people with a cervix.
- *Anal cancer:*
 - o Anal cancer is rare globally. The burden of disease is highest in people living with HIV, men who have sex with men (MSM), individuals who have undergone solid organ transplantation, and those with a history of multifocal HPV-related genital disease.^{2,3}
 - o Options for anal cancer screening, including anal cytology and HPV testing, are being explored but at the time of publishing these guidelines, these are not currently available in Aotearoa New Zealand. Annual digital anorectal examination (DARE) is recommended for HIV-positive MSM who are aged 50 years or over (see www.ashm.org.au/hiv/management-hiv/anal-cancer). Treatment of precancerous precursors has been shown to reduce, but not eliminate, the risk of anal cancer.⁴
- *Oropharyngeal cancer and recurrent respiratory papillomatosis:*
 - o HPV-associated oropharyngeal cancer is increasingly common, especially in men.
 - o A higher number of lifetime oral sex partners is associated with increased risk.

- o Individuals with oropharyngeal cancer often present with lymph node metastases.
- o People with HPV-positive oropharyngeal cancers have a better prognosis than those with HPV-negative cancers.
- o In contrast to cervical cancer, no clinically apparent premalignant condition exists in the vast majority of individuals with oropharyngeal cancer, and there is no reliable laboratory screening test. Therefore, there is currently no indication for population screening for HPV-related head and neck disease.
- o The incidence of HPV-related oropharyngeal cancers can be expected to decline due to vaccination of young people through the school-based immunisation programme.
- o Recurrent respiratory papillomatosis is a benign HPV-related disease of the upper airway that typically presents in young children or young adults and can have a variable course.

Cervical cancer

Epidemiology

Most sexually active people with a cervix will acquire HPV infection at some point in their life but only a few will go on to develop cervical cancer.⁵ HPV infection typically occurs in younger age groups whereas cervical cancer usually develops later in life. This indicates that it usually takes many years for a precursor lesion to develop into a cancer.

Cervical cancer is the fourth most common cancer in females worldwide, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020.⁶ The incidence of cervical cancer in Aotearoa New Zealand is among the lowest in the world. In 2019 there were 186 new diagnoses of cervical cancer, and the age-standardised registration rate was 6.7 per 100,000 population overall and 7.8 per 100,000 for Māori women.⁷

The evidence linking HPV to cervical carcinoma is extensive, with HPV 16 accounting for approximately 50% of cases and HPV 18 for 20%; together HPV 16 and 18 account for about 70% of all cervical cancers worldwide.⁸⁻¹¹ The prevalence of HPV 16/18 in confirmed high-grade disease in Aotearoa New Zealand is comparable to that observed in Australia and European countries.^{12,13} The prevalence of HPV 16/18 is almost identical for both Māori and non-Māori populations in Aotearoa New Zealand.¹⁴ The most common HPV types in females with high-grade cervical intraepithelial neoplasia (CIN-2/3) were HPV 16 (51%), 18 (21%), 31 (4%), 45 (3%) and 52 (3%).¹³

Although cervical screening has reduced the incidence of cervical cancer by at least 70% in regions where screening has been effectively implemented, it remains a leading cause of death in countries that do not have an effective screening programme.¹⁵

Classification of abnormalities

Abnormalities are classified by whether it is a cytologic or histologic specimen and by their severity. For example, exposure to HPV results in productive viral infections that may cause mild abnormalities; these are referred to as low-grade squamous intraepithelial lesions (LSILs) by cytologists or cervical intraepithelial neoplasia 1 (CIN-1) by pathologists. These lesions can be caused by either low-risk (lr) HPV or hrHPV so indicate the presence of HPV infection. Most HPV infections, including high-risk genotypes, typically become undetectable within 6–12 months.¹⁶ Persistent (detectable) infection is associated with the development of high-grade CIN (CIN-2+).^{17,18}

Risk of progression to cancer

Histologically confirmed CIN-3 must be regarded as the precursor for cervical cancer, although many high-grade precursors will not progress to cancer even after prolonged follow-up of up to 30 years.⁵

The median age of women with CIN-3 is 27–30 years, but the median age for women with a cervical screen-detected invasive cancer is 10 years or more older than this.¹⁹

Data from Aotearoa New Zealand showed that the cumulative incidence of invasive cancer of the cervix was 50% in women with CIN-3 managed only with small diagnostic biopsy and who have persistent abnormal smears.²⁰ Previously it was thought that it took many years to progress from incident HPV infection to high-grade precursor lesion. However, intensive prospective follow-up of women in their early 20s has demonstrated that rapid development of CIN-2 and 3 can occur, often within a few months of incident infection.²¹ However, in most cases it does take many years to progress from a high-grade precursor to invasive cervical cancer.

Some CIN-2 lesions will regress, particularly in young women, while others persist with risk of progression. The risk of progression is considerably higher with HPV 16 or 18 infection than with other high-risk genotypes. HPV 16 persists longer than other types, with an absolute risk of CIN-3 approaching 40% after infection has persisted for 5 years.²²

Risk factors

Cigarette smoking,^{23,24} and coinfection with HIV²⁵ have been consistently shown to be co-factors for cervical cancer. Long-term use of hormonal contraceptives²⁶ and high parity²³ are less important cofactors.

Elimination of cervical cancer

If high rates of HPV immunisation and cervical screening are achieved then there will be a marked reduction in the incidence of cervical cancer, with the prospect of eliminating cervical cancer globally long term. The International Papillomavirus Society has released a call to action for the elimination of cervical cancer²⁷ and the World Health Organisation has adopted a Global Strategy for Cervical Cancer elimination.²⁸

Anal cancer

Although a relatively uncommon cancer, the incidence of anal cancer in the United States has been rising for many years, and anal cancer is more common in men than in women.^{29,30} In 2020, an estimated 50,685 people worldwide were diagnosed with anal cancer and an estimated 19,293 people died of anal cancer.³⁰ The rate of anal cancer in North American cohorts between 1996 and 2007 was 35/100,000 in MSM and 137/100,000 in HIV-positive MSM.³¹ Approximately 90% of all anal cancer cases are linked to infection with HPV (most often HPV 16).³²

Vulval and vaginal cancers

Vulval and vaginal cancers are rare globally: vulvar cancer accounts for 4% of all gynaecological cancers.³³ In Aotearoa New Zealand, the incidence of vulvar cancers is 1.4 per 100,000 women aged 20 years and older.³⁴ Vulvar squamous cell carcinoma has two different aetiological pathways, human papillomavirus-associated (HPV associated) and human papillomavirus-independent (HPV independent). These cancers behave very differently in terms of risk and frequency of recurrence and overall survival. The majority of vulvar squamous cell carcinomas are HPV-independent and occur more frequently in older women than HPV-associated tumours.³⁵ In Oceania, it is estimated that 40% of vulval cancers are due to HPV (86% for warty/basaloid squamous cell carcinoma [SCC] and 14% for keratinising SCC).³⁶

Recent studies have demonstrated the two types of cancer are changing with HPV-associated cancers becoming more common in women.³⁷ Many authors have demonstrated that HPV-independent tumour have a worse prognosis.³⁸ The reasons are unclear but contributing factors include the age of the population presenting with these

tumours. HPV-independent tumour precursors such as lichen sclerosus with differentiated type (dVIN) are more common in older women.³⁵

Seventy percent of vaginal cancer cases are estimated to be due to HPV.¹ Studies in Aotearoa New Zealand have shown usual-type HSIL to have a significant invasive potential in women age 30 years and over, with a mean transit time to invasion of 4 years.³⁹ Investigation of the role of co-factors for persistence and progression of vulval and vaginal cancers is difficult because of the ubiquitous and transient nature of HPV infection.

Penile cancer

Penile cancer is also rare, with approximately half of all cases attributable to HPV.¹

Oropharyngeal cancer

Epidemiology

Similar to other head and neck cancers, SCC of the oropharynx has traditionally been associated with smoking and alcohol consumption. However, in the last 30 years the incidence of smoking-related head and neck cancer has declined in most countries.⁴⁰ In contrast, the incidence of oropharyngeal cancer has been steadily increasing in many countries, including Aotearoa New Zealand. This has coincided with an increasing incidence of HPV as the aetiological factor in these cancers.^{41,42} HPV, along with other viruses and bacteria, preferentially accumulates in the lymphoid tissue of the palatine and lingual tonsils. Because of this, hrHPV is more likely to cause SCC in these locations than at other sites in the upper aerodigestive tract. In the tonsils and base of the tongue, up to 93% of SCC is now attributable to HPV, with significant international geographic variation.⁴³⁻⁴⁶ A study conducted in Aotearoa New Zealand found that 75% of oropharyngeal cancers were attributable to HPV.⁴⁷ HPV is an uncommon contributing factor to cancers of the oral cavity, hypopharynx and larynx.

Risk factors

HPV-related oropharyngeal cancers are approximately four times more common in men than in women.^{41,48} In the United States, the rate of oropharyngeal cancer in men is now higher than the rate of cervical cancer in women.⁴¹ The exact reason for this gender bias is not clear; potential reasons include a greater viral load in the female genital tract and a greater immune response in females than in males.⁴⁹ The average age at diagnosis of HPV-associated oropharyngeal cancer is lower than that for smoking-related cancer, although the latency after HPV infection is typically at least 10 years, and can be several decades.

The HPV subtypes implicated in oropharyngeal SCC are similar to those involved in cervical cancer. HPV 16 fulfils epidemiological criteria for being high-risk in the oropharynx, and is implicated in up to 90% of HPV cases.⁵⁰ HPV types 18, 31, 33, 35 and 52 have not been studied as thoroughly, and are classified as potentially high-risk.^{46,51} There is a strong correlation between higher numbers of oral sexual partners and the development of oropharyngeal SCC, especially when the number of lifetime sexual partners is six or more.^{52,53} Other features of sexual behaviour which are less strongly associated with head and neck cancer include younger age at sexual debut, history of genital warts or sexually transmitted infections, rare or non-use of condoms and oral-anal sex.⁵³ Similarly, the prevalence of HPV positivity in oral samples is greater in individuals with a higher number of lifetime sexual partners.⁴⁴ Therefore, oral sex is believed to be the mode of transmission of HPV to the oropharynx in most cases.

Clinical presentation

Oropharyngeal SCC can present with throat symptoms and an ulcerated or non-ulcerated mass visible on oral examination. However, many individuals have lateral cervical lymph node metastases at the time of diagnosis, and a neck mass is often the only clinical finding at diagnosis. Therefore, HPV-related oropharyngeal SCC should be considered in any individual, especially males, presenting with a painless lateral neck mass.

Treatment and prognosis

In recent decades, the preferred treatment for oropharyngeal SCC in most centres has been concurrent chemoradiation therapy. The prognosis for individuals with HPV-related oropharyngeal cancer is much better than that for those with HPV-negative, smoking-related oropharyngeal cancers; HPV-positive tumours in smokers are associated with an intermediate prognosis.^{48,54} Due to the better outcome in individuals with HPV-versus smoking-related disease, many oncologists thought that it might be possible to reduce treatment intensity, thereby reducing the not insignificant side effects of treatment while still achieving a good prognosis/outcome. De-intensification could include omitting chemotherapy, reducing the radiation therapy dose, and reintroducing surgery as the primary treatment modality. The latter has become more attractive with the development of trans-oral robotic surgery. However, it is current accepted that treatment de-intensification only be adopted in the context of a formal clinical trial, many of which are underway.⁵⁵

Counselling

As for anogenital HPV-related disease, a viral aetiology for oropharyngeal cancer raises questions for the affected individual, their partner and health practitioners. Common

concerns are how the virus was acquired, whether there have been sexual partners outside of the couple, and how to manage an ongoing sexual relationship. It is important to emphasise that a diagnosis of HPV-related cancer does not necessarily imply multiple sexual partners or other partners outside the relationship. There is no need to alter sexual activity with a stable partner because sharing of HPV would have occurred long before the clinical appearance of the cancer. There is currently no clear evidence for transmission of HPV through kissing. Female partners are not known to be at higher risk of developing cancer (at any site), but should follow standard cervical screening guidelines. A useful [guide](#) to discussing these issues was developed by Fakhry and D'Souza (2013) and includes a printable patient information sheet.⁵⁶

Prevention

In contrast to cervical cancer, no clinically apparent premalignant condition exists in the vast majority of individuals with oropharyngeal cancer and there is no reliable laboratory screening test. Therefore, there is currently no indication for population screening for HPV-related head and neck disease.⁵⁷ However, this is an increasingly prevalent disease, and increased awareness of the disease among health professionals and the general population is to be encouraged. Limiting the number of sexual partners, delaying the onset of sexual activity and using barriers such as condoms and latex dams while performing oral sex, could minimise the risk of developing HPV-related oropharyngeal cancer.

As with anogenital HPV-related disease, HPV vaccination is a promising approach to prevent the development of benign and malignant head and neck HPV-related disease. Vaccination of individuals of all genders prior to the onset of sexual activity is strongly recommended.⁵⁷

Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis (RRP) is a benign condition characterised by papillomatous growths in the respiratory tract. The larynx is the most commonly affected site, and individuals can present with hoarseness or airway symptoms. RRP has a bimodal incidence, occurring in young children and in adults. It is an uncommon condition, affecting approximately four per 100,000 children and four per 100,000 adults.⁵⁸ It is related to HPV subtypes 6 and 11 in particular.

In children, transmission is thought to be vertical via an infected birth canal in the majority of cases, although intrauterine infection also appears to occur. Vaginal delivery, prolonged labour and being the first-born child of a young mother (<20 years) are associated with an increased risk of developing RRP.⁵⁹ Juvenile-onset RRP is estimated to

be over 200 times more common in children born to mothers with a history of genital warts during pregnancy than in those without clinical warts, but only one in a few hundred children of mothers with a history of genital warts will develop RRP.^{60,61}

Caesarean section has been considered as an option for preventing RRP. However, it is not completely protective and is associated with higher maternal morbidity and mortality and a greater economic cost than vaginal delivery. As a result, Caesarean section is not recommended for all pregnant people with genital warts. There may be some benefit in managing genital warts during pregnancy, as long as this does not result in an increased risk of miscarriage.⁶²

In adults, development of RRP is associated with male gender, increased numbers of lifetime sexual partners, and frequency of performing oral sex.^{59,63} In individuals with adult-onset RRP, the virus may have been acquired later in life compared to those with juvenile-onset RRP, or the development of disease may represent reactivation of a latent infection acquired at birth.⁶²

The mainstay of treatment in both adults and children with RRP is surgical debridement of the papillomas. This requires specialist referral. Immunisation with a vaccine including HPV types 6 and 11 has the potential to significantly reduce the incidence of RRP. There is some evidence from Australia that this may already be occurring.⁶⁴

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