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Cancers attributable to human papillomavirus infection

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Abstract. Although the human papillomavirus (HPV) vaccine was introduced primarily as a cervical cancer prevention vaccine, HPV has a causal role in several types of cancer. This article reviews the epidemiological evidence for the role of HPV in human cancer, and describes Australian trends in these cancers. HPV is a necessary cause of cervical cancer. The currently vaccine-preventable subtypes of HPV 16 and 18 are responsible for ~70% of cervical cancer. The introduction of an organised Pap smear program in Australia led to a steep decline in incidence over the past decades. HPV can be detected in ~40% and 70% of vulval and vaginal cancers respectively. Rates of these cancers have been stable over the past 20 years. The prevalence of HPV in penile cancer is ~50% and incidence has not recently changed. For anal cancer, ~85% of cases are HPV positive, and incidence has increased significantly in both men and women over the past 20 years. In the oral cavity, ~35% of oropharyngeal cancers and ~25% of other oral cavity cancers are HPV positive. The incidence of HPV-related oral cavity and oropharyngeal cancers is increasing, whereas incidence at HPV-unrelated sites is decreasing. Overall, 1154 HPV-related cancer cases were potentially preventable by vaccination. If HPV-related cancers at non-cervical sites are prevented by vaccination, then a similar number of cancer cases will be prevented as in the cervix. However, almost one-quarter of the potentially preventable cancer cases are in men, who are not included in the current national immunisation program.

Additional keywords: Australia, cervical cancer, HPV vaccine.

Introduction

Human papillomavirus (HPV) is regarded as a necessary cause of cervical cancer, and also causes a substantial proportion of cancers of the vulva and vagina, penis, anus, and oral cavity and oropharynx.[1] Currently available HPV vaccines have been shown to be highly efficacious in preventing intraepithelial neoplasia of the cervix, vulva, vagina and anus related to HPV-16 and HPV-18, and trial results of prevention of HPV-related anal intraepithelial neoplasia are expected soon.[2] Although the HPV vaccine was developed primarily as a cervical cancer preventive agent, there is therefore substantial promise that other HPV-associated cancers may also be prevented in vaccinated individuals. In this report, we present a narrative review of the incidence and aetiology of acknowledged HPV-associated cancers,[3] with a particular focus on the proportion of specific HPV-associated cancers likely to be caused by HPV, and present Australian data on recent incidence trends of these cancers.

Methods

For the analysis of Australian trends, annual cancer incidence rates, age-standardised to the Australian 2001 standard population were obtained from the National Cancer Statistics Clearing House database at the Australian Institute of Health and Welfare for the 1982–2005 period.

We included HPV-related cancers based on the classification of the International Agency for Research on Cancer.[3] HPV-associated cancers mapped to International Classification of Diseases (ICD10) included cancer of the cervix (C53), anus (C21), vulva (C51), vagina (C52), penis (C60) and oral cavity. Cancers of the oral cavity were further divided based upon their published association with HPV infection. The HPV-related sites included the base of the tongue (C01), the tonsils (C09) and the oropharynx (C10). Oral cavity comparison sites which are considered largely unrelated to HPV included other parts of the tongue (C02), mouth (C03–C06) and larynx (C32).[4]

Time trends in standardised incidence rates by year of cancer diagnosis were analysed using generalised linear models with a logarithmic link function and are expressed as annual percentage change in incidence. Goodness of fit of the model was checked using the Pearson statistic and the reported models fit the data adequately ($P > 0.350$ for all models). Statistical analyses were performed using Stata version 11.0 (StataCorp, College Station, TX, USA).

We also estimated the number of cases of HPV-associated cancer that are potentially preventable by the currently available HPV-16 and -18 vaccines. The number of cases occurring

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at each site in 2005 was multiplied by the most recent estimates of the proportion of cases that were estimated to be due to HPV-16 and HPV-18 at that site (references given in Table 2).

Results

Cervical cancer

Cervical cancer is the second most common cancer among women in developing countries and the seventh most common cancer among women in developed countries.[5] While cervical screening has led to a reduction in cervical cancer incidence and mortality in developed countries, this is not the case for developing countries. An estimated 500 000 new cases are diagnosed each year and 274 000 women die from the disease, with over 80% of cervical cancers occurring in developing countries (Fig. 1).[6]

In Australia, the introduction in 1991 of an organised program of two-yearly Pap smear screening targeting women aged 20 to 69 years has been very successful at reducing cervical cancer incidence and mortality. Cervical cancer is now the 13th most common cancer affecting Australian women, with an age standardised incidence of 6.9 new cases per 100 000 women in 2005 (734 cases) and the 19th most common cause of cancer mortality, with an age standardised mortality of 1.9 deaths per 100 000 women in 2006 (224 cases)[7] (Fig. 2). Australia has the second lowest cervical cancer incidence in the world and the lowest mortality.[8] The large disparity in cervical cancer incidence between developed and developing countries is largely attributable to health care access and lack of cervical cancer screening programs. High parity and deficient diets of women in developing countries may be additional contributory factors for the high incidence rates of cervical cancer observed in these areas.[9]

Cervical cancer incidence among Australian women shows a bimodal pattern with age. Incidence rises to a peak among women aged 40 to 44 years (13.6 per 100 000 women) then drops, rising gradually again from age 60 to 15.4 per 100 000 women among those aged 85 years and older. Similar bimodal patterns are seen elsewhere in the developed world and may reflect a cohort effect associated with cervical cancer incidence.[10,11] Other possible explanations for this finding include increasing sexual activity of these older women or their sexual partners, or a decreased age-related immune response, possibly caused by hormonal changes related to menopause that result in a re-activation of latent HPV infection.[12–14]

Despite the success of the cervical screening program, marked disparities continue to be observed in cervical cancer incidence and mortality between Indigenous and non-Indigenous Australia women. Data for the period from 2003 to 2006 show that Indigenous women in Australia were over five times more likely to die from cervical cancer.[7] This excess incidence and mortality has been largely attributable to inadequate health care access and, as a consequence, poor participation in the screening program.[15]

Histological type

In 2005, squamous cell carcinomas of the cervix accounted for 66.1% of all new cases of cervical cancer in women aged 20 to 69 years in Australia, adenocarcinomas accounted for 19.8%, adenosquamous for 3.2% and the remaining 11.0% had a range of mixed and unknown histology.[7] While the incidence of adenocarcinoma of the cervix did not decline in

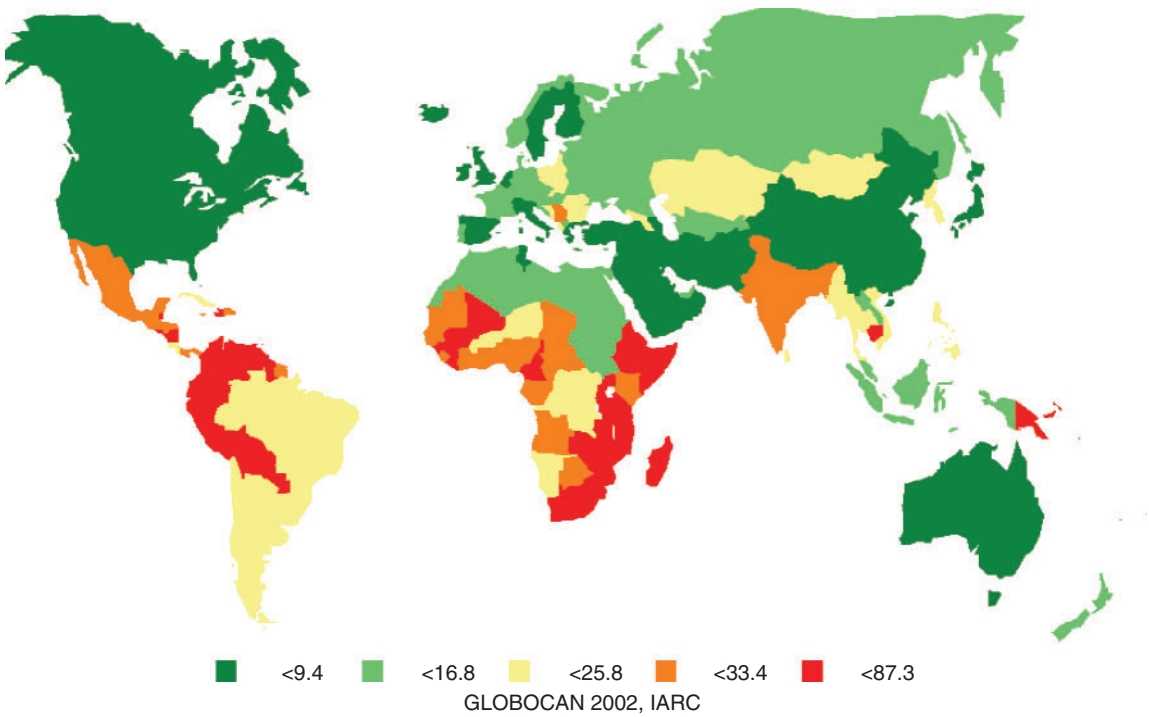

Fig. 1. Age standardised incidence of cervical cancer around the world, 2002.

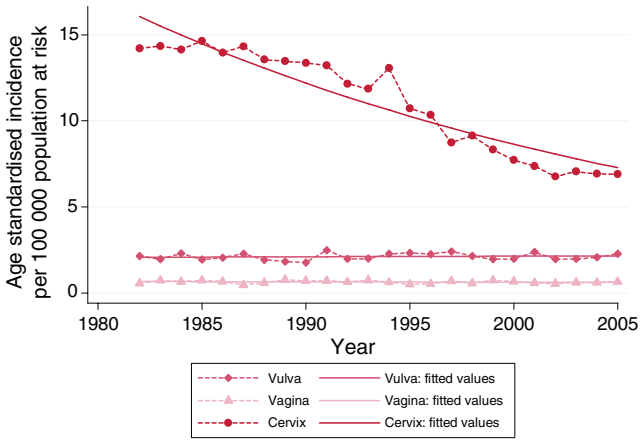

Fig. 2. Age standardised incidence of HPV-associated genital tract cancers in women, Australia, 1982–2005.

the early 1990s despite increasing participation rates in cervical screening in Australia, the impact of improved endocervical sampling and better recognition of the cytological precursors to adenocarcinoma, has led to significant reductions in adenocarcinoma over the last decade. An analysis of Victorian Cervical Cytology Registry data published in 2003, found that the Pap smear did confer significant protection against being diagnosed with invasive adenocarcinoma.[16]

The role of HPV

It has been established that HPV is a necessary cause of cervical cancer.[17] The International Agency for Research on Cancer has identified HPV type 16 (HPV-16), HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59 and HPV-66 as oncogenic types for the cervix.[18] Of these, HPV-16 and HPV-18 have been found to account for ~70% of all cervical cancers. A recent meta-analysis that aimed to estimate the proportion of cervical cancer attributable to high risk types among Australian women evaluated studies that used polymerase chain reaction (PCR)-based assays to identify HPV DNA. It found that of the seven studies including 533 eligible cervical cancers, the most frequent high risk HPV types present were HPV-16 (60.4%), HPV-18 (19.7%) and HPV-45 (4.6%). Overall, 80.1% (95% confidence interval (CI): 72.7%–87.8%) contained HPV-16 or -18,[19] a finding consistent with the international literature.[20] In two studies involving 83 cases of adenocarcinoma included in this meta-analysis, HPV-16 was present in 28% of cancers and HPV-18 in 41%. This finding that HPV-18 is more prevalent than HPV-16 in adenocarcinoma is also consistent with the international literature.[20]

Other risk factors

Epidemiological studies have shown that cervical cancer is consistently associated with sexual activity: number of sexual partners, early coitarche and the behaviour of the woman's male partners.[9] Each of these factors may lead to a greater exposure to and higher burden of HPV infection and HPV-related disease in young women, and it is likely that it is this exposure that increases the risk of cervical cancer.[21] Cigarette smoking is an established risk factor for both persistent HPV infection and progression to cervical cancer. It has been shown that nicotine metabolites can be found in the cervical mucus of women who smoke.[22] Very high parity, long-term use of oral contraceptives, poor diet and other sexually transmissible infections (STIs) such as *Chlamydia trachomatis* and herpes simplex have also been found to be risk factors for cervical cancer.[9,21,23] Socioeconomic status variables such as poverty and education have also been shown to be associated with increased risk of cervical cancer.[24] Immunosuppression, which may occur as a result of HIV infection or appear among transplant recipients, is a risk factor for HPV infection and there is consistent evidence that HIV-positive women have higher prevalence of HPV infection and increased risk of cervical cancer.[25,26] It is possible that the higher parity, higher STI rates, higher immunosuppression due to diabetes or HIV, and higher smoking rates among Indigenous Australian women compared with non-Indigenous Australian women[27–29] may contribute to their disproportionately higher cervical cancer incidence.

While several factors have been found to be associated with an increased risk of cervical cancer, it is difficult to determine whether these factors are truly risk factors associated with cervical cancer or merely co-incidental findings, given the challenges of effectively eliminating confounding by HPV in any analysis of cervical cancer.

Vulval cancer

Cancer of the vulva is generally rare among women worldwide. About 60% of vulvar cancer cases occur in developed countries. Vulvar cancer occurs mainly in older women, with ~66% of cases diagnosed among women older than 70 years. The majority of cases are squamous cell in origin (90%) and there are two distinct histological patterns with two different risk profiles. These are the basaloid (warty) types and the keratinising types.[30] The majority of vulvar carcinomas are of the basaloid type; these occur mainly in younger women, are associated with HPV and have similar risk factors to those for cervical cancer. In contrast, keratinising vulvar carcinomas are more likely to be HPV negative and to occur in older women.[30] A recent meta-analysis of 63 studies including 1873 cases of vulvar cancer found an overall HPV prevalence of 40.4% with HPV-16 present in 32.2% of cases, HPV-33 in 4.5% and HPV-18 in 4.4% cases; 2.8% of cases had multiple HPV types.[31]

Vulval cancer is rare in Australia (264 cases diagnosed in 2005), with an age standardised incidence of 2.3 per 100 000 women.[32] There has been no change in the incidence of vulvar cancer over the past two decades (Table 1, Fig. 2).[33] However, there is evidence of an increasing number of cases of vulvar cancer being diagnosed in younger Indigenous women. A recent analysis of vulvar cancer cases diagnosed in the Northern Territory found that the age adjusted incidence of vulvar cancer among Indigenous women aged 0 to 49 years living in remote communities in the East Arnhem district on the north coast of the Northern Territory was 31.1 per 100 000 (95% CI: 13.1–49.1), over 50 times higher than the national Australian rate for the same age group.[34] Possible causes for this high

Table 1. Estimated annual percentage change in age standardised incidence rates of human papillomavirus (HPV)-associated cancers and control HPV-unrelated cancers of the oral cavity between 1982 and 2005

Cancer site	Sex	Estimated annual percentage change	*P*-value
Cervix	Female	–3.38% (–3.91%, –2.86%)	<0.001
Anus	Female	1.59% (0.99%, 2.19%)	<0.001
Anus	Male	2.58% (1.80%, 3.36%)	<0.001
Vulva	Female	0.15% (–0.39%, 0.70%)	0.579
Vagina	Female	–0.31% (–1.06%, 0.44%)	0.412
Penis	Male	–0.49% (–1.26%, 0.28%)	0.209
HPV-related oral cavity and pharynx	Male	0.98% (0.62%, 1.34%)	<0.001
HPV-related oral cavity and pharynx	Female	1.00% (0.38%, 1.63%)	0.002
HPV-unrelated oral cavity and pharynx	Male	–1.74% (–2.01%, –1.46%)	<0.001
HPV-unrelated oral cavity and pharynx	Female	–0.36% (–0.78%, 0.05%)	0.084

incidence are unclear, but possibilities include a very high prevalence of oncogenic HPV genotypes, presence of a highly virulent variant of an oncogenic HPV genotype, genetic susceptibility to another cause of vulvar cancer, high prevalence of immunosuppressive conditions such as diabetes or HIV, a very high prevalence of smoking; or a combination of these factors.[34]

Vaginal cancer

Cancer of the vagina is also a rare cancer. Unlike vulval cancer but similar to cervical cancer, the majority of cases (68%) occur in developing countries. Most vaginal cancers are squamous cell carcinomas. Vaginal cancer is diagnosed primarily in older women over the age of 65 years, with a median age of diagnosis of 69 years.[30] Vaginal cancer is very rare in Australia, with 76 cases diagnosed in 2005, giving an age standardised incidence of 0.7 per 100 000 women.[32] The incidence of vaginal cancer increases with age and has been static over the past two decades[33] (Table 1, Fig. 2).

Vaginal and cervical cancer share similar risk factors, including a strong association with HPV. Women with vaginal cancer are more likely to have a history of other ano-genital cancers, particularly of the cervix.[30] A recent meta-analysis of 14 studies including 136 cases of vaginal cancer found that HPV was present in 69.9% of cancers, with HPV-16 in 53.7% of cases, HPV-18 in 7.6% and HPV-31 in 5.6% of cases; 3.4% of cases had multiple HPV types.[31]

Data from two recently conducted randomised trials of HPV vaccines in young women demonstrated a 95% reduction in a combined endpoint of high grade vaginal or vulval intra-epithelial neoplasia realted to HPV-16 and -18 in women who were initially unexposed to HPV.[35]

Penile cancer

Internationally, rates of penile cancer in developed countries vary from 0.1 to 1.5 per 100 000 but exceed 4 per 100 000 in some less developed countries.[36,37] It is rare in countries where universal infant circumcision occurs.[37] Almost all cases (95%) of penile cancer are of squamous cell origin. The most common histological type, comprising ~50% of cases, is the keratinising type, and the next most common type is the basaloid (warty) type. Generally, penile cancer is a disease of older men, with a mean age of diagnosis of around 60.[37] In Australia, rates of penile cancer were constant over the period 1982–2005 (Table 1). In 2005, only 69 cases were diagnosed, giving an age-standardised incidence rate of 0.7 per 100 000 (Fig. 3).[32]

HPV is found in a substantially lower proportion of cases of penile cancer than for cervical or anal cancer, and it is hypothesised that there may be two aetiologically distinct forms, with one being unrelated to HPV. Two recent meta-analyses have examined HPV prevalence in penile cancer.[36,38] These reviews of more than 1000 cases reported an overall HPV prevalence of almost 50%, ranging from ~65% in the basaloid types to ~20% in the verrucous type. HPV-16 is the most common subtype detected, followed by HPV-18, HPV-6 and HPV-11. In addition to HPV, risk factors include being uncircumcised and phimosis (which only occurs in the uncircumcised). A recent randomised controlled trial of adult circumcision demonstrated that circumcised men had a lower prevalence of penile HPV infection. These data suggest that circumcision may protect against penile cancer by prevention of penile HPV infection.[39]

Anal cancer

The anal canal covers a region comprising columnar epithelium in the upper zone, a transitional zone and squamous epithelium in the lower zone. Most anal cancers arise at or around the squamo-columnar junction. For this reason, anal cancers can be either squamous cell carcinomas or adenocarcinomas. As adenocarcinomas may have actually arisen in the rectum, it is usually regarded as preferable to examine squamous

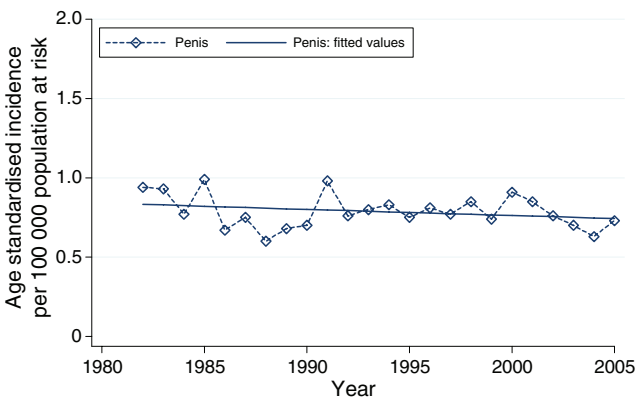

Fig. 3. Age standardised incidence of penile cancer in men, Australia, 1982–2005.

cell carcinomas of the anus separately.[40] Squamous cell carcinomas comprise ~70% or more of anal cancer diagnosed in populations of European origin[40] and now comprises ~85% of anal cancer in the US.[41]

Internationally, the incidence of anal cancer is less than 2 per 100 000 per year in most populations.[42] However, data from Europe, the USA and Australia are consistent in showing that the incidence has increased substantially in men and women over the past 30–50 years.[40,43] In the UK, this has applied particularly in those born since 1940.[43] In most settings, the incidence of anal cancer is higher in women than in men. Survival from anal cancer is highly dependent on the stage of diagnosis. Five year survival varies from ~80% with localised anal cancer to 20% for those with metastatic disease.[40]

In Australia, incidence of anal cancer increased significantly ($P < 0.001$) in both sexes from less than 1 per 100 000 in 1982 to around 1.5 per 100 000 in 2005 (176 diagnoses in women and 149 diagnoses in men in 2005). The average rate of increase was 1.6% in females and 2.6% in males (Table 1). Although this cancer was previously more common in women, by 2005, the sex ratio was almost 1 (Fig. 4).

HPV is causally associated with anal cancer.[3] About 85% of anal carcinoma specimens are HPV positive[31,44] and evidence suggests an even higher proportion among homosexual men.[45] Of HPV positive specimens, HPV-16 accounts for a large majority of cases (>75%), and HPV-18 is less frequent than in cervical cancer (<10% of HPV positive specimens).[31] In total, ~80% of cases are associated with those oncogenic HPV types covered by the currently available vaccines.

Given the causal association of anal HPV infection with most cases of anal cancer, it is not surprising that risk factors for anal cancer are mostly those of anal HPV infection and for disturbed control of anal HPV infection.[42] The first of these risk factors is a history of receptive anal intercourse. Anal HPV infection is almost universal in sexually active gay men in Australia,[46] and rates of anal cancer are ~30-fold higher in homosexual men compared with other men.[47] Immune deficiency leads to disturbed control of anal HPV infection, and rates of anal cancer are increased ~30-fold in men and women with HIV and ~5-fold in organ transplant recipients receiving immune suppressive medication.[48] Rates of pre-invasive anal intra-epithelial neoplasia are also greatly increased in people with HIV, especially in those with the most severe immune deficiency.[49] Although rates of many other HIV-associated cancers have declined since the widespread introduction of antiretroviral therapy, this has not been the case for anal cancer, and there is some evidence that rates have even increased in some populations. In HIV-positive homosexual men, standardised incidence ratios of 40 have recently been reported in Australia,[50] and rates of more than 50 per 100 000 have been reported in some populations.[49] Tobacco smoking is an additional risk factor for anal cancer, both among cases where the tumour is HPV positive and HPV negative.[45]

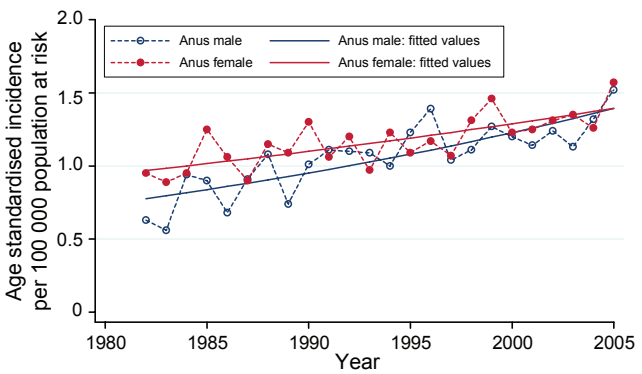

Fig. 4. Age standardised incidence of anal cancer in women and men, Australia, 1982–2005.

An ongoing randomised controlled trial of the efficacy of the quadrivalent vaccine in young men has included a substudy of young men who have sex with men, and the efficacy of the vaccine in preventing persistent anal infection was measured in this subgroup.[2] Results presented at a conference in early 2010 demonstrated a 78% HPV vaccine efficacy against anal intraepithelial neoplasia and anal cancer related to HPV-6, -11, -16 and -18 (95% CI: 40–93%).[51]

As anal cancer morbidity is concentrated greatly among homosexual men, screening for cancer precursors in a manner analagous to cervical cancer screening has been advocated by some.[49] However, the lack of prospective data showing that anal cancer screening reduces mortality, and the lack of availability of a highly efficacious treatment, has hindered the wider introduction of screening. In addition, the natural history of the pre-invasive lesion is poorly understood, and high progression and regression rates have been described.[52]

Oral cavity and oropharyngeal cancers

Oral cavity and oropharyngeal cancers comprise a heterogenous group of squamous cell carcinomas that arise from the mucosal lining of the oral cavity and oropharynx. They are categorised anatomically as arising from the tongue, tonsil, oropharynx, mouth and larynx. For therapeutic purposes and for epidemiological description, they have often been combined with adjacent sites to form the grouping of 'head and neck cancers'. In fact, it is clear there is substantial aetiological heterogeneity among these subtypes. Those sites known to be most closely related to HPV infection (base of the tongue, tonsils and oropharynx) appear to occur at younger ages and are increasing in incidence.[4] Those sites that appear to be mostly related to alcohol and tobacco exposure (tongue, gums, floor of mouth, palate and other sites within the mouth) occur at older ages and are decreasing in incidence.[4]

Internationally, incidence rates of oral cavity and oropharyngeal cancers vary widely and tend to be highest where alcohol and tobacco exposure (whether smoked or chewed) is high.[53] In the USA, rates of HPV-related oral squamous cell carcinomas increased during 1973–2004, whereas the incidence of HPV-unrelated oral cavity squamous cell carcinomas declined,[4,54] probably in relation to declining cigarette consumption.[55] Incidence has increased most dramatically for tonsillar cancer,[56,57] the oral cancer site most closely linked with HPV infection. In Australia between 1982 and 2005, the incidence of HPV-related sites in the oropharynx increased by ~1% per year in men and women ($P < 0.001$ and $P = 0.002$, respectively). The incidence of HPV-unrelated sites

decreased by 1.7% per year in men ($P<0.001$) and 0.4% per year in women ($P=0.08$). (Table 1, Fig. 5).

Recent reviews of HPV prevalence in head and neck cancer[58,59] have concluded that the prevalence of HPV is higher in oropharyngeal cancers (35%) than in oral cavity and laryngeal cancers (~25%). The association appears strongest for the tonsils, where the prevalence of HPV has increased in recent years and is now reported as being up to 80%.[57] HPV positive oropharyngeal tumours appear to be a distinct clinical entity, with an improved survival over HPV negative cases.[60]

The role of HPV in oropharyngeal cancers has been supported by recent findings that a history of higher numbers of sexual partners is associated with oropharyngeal cancer[61] and that oral sexual behaviours increase the risk of oral HPV infection in young adults.[62] In one case-control study, sexual behaviour was a risk factor for HPV-positive oral cancers, but was not a risk factor for HPV negative tumours.[63] Globally, tobacco and alcohol exposure remain the most common causes of head and neck cancers, despite what appears to be an increasing role of HPV infection.[64]

Number of cancer cases potentially preventable by HPV vaccination

In Table 2, data are summarised on the percent of cancers at each of the above sites that are believed to be causally attributed to HPV, and the proportion of those cases that are due to HPV types

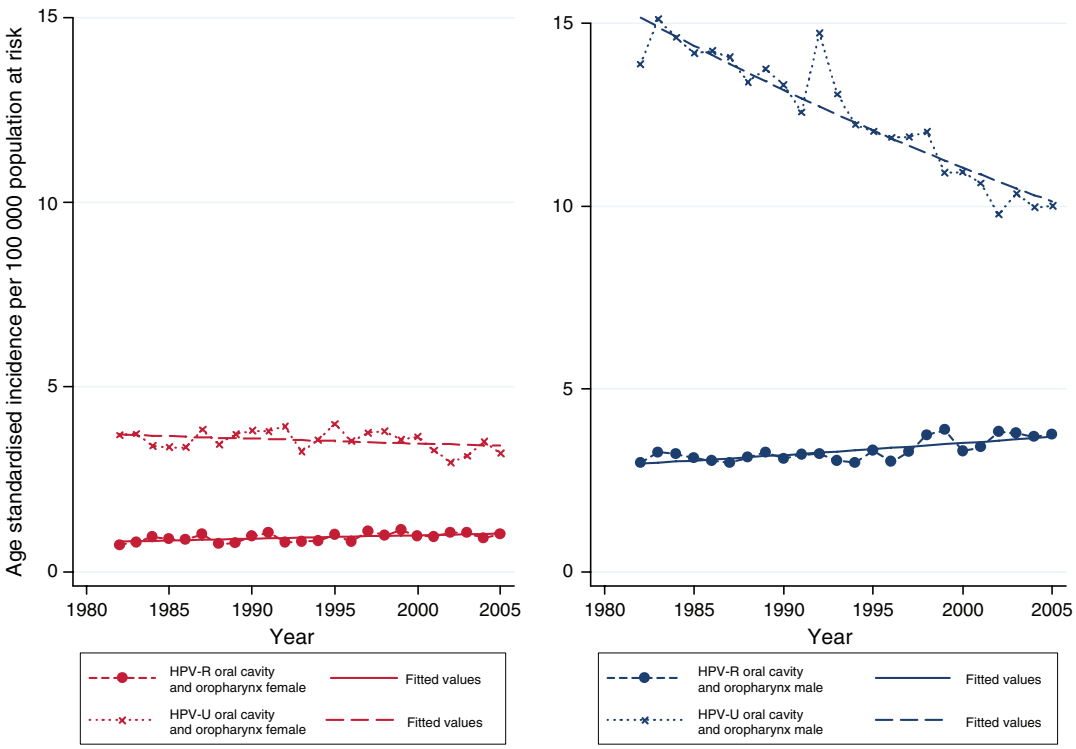

Fig. 5. Age standardised incidence of HPV-related (HPV-R) and HPV-unrelated (HPV-U) cancers of the oral cavity and oropharynx in women and men, Australia, 1982–2005.

Table 2. Number of incident cancers in Australia in 2005 at human papillomavirus (HPV)-related sites by sex,[32] percent due to HPV, and percent due to HPV-16 and HPV-18: potentially preventable cases

	Women (*n*)	Men (*n*)	% of cases due to HPV (references)	% of HPV associated cases due to HPV-16 and -18 (reference)	Cases potentially preventable by the HPV-16 and -18 vaccine Women (*n*)	Men (*n*)
Cervical cancer	734	–	100[17]	76[65]	558	–
Vulval cancer	264	–	40[31]	86[65]	91	–
Vaginal cancer	76	–	70[31]	88[65]	47	–
Penile cancer	–	69	50[36,38]	87[65]	–	31
Anal cancer	176	149	85[31]	93[65]	140	118
Cancer of the base of tongue and oropharynx	114	395	35[58]	95[65]	38	131
Total	1364	613			874	280

16 and 18. The total number of cancers related to HPV-16 and HPV-18 was 1154; 558 (48%) were in the cervix and 596 (52%) were at other sites.

Conclusion

The introduction of the HPV vaccine in Australia heralds a new era in cancer control, with prophylactic vaccination joining the toolbox of cancer prevention. Although the vaccine was introduced to prevent cervical cancer, the evidence presented in this review suggests it is likely to protect from a range of other HPV-related cancers. Randomised trial data have already demonstrated a high degree of protection against pre-cancerous lesions of the vulva and vagina,[2,35] and anus.[51] New methods of diagnosing HPV infection in the pharynx are required to allow the determination of the potential benefit of HPV vaccination in preventing oral cavity and oropharyngeal cancer.

If the HPV vaccine is as effective in preventing other HPV-related cancers as it is in preventing cervical cancer, then this vaccine shows even greater promise in cancer prevention. It was notable that 52% of preventable cases occurred at sites other than the cervix. This proportion is likely to be an under-estimate, as the potential role of HPV in head and neck sites other than the oropharynx was not included. Twenty-four percent of all cases related to HPV-16 and -18 (280) occurred in men. Although heterosexual men are likely to gain some protection against HPV-16 and -18 infection from the rollout of vaccination in women through herd immunity, this will not offer complete protection, and homosexual men will not be protected from infection at all. HPV-16 and -18 vaccination of men has the potential to prevent a substantial cancer burden.

Conflicts of interest

Andrew Grulich is on the advisory board for the Gardasil quadrivalent human papillomavirus vaccine, and has received research funding from CSL, the Australian distributor of the Gardasil vaccine. Alicia Stein and Lynne Conway are employees of CSL.

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