HPV-associated Oropharyngeal Cancer: A Distinct Clinical Entity

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It is now widely accepted that cervical cancer cannot develop in the absence of Human papillomavirus (HPV) infection. Less well known is the link between HPV and oropharyngeal cancer (OPC). With falling smoking rates, OPC rates were expected to decline. However this has not occurred, potentially due to a rise in HPV-associated OPC. This literature review aims to provide a summary of the most recent data regarding risk factors, biomarkers and prognosis for HPV-positive OPC, and to compare these findings with HPV-negative OPC. In light of its improved prognosis, this paper will also discuss the potential merits of treatment de-escalation in cases of HPV-positive OPC. A search was carried out on PubMed with the keywords Human papillomavirus, oropharyngeal cancer, and head and neck cancer. The search focused on papers published in the past 5 years but did not exclude seminal or relevant studies published earlier. Conclusion: HPV-associated oropharyngeal cancer should be recognised as a distinct clinical entity, which stands in contrast to HPV-negative OPC with regards to its aetiology, risk factors, chemotherapy and radiation therapy sensitivity and therefore also prognosis. More research is required to determine appropriate treatment and public health strategies.

Introduction

Human papillomavirus (HPV) is a double-stranded DNA virus with over 100 genotypes, of which approximately 15 are considered to be oncogenic (Munoz et al, 2003). The causal relationship between HPV and the development of cervical cancer is now well established. In 1999, Walboomers et al. published findings that HPV infection is related to cervical cancer in 99.7% of cases, resulting in HPV being labelled a 'necessary cause' of cervical cancer (Walboomers et al, 1999). As a result, it is now widely accepted that cervical cancer cannot develop in the absence of HPV infection. This finding is of significant clinical importance, particularly with regards to implementation of public health campaigns. In Ireland, the HPV vaccine was introduced in 2010 for all girls in their first year of secondary school to induce HPV immunity in young women prior to virus exposure (usually before they become sexually active). This national initiative is supported by findings that the quadrivalent HPV vaccine against serotypes 6, 11, 16 and 18 was able to reduce rates of HPV infection by 90% and of high-grade cervical changes by 85% (Garland et al, 2016).

While the connection between HPV and the development of cervical cancer has now been proven beyond reasonable doubt, evidence for relationship between HPV and OPC is less well-known. However, it has been suggested that OPC will overtake cervical cancer as the most common HPV-related cancer (Chaturvedi et al, 2011). OPC is a cancer of the head and neck, with over 90% of head and neck cancers being of the squamous cell carcinoma (HNSCC) type. It has been found that the incidence of HNSCC has remained largely static in recent years. This is a surprising result, as traditionally HNSCC has been most strongly associated with tobacco smoking, and with decreasing smoking rates in the developed world one might expect to see a subsequent overall decrease in HNSCC rates (Ng et al, 2012). However, the decrease in smoking rates appears to have been balanced by an increased relative contribution to HNSCC by HPV-associated OPC, even being described as an 'epidemic' by some authors (Gillison and Shah, 2001; Pytynia et al, 2014; Okami, 2016).

HPV was initially thought to be the causative agent in only a minority (approximately 16-25%) of OPC cases (Gillison et al, 2000). However, evidence now suggests that HPV prevalence in OPC may be as high as 72%, with up to 90% of these cases being caused by serotype 16 (Leoncini et al, 2014; Kreimer et al, 2005). As HPV-positive rates increase across the world, HPV-negative (smoking-related) OPC rates have decreased by over 50%, much like other types of HNSCC (Maasland et al, 2014). Taking into consideration the striking increase in HPV-associated OPC rates, the remainder of this paper will briefly focus on the most recent data about risk factors and prognosis in relation to HPV-associated OPC. This paper will also discuss the potential merits of treatment de-escalation and vaccine prevention in cases of HPV-positive OPC.

Methods

A literature review was conducted using the biomedical search tool PubMed using keywords oropharyngeal carcinoma, human papillomavirus, HPV carcinogenesis, HPV biomarkers, OPC prognosis, HPV vaccination. An analysis on the current understanding of Human Papillomavirus and its role in oropharyngeal carcinoma was then carried out. Aspects such as risk factors for infection, pathogenesis, biomarkers, treatment and vaccination were considered.

Discussion

Risk factors for Oropharyngeal Carcinoma

Tobacco and alcohol consumption have long been associated with HNSCC (Leoncini et al, 2014; Maasland et al, 2014; Wyss et al, 2013; NIH, 2009). Thus patients with OPC in the 20th century characteristically were middle aged, of a low socio-economic status and smoked or drank alcohol. However, with the proportion of OPC attributed to HPV infection on the rise, the demographic characteristics of people diagnosed with OPC have shifted significantly. Patients now tend to be younger, with the primary risk factor being their level of sexual activity.
Genital HPV infection is the most commonly acquired sexually transmitted infection (Ankit et al, 2013). The incidence of oral HPV is on the rise, and disproportionately affects the young (30-50 years), leading to an increased rate of HPV-associated OPC in this group (Nguyen et al, 2010).

This pattern is hypothesised to result from changing patterns of sexual behaviour among younger generations. It has been observed for many years that increased sexual activity was correlated with an increased risk of developing OPC. With the development of technology to detect HPV DNA in mucosal cells, it has now been demonstrated that the above observation had been serving as a marker for an increased risk of exposure to HPV and thus an increased possibility of developing OPC. A case-control study in the USA found that recent oral sex and tongue-kissing were both connected with HPV infection of the oral mucosa, independent of vaginal sex (Jones, 2015). It was suggested that the relative popularity of oral sex among young adults may account for the rise in HPV-associated OPC in this age group (Nguyen et al, 2016).

A recent systematic review found that not only is oral sex a risk factor for developing HPV-associated OPC, but that the number of lifetime sexual partners also carries risk (Chancellor et al, 2016). The review notes, however, that some of the studies were poorly controlled.

For HPV to cause infection it must access the basal epithelioid cells (Cox, 2006), which is increased in likelihood by damage to

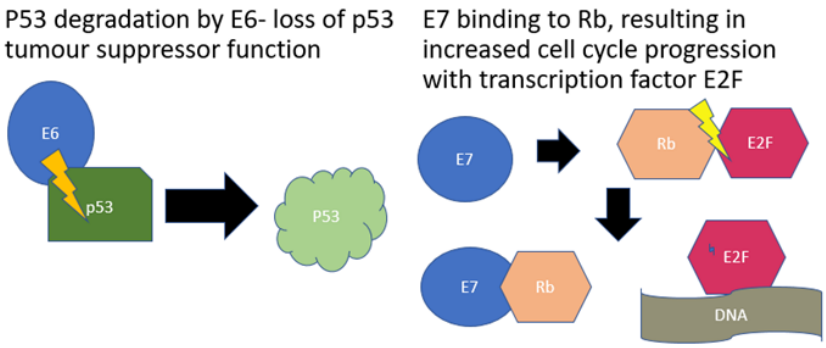

Figure 1: HPV DNA integrates into host DNA and amplifies transcription of oncogenic proteins E6 and E7. These proteins downregulate the action of tumour suppressor genes p53 and Rb, resulting in uncontrolled proliferation and thus cancerisation of the epithelial tissue.

the epithelium (Bui et al, 2013). Therefore, poor oral hygiene, chronic ulceration and inflammation might increase the ability of HPV to enter oral mucosa cells and cause infection, and thus increase the risk of OPC. Further studies are needed to clarify the exact risk oral sex, number of sexual partners and oral mucosal health play in the development of HPV-associated OPC.

Differentiating HPV-positive and HPV-negative Oropharyngeal Carcinoma

It has been found that the prognosis of an OPC diagnosis differs considerably depending on HPV status, making the distinction between the two aetiologies clinically significant (Weber et al, 2010). Research in the last decade has centred on the characterisation of proteins associated with HPV infection and carcinogenesis in an attempt to find suitable biomarkers to differentiate the two forms of OPC.

It has been found that HPV DNA integrates into host chromosomes and upregulates the production of several oncoproteins, such as E6 and E7 (Refer to Figure 1). P53 is a protein known as the 'guardian of the genome', which acts to induce apoptosis in damaged cells and therefore prevents cancer. E6 is upregulated by HPV and inhibits p53's protective actions.

P16 is a cyclin-dependent kinase (CDK) inhibitor, which acts as a check point inhibitor to control proliferation. P16 normally prevents Retinoblastoma protein (pRb) phosphorylation. This unphosphorylated pRb associates with E2F, a transcription factor, and prevents E2F from inducing cell proliferation. In a HPV-infected cell, oncoprotein E7 is produced, which causes dissociation of the pRb-E2F complex. This free E2F increases unregulated cell cycle progression and thus carcinogenesis (Zhang et al, 1999). P16 expression is reactively upregulated in HPV-associated OPC an attempt to counteract this E7-induced cell proliferation (Lewis James et al, 2013). Thus HPV-positive oncogenesis is characterised by p53 degradation, pRb inhibition and p16 upregulation. In contrast, HPV-negative (tobacco-related) OPC is typified by p53 mutation and p16 down-regulation (Elrefaey et al, 2014). Updates to the staging of OPC were devised in 2017 by the American Joint Committee on Cancer (AJCC) Staging Manual, Head and Neck Section to reflect these differences (Lydiatt et al, 2017). The AJCC found the tumour suppressor protein p16 to be a reliable surrogate biomarker and an independent prognostic factor in HPV-positive OPC. Identifying HPV-positive OPC via P16 immunohistochemical staining is also endorsed by the AJCC as it is an inexpensive test has near global availability, allowing for international adoption. Hence, OPCs are now staged according to two distinct sets of guidelines, depending on whether or not they overexpress p16.

Improved Prognosis for HPV-positive OPC

HPV-positive OPC is has been found to have a favourable prognosis when compared with HPV-negative OPC. For example, one study reported a 3-year overall-survival rate of 82.4% in the HPV-positive subgroup and 57.1% in the HPV-negative subgroup (Weber et al, 2010. High levels of p16 expression is associated with locally advanced stages of HPV-positive OPC at diagnosis. Paradoxically though, p16 expression has been shown to be an indicator of good prognosis (Weinberger et al, 2006).

There are several theories about why this may be. When considering the risk factors highlighted above, it is clear that the increase in popularity of oral sexual activity among young adults results in an increase exposure of HPV and thus increased risk of HPV-positive OPC among that age group. In contrast, patients with HPV-negative OPC tend to be of an older age group with a long history of tobacco and alcohol use (Nguyen et al, 2010). This raises the likelihood of co-morbidities as well as field cancerization (for example, smoking may result in a concurrent HNSCC and lung carcinoma). These demographic factors can strongly influence the prognosis of the respective OPC groups. HPV-positive OPC is mainly characterised by inhibition of tumour suppressor genes p53 and Rb without somatic mutation. In comparison, HPV-negative oncogenesis usually results from several mutations, especially in p53 and upregulation of epidermal growth factor receptor (EGFR). EGFR overexpression is correlated with high rates of recurrence and distant metastases. Thus, multiple and variable mutations in the HPV-negative OPC group may lead to poor treatment response and prognosis (Elrefaey et al, 2014).

The increased survival rate of HPV-positive OPC has also been attributed to the increased chemo-radiation therapy (CRT) sensitivity profile of HPV-positive OPC. Genome-Wide Association Studies have found that cells which express high levels of histone binding protein RBBP4 tend to be RT-sensitive (Ng et al, 2012), and studies have demonstrated an upregulation of RBBP4 in HPV-positive OPC (Lohavanichbutr and Houck, 2009; Kim et al, 2014). In addition, low p53 expression levels, as seen in HPV-positive OPC, correlated with a complete response to induction chemotherapy. Conversely, HPV-negative patients were found to highly express class III beta-tubulin, which was associated with a poor 3 year overall survival (Kim et al, 2014). Studies such as these highlighted the fact that HPV-positive and -negative OPC are distinct cancer disorders with respect to aetiology, prognosis and treatment.

Current & Future Treatment Regimens

Until recently, patients who present with OPC are treated similarly regardless of their HPV status, with surgery, radiotherapy and chemotherapy. This multi-modal approach

of surgery and CRT was associated with significant morbidity and mortality. Pauloski et al. studied the long-term sequelae of oropharyngeal surgery and found that the level of speech impairment and intelligibility was associated with the volume of tongue and soft palate removed (Pauloski et al, 1998). Nguyen et al. looked at acute and chronic toxicities in patients who underwent CRT for OPC. They noted significant mucositis, dysphagia, speech impairment, and high levels of haematological effects such as anaemia and neutropenia. Oesophageal strictures and chronic dysphagia with associated aspiration were also found, both of which can require long-term gastrostomy tubes (Nguyen et al, 2007). It is clear then that surgery and CRT for OPC is not without risks and complications, thus a decrease in intensity of these therapies would be beneficial to a patient provided their cancer control is not compromised.

Considering the difference in CRT sensitivity between HPV-positive and HPV-negative OPC, it is reasonable to question if current treatment regimens are more intense and toxic to HPV-positive OPC patients than is necessary to achieve a cure. A less noxious regimen may be more suitable for patients with HPV-positive OPC.

Methods in achieving cure without excessive toxicity can range from altering the chemotherapeutic agent, radiation dose, or the use of less-invasive surgical techniques. However, the benefit of less intense treatment for some must be balanced against the risk of cancer spread in others. Therefore, there needs to be an accurate method of choosing patients for whom treatment de-escalation would be appropriate. Several trials are underway to try and clarify these issues, such as the De-Escalate study and the QUATERBACK trial (both in Phase 3), and the PATHOS study (currently in Phase 2). Time will tell if any or all of these toxicity-sparing tactics are defensible.

Prevention

The HPV vaccine is indicated among young girls as a prevention strategy for cervical cancer. Randomised controlled trials have supported both the bivalent HPV16/18 vaccine (Ceravix) and the quadrivalent HPV 6/11/16/18 vaccine (Gardasil) against cervical, vaginal, vulvar, and anal infection in women (Munoz et al, 2010; Kreimer et al, 2012). The vaccine is typically administered to girls before the age of 15 years; statistically prior to viral exposure via sexual contact.

Several studies, such as Chaturvedi et al. in 2011, have demonstrated that by 2020, OPC is set to surpass cervical cancer as the most common HPV-associated cancer (Chaturvedi et al, 2011). In addition, the majority of HPV-positive OPC is expected to occur among the male population. Perhaps, then, the indication for the vaccine should also be carefully considered. It would seem logical to include males in the vaccination program in light of this evidence in order to tackle what is rapidly becoming the most common HNSCC. This change was supported in 2011 by the Centre for Disease Control (CDC), who recommend that HPV vaccination should include males under 12 years (Gillison and Shah, 2001).

However, this CDC recommendation has yet to be implemented in Ireland, and the decision of whether to fund a broadened vaccination program will inevitably be driven by the efficacy and cost-effectiveness of such an initiative. A systematic review published in 2017 found that inclusion of non-cervical HPV-associated cancers in economic assessment suggests the measure would be cost-effective and supports the expansion of the HPV vaccine to include boys (Anita et al, 2017). With respect to efficacy, HPV vaccination has been shown to reduce prevalence of oral HPV infection, and thus may be effective at reducing HPV-mediated oral carcinogenesis (Herrero et al, 2013). Further research is needed to determine the true efficacy of the HPV vaccines in reducing HPV-positive oropharyngeal carcinoma. However, given the vaccines' effectiveness against cervical and other genital lesions, it seems likely that the vaccine will be effective in this respect.

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