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REVIEW PAPER

Human Papillomavirus Associated Cancers of the Head and Neck: An Australian Perspective

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Abstract Human papillomavirus (HPV) associated head and neck squamous cell carcinomas (HNSCCs), have become a serious global health problem. Despite decreases in HPV-negative HNSCCs, the prevalence of HPV-positive HNSCCs has significantly increased. HPV-positive cancers are associated with superior survival outcomes when compared to HPV-negative cancers, which appears likely to be associated with differences in the molecular pathogenesis of the two diseases. While therapies are still problematic, the current HPV vaccine programs hold a promise for the primary prevention of HPV-related HNSCCs and since Australia was the first to introduce a nationwide HPV vaccine program, it is in a unique position to observe the effects of the vaccine on HNSCCs. This review discusses the epidemiological trends associated with HPV in HNSCC, with reference to the differences between HPV-positive and HPV-negative HNSCCs and the prevention potential of HPV vaccines.

Keyword Human papillomavirus · Head and neck squamous cell carcinoma · Oropharyngeal squamous cell carcinoma · Vaccine

Introduction

Head and neck squamous cell carcinoma (HNSCC) is an emerging disease that is relatively common, and characterized by high morbidity and high mortality. Collectively, HNSCC is among the six most commonly diagnosed malignancies worldwide [1]. Most of these carcinomas arise in the epithelial lining of the oral cavity and differ in biology, pathogenesis, histological features, location, and treatment response [1]. According to the Australasian Association of Cancer Registries (AACR), there are 18 different anatomical sites categorised as head and neck cancers, including the oral cavity, larynx, oropharynx, hypopharynx, nasopharynx, and sinonasal tract [2]. Globally, head and neck cancer incidence varies by geographical location and gender, much of which can be attributed to the differences in the prevalence of smoking and alcohol consumption, betel quid/areca nut consumption in different populations as well as the emergence of the human papillomavirus (HPV) as a causative agent [3, 4]. In general, the age—standardization frequency of head and neck cancer worldwide is 8.1 per 100,000. In 2008, some 550,319 new head and neck cancer cases were diagnosed worldwide, while in 2012 that number grew to 599,637 with 324,834 related deaths [5, 6].

Globally, the highest incidence rate estimated is in Europe with 99.6 cases per 100,000 while Middle Africa (3.4/100,000) has the lowest rate [3, 7]. North and South America, Australia and New Zealand as well as the Caribbean Islands have reported estimates that are above the worldwide estimates while rates through Asia and Africa are below the worldwide rate [3, 6]. Interestingly, males account for much higher proportion of head and neck cancer cases worldwide, estimated to be threefold higher compared to females, male to female ratio ranges from 2:1 to 4:1 [3, 6]. The global death rate from head and neck cancer is 4.4 per 100,000 with females, showing a mortality rate that is nearly fourfold lower than males (2.0/100,000 vs. 7.1/100,000) [3, 6].

In Australia, the number of new cases diagnosed with head and neck cancer is rising, where the number of cases

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increased from 2475 in 1982 to 3121 in 2011, accounting for 3.4% of all cancer cases. Australian males have a higher proportion of HNSCC, accounting for 73.8% (2875) of cases compared to 26.2% (1021) female cases diagnosed in 2009 [2].

In 2012, the total numbers of deaths due to HNSCC accounted for approximately 2.2% (973) of all cancer deaths in Australia. Death rates due to HNSCC were higher for males with 691 deaths (73.2%) compared to 253 (26.8%) for females reported in the same year [2]. In addition, the 5-year survival rate between 2006 and 2010 was relatively stable, at 68.2% of all head and neck cancers combined in Australia [2].

This review examines the causes of HNSCC together with emerging trends of this disease in Australia, as well as the possible impact of the HPV vaccine. Since Australia was the first country to introduce a nationwide HPV vaccine programme, it is in a unique position to observe the early effects of the HPV vaccine on HNSCC.

Epidemiology of Head and Neck Squamous Cell Carcinoma (HNSCC)

Tobacco use and alcohol consumption are the well-known behavioural risk factors associated with head and neck cancer [8, 9]. In addition chewing betel quid/areca nut in the Indian sub-continent and Southern Asia has been shown to be associated with oral cancers [4]. Other factors may include genetics, environmental and occupational hazards [9, 10]. Interestingly, people in occupations related to wood and/or leather work have a 20 fold increase in sinonasal squamous cell carcinoma while smoking only increases the risk by two or three fold [11]. In the last 20 years, smoking and alcohol use has declined considerably in the developed world [12–16], which contributed to a significant decrease in HNSCC cases related to smoking and alcohol [14, 17]. In Australia, tobacco use in males was highest (70%) in the 1930s–1940s [18] and has declined significantly over time to 16.4% in 2010 in males aged 14 and older. In 2010, 38% of Australians smokers aged 14 years or older also consumed alcohol at high levels, compared to people who had never smoked [18].

Oropharyngeal squamous cell carcinomas (OPSCC) are increasing markedly worldwide, and have been linked to the emergence of HPV as a risk factor [14, 16]. In 2008, there were 85,000 OPSCC cases globally and approximately 22,000 of these cases were HPV positive [19]. Chaturvedi et al. estimated that HPV-positive OPSCC incidence will be greater than cervical cancer by 2020, and 50% of these cases will be related to HPV by 2030 [20]. The increase in incidence and mortality rates of HPV-associated OPSCC is well reported in Australia, European countries, and North America [20–24], but such a trend has not been well documented in Asia, South America, and Africa [22, 24]. This worldwide variation in the incidence of OPSCC could be due to activities related to differences in culture, socioeconomics, and geographical background [25].

According to the Australian Institute of Health and Welfare, the number of pharynx including nasopharynx and oropharynx (the base of the tongue, and the tonsils) as well as hypopharynx cancer cases diagnosed is rising [2]. Pharynx cancer rates increased from 2.9/100,000 in 1982 to 3.2/100,000 in 2009, which accounted for approximately 19% of all new cancers diagnosed in 2009 [2]. In addition, death rates for pharynx tumours remained relatively stable over that period at around 1.2 deaths/100,000, with males accounting for a much higher mortality rate [2]. In general, 5-year relative survival between 2006 and 2010 was higher for all HNSCC cancers, with 55.5% (54.8% for males and 58.2% for females) than for pharynx cases [2].

Several studies have hypothesised that changes in sexual behaviour such as increasing the number of sexual partners and oral-sex partners, early age sexual debut and same sex sexual contact, might contributed to the increase incidence of HPV-positive OPSCC cancers [23, 26, 27]. Rissel et al. reported that number of sexual partners, oral and anal sex experiences have increased between 2001–2002 and 2012–2013 among Australian adults [28]. Increasing HPV-positive oropharyngeal cancers are consistent with differences in sexual behaviour; however, it is unclear whether the higher prevalence of these malignancies in the oropharynx is due to the natural history of oral HPV or changes in sexual behaviour [15, 23, 26].

Human Papillomavirus

HPV is a circular, non-enveloped, double-stranded DNA virus. The viral genome, consisting of approximately 8 kb in size, encodes two regulatory proteins (early genes E1 and E2), three oncoproteins (E5, E6, and E7), and two structural capsid proteins (late genes L1 and L2) [29, 30]. To date, over 150 strains of HPV have been completely sequenced [31]. HPV can infect cutaneous or mucosal sites; cutaneous types include HPV 2, 3, 10, and 57 causing common warts and flat warts [31]. Mucosal HPV are categorized into high-risk HPV and low-risk HPV groups, according to their ability to transform epithelial cells [3]. The WHO defines 12 HPV types as being high-risk cancer causing types, and further eight types are regarded as possible cancer causing [31]. High-risk HPV genotypes such as HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 are capable of transforming mucosal epithelial cells and introducing malignant lesions, while low-risk HPV genotypes such as HPV 6, 11 are associated with benign lesions

such as warts or condylomas [3, 30, 31]. Benign lesions in the oral cavity are common, and most often involve HPV 6 and 11. These HPV genotypes are also often associated with uncommon benign conditions in the larynx such as laryngeal papillomatosis and laryngeal polyps [3]. Epidemiological studies have shown that HPVs are present in humans almost globally, however, infection with high risk strains can lead to development of cancer only in a small fraction of cases [32].

HPV Oncogenic Mechanisms

The association between HPV and cancer has been extensively studied in cervical squamous cell carcinoma, where HPV 16 and 18 are the causative agents for most cervical carcinomas [33, 34]. Mucosal HPVs are mostly sexually transmitted and infect the genital region. These viruses are crucial but not sufficient on their own to cause cervical cancer. In addition, HPV has also been reported to be connected to the development of other squamous cell cancers such as HNSCC [15], and it has been reported that HPV 16 is responsible for at least 90% of HPV-HNSCCs [27, 31–34]. The malignant transformation starts by the integration of high-risk HPV DNA into the host cellular genome that disrupts the expression of the gene encoding the E2 protein [34, 35]. This disruption results in overexpression of the viral E6 and E7 oncogenes, as E2 act as a transcriptional repressor of these oncogenes [35]. The E6 onco-protein binds to the tumour suppressor protein p53 and signals the cellular degradation of p53, which results in genomic instability through deregulation of both G1/S and G2/M cell cycle checkpoints [36–39]. The HPV E7 can induce cellular proliferation by binding and mimicking phosphorylation of the retinoblastoma tumour suppressor protein (pRb) leading to uncontrolled G1/S phase of cell cycle [36–39].

In addition, pRb inactivation results in upregulation of $p16^{INK4A}$ (p16) tumour suppressor protein, and most HPV associated HNSCC show p16 overexpression as detected by immunohistochemistry assay [40]. One study reported that p16 overexpression in lymph node metastases in HNSCC is a marker for HPV-positive oropharyngeal cancers [35]. In contrast, downregulation of p16 expression is common in HPV-negative HNSCC, and usually is associated with mutation in the TP53 gene that encodes for p53 [35].

The molecular mechanisms between HPV infection in cervical cells and in oropharyngeal cells are likely to be similar [31], however, HPV genome integration and E6/E7 mRNA expression in various HNSCC subtypes is more complex. In a HPV E6/E7 expression study, it was reported that unlike cervical cancer, HPV 16 E6/E7 mRNA transcription in malignant tonsillar tumour can occur in the absence of HPV DNA integration [35], while in a recent study it was reported that 88% of oropharyngeal squamous cell carcinomas had some integrated HPV and that solely episomal HPV was uncommon [34]. At present, the significance of episomal HPV and the ability of the virus to proliferate in an episomal form with a high copy number in host cancer tissues remain unclear [34, 35].

HPV-Positive and HPV-Negative Cancers

HPV-associated HNSCC have different risk factors, clinical characteristics and tumour biology when compared to tobacco/alcohol-associated HNSCC [38]. The disease entities of HPV-associated HNSCC are remarkably distinct from those of HPV-negative [30]. HPV-positive cancers are driven by oncogenes E6 and E7 interaction with p53 and pRb pathways, and have the feature of p16 upregulation [15, 30, 37–41]. By contrast, HPV-negative HNSCC are characterized by mutations in TP53 and pRb genes with p16 downregulation [15, 16]. The most common alterations in HPV-negative HNSCCs are p53 mutations resulting in genomic instability, drug resistance as well as reduced survival after surgery [16] (Table 1). In an exome sequencing study, higher p53 mutations rate were reported in tobacco-related tumours compared with HPV-positive HNSCC [42].

In addition, patients with HPV-associated HNSCC cancers have more favourable survival outcomes compared to HPV-negative individuals [15, 23]. Patients with

Table 1 Characteristics of HPV-positive and negative HNSCC

Characteristic	HPV-positive	HPV-negative
Incidence	Increasing	Decreasing
Subsite	Primarily oropharyngeal	All HNSCC
Main risk factors	Sexual behaviour	Alcohol and tobacco
Mean age at diagnosis (years)	~55	~60
p53 status	Wild-type	Mutated
p16 expression	Over expression	Decreased expression
Chemo-radiotherapy and recurrence	Better	Comparatively less
Prognosis (5 years OS)	75%	25%

HPV-positive malignancies are usually diagnosed at later stage (65–93%) based on nodal involvement [15] (Table 1). In a recent study, Klozar et al. compared prognostic parameters in patients with HPV-related, and HPV-negative HNSCC tumours, and results showed a better survival in those with HPV-positive tumours, regardless of lymph node metastasis [43]. Similarly, a meta-analysis of 37 studies concluded that patients with HPV-positive HNSCC had lower risk of overall death and recurrence as compared with HPV-negative patients [44].

Patients with HPV-associated HNSCC often had less history of smoking and drinking [22, 24]. These patients usually are younger than HPV-negative patients [21, 23] (Table 1). Hocking et al. investigated oropharyngeal and oral-cavity cancer rates in Australia in 1982–2005 and showed that HPV-positive patients were diagnosed at younger age compared to HPV-negative individuals [23]. Similarly, a phase 3 clinical trial showed a strong association between tumour HPV status and overall survival among patient with HPV-positive oropharyngeal cancers receiving radiotherapy and cisplatin. This study reported that patients with HPV-positive cancers were younger and had a reduced amount of smoking exposure [45].

Furthermore, HPV-positive HNSCC are likely to be preventable by vaccination [37]. A randomize clinical trial by Herrero et al. showed that bivalent HPV vaccination reduces the prevalence of oropharyngeal HPV 16/18 infection by 93.3% in the vaccine cohort compared to the control group [46]. This suggests that HPV vaccination may have strong protection against oral HPV infection, and potentially reduce the incidence of HPV-positive oropharyngeal cancer in the future.

HPV-Positive Head and Neck Cancers

HPV associated malignancies of the head and neck vary by site and arise mainly in oropharyngeal sites [3, 23], such as tonsils, base of tongue, and other oropharynx, while other oral sites, such as the ventrolateral tongue, gingivae, cheek, palate, and floor of mouth shows less HPV association and are mainly attributed to tobacco and alcohol use [3, 47]. The incidence of HPV-positive OSCC has increased worldwide [38, 48, 49]. In the oropharynx, tonsillar tumours followed by base of tongue cancers have the highest HPV prevalence rate [3, 12, 22, 50, 51], and these two carcinomas account for 90% of all oral squamous cell carcinomas [3]. Increased incidence of oropharyngeal cancers has been observed in developed countries, where HPV has consistently been detected in these cancers [3, 22]. In Europe, the incidence of HPV-related tonsillar cancers increased from 23% during 1970–1979 to 93% during 2006–2007 [52] and similar increases in HPV-positive base of tongue cancers has been reported [7, 12]. Furthermore, the association between HPV and oropharyngeal cancer was demonstrated by HPV DNA isolated from OPSCC tumours and an increase in seropositive for HPV antibodies in OPSCC patients [22]. Gillison et al. reported that oropharyngeal tumour samples were more likely to have HPV DNA compared to non-oropharyngeal specimens [17].

In Australia, HPV-positive tumours are also highest in the tonsil and base of tongue cancers [23]. During the period from 1982 to 2005, 8844 cases of HPV-positive oropharyngeal cancers were reported, of these tonsillar cancers accounted for 44.1% followed by tongue cancer (29.5%) and other oropharyngeal cancers (26.4%) [23]. In addition, the annual percentage of HPV-positive cancers for both males and females significantly increased during this period [23].

Treatment and Vaccination

Traditionally, HNSCC were treated using extensive surgical removal of tumours. However, surgery has a high rate of mortality due to the difficulty to access tumours within the oropharynx. In addition, these therapies affect critical functions such as speech and swallowing [24]. Non-surgical treatment options, such as radiotherapy and chemotherapy are often added to standard treatments and improve treatment outcomes [24, 40]. As with many other solid tumours, the effectiveness of HNSCC treatment reduces with more advanced stage of the disease [53]. In a randomized study that included oropharyngeal cancer patients with advanced stage cancers, radiation therapy alone or in combination with chemotherapy were tested. Results showed significant improvement up to 3-years survival and longer disease-free period in the combination therapy group [54]. However, even with the noticeable improvement using these techniques, several side effects can affect outcomes. Surgery carries high risk of morbidity and chemotherapy has the risk of post-treatment swallowing dysfunctions. In addition to several side effects, these treatment therapies are costly and do not prevent HPV infections and cancers [54]. It is also emerging that there is a subset of HPV positive head and neck cancer that are less responsive to chemo-radiation therapy and gene expression biomarkers may be needed to identify these [55].

According to the Australian Institute of Health and Welfare, the number of surgeries performed for HNSCC increased from 16.5/100,000 in 2002–2003 to 18.7/100,000 in 2011–2012. Over the same period, rates for HNSCC involving radiotherapy changed from 0.1/100,000 to 0.6/100,000 and for chemotherapy from 12.9/100,000 to 19.8/100,000 [2].

Table 2 Estimated reductions in new HPV 16 infections in males and females, relative to pre-vaccination levels in Australia

Proportional reduction in HPV 16 infections, relative to pre-vaccination levels in 2006	Current program		PLUS male vaccination (with catch-up)—low coverage		PLUS male vaccination (with catch-up)—high coverage	
	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
2010	26	41	26	41	26	41
2020	44	62	54	64	62	67
2050	68	85	81	89	92	94
Post-vaccination equilibrium (~2075–2085)	73	89	87	93	99	99

Smith et al. [61]

Unlike HPV-negative HNSCCs, HPV-positive tumours are quite sensitive to treatment [30], however, regardless of the available treatments for the cancer, there is currently no specific treatment for the HPV infections [54]. Two HPV prophylactic vaccines, however, have been developed and are currently used against HPV infection. A quadrivalent vaccine, Gardasil, developed by Merck & Co., targets HPV types 6, 11, 16, and 18. This vaccine was first licenced in 2006 for use in females aged 9–26 years old for the prevention of cervical cancer, vulvar, and vaginal cancer [56–58]. The licence was expanded to include males aged 9–26 in 2009, where clinical trial data demonstrated the effectiveness of the vaccine in preventing anal cancer [59] and genital warts [30]. Another bivalent vaccine, Cervarix®, developed by GlaxoSmithKline targets HPV types 16 and 18. Cervarix was licenced in 2009 for use in females aged 10–25 years old [30, 46, 56]. These vaccines are currently used for the prevention of cervical cancer and vulvar neoplasia in females and anal cancer in both males and females in the United States, Australia, and the European Union [56, 60–63].

Since the majority of HPV-related oropharyngeal cancers are caused by HPV 16, both vaccines would likely be effective in preventing HPV-positive HNSCCs. Nevertheless, clinical trials to study the impact of these vaccines on oral HPV infection have not been conducted, although clinical data have shown a decrease in the development of HPV oral lesions in immunized animal models. There does not exist a routine screening for HPV-positive oropharyngeal carcinomas [30] as there are no easily identified pre-cancerous lesions with HNSCCs [62]. Screening tests would allow the natural history of oral HPV infections in persons and the proportion of people with persistent oral HPV infection, who might develop HNSCC to be determined [30]. In addition, as the incubation period within HNSCC patients has not been fully defined, so the impact of vaccination on HPV-positive OPSCC could take several decades [61–63].

In 2007, Australia launched a National HPV Vaccination Program (NHVP) that provided HPV vaccine for females aged 12–13 years and in 2013 this was extended to include males [62]. In 2011, 71.2% of Australian females aged 15 participated in NHVP program and it has been suggested that this program may have an impact on the future incidence of HNSCC [23]. In addition, this existing program is predicted to reduce new HPV 16 infections in males by 68% by 2050 [61]. By expanding the routine vaccination program to include males 9–26 years of age in a catch-up program, it is estimated that this would result in an overall reduction in HPV 16 infection by 81–92% in males [61]. This would also presumably reduce HPV-related HNSCCs (Table 2).

Until recently, there were no studies to evaluate the effect of vaccines on HPV-associated OPSCC prevention [22]. Herrero et al. showed a reduction of 93.3% (95% CI = 62.5–99.7%) in HPV oral infections in those vaccinated against HPV 16/18 [46]. Longitudinal studies examining the effect of HPV vaccines on HPV-positive OPSCC have not been conducted, and are unlikely to happen soon as the long interval between HPV exposure and cancer diagnosis make such studies challenging and costly [62]. However, observational results on the effect of vaccine on HPV oral infections are encouraging and because most HPV-related OPSCC are caused by high-risk HPV16, it is likely that the vaccination would prevent oral HPV infections and consequently the development of OPSCC [22, 61]. Vaccine dose requirements have been investigated for cervical cancer but not for HNSCC [63]. Therapeutic vaccines are being investigated for HPV-positive carcinomas and the impact of these on HNSCC are yet to be addressed [3, 62]. Also, a cost per life saved analysis would be useful in determining benefits of the expanded vaccination programme for males.

In December 2014, the FDA approved the use of the nonavalent V503 vaccine (traded as Gardasil 9) which covers HPV genotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58. This vaccine appears to be safe and effective at preventing infection with the HPV genotypes listed [64]. Since HPV 16 is the cause of 90% of HPV positive head and neck cancers it would be unlikely that the nonavalent vaccine would

have a significantly greater impact than the current quadravalent vaccine. In a French study by Riethmuller et al. it was estimated that only 0–1.6% additional cases of oropharyngeal carcinoma would be prevented by the nonavalent vaccine over the quadravalent vaccine [65]. From this it would seem that both vaccine types would probably have the same approximate effectiveness in relation to head and neck cancers in Australia.

Conclusion

In summary, HPV infection is now recognized as a major risk factor for HNSCC. Over the past decade, epidemiological evidence reported a significant increase of HPV-positive OPSCC in Australia and worldwide [24]. HPV produces oncoproteins that induce malignant transformation by disrupting cell cycle control and proliferation [16]. HPV-positive HNSCC represents a distinctive pathological entity with different epidemiological characteristics compared to HPV-negative cancers, which result in different biological and clinical tumour behaviour. The growing burden of HPV-related carcinomas indicates a need for targeted therapies as well as prevention strategies for patients with such carcinomas [66]. HPV vaccination will likely prevent the development of HPV-associated HNSCC; however, further studies are needed to evaluate the efficiency of vaccines on these difficult tumours. Since Australia was among the first countries to implement a national HPV vaccination program, it is in a unique position for observing the effects of the vaccine on these cancers.

Compliance with Ethical Standards

Conflict of interest The authors (Brian Brestovac and Marwah Aldalwg) have no conflict of interests.

Research Involving Human and Animal Participants This article does not contain any studies with human participants or animals performed by any of the authors.

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