Human papillomavirus in head and neck squamous cell carcinoma

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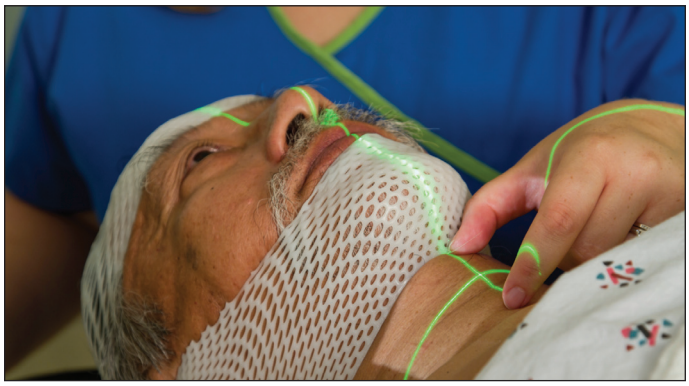
Background: Head and neck squamous cell carcinoma (HNSCC) is a significant global health burden. Approximately 25 percent of HNSCC cases are caused by human papillomavirus (HPV). These particular cancers of viral aetiology have been found to have distinct characteristics in regards to presentation, treatment and prognosis. Current advances in vaccinology have the capability to drastically decrease the incidence of HPV-positive HNSCC. **Methods:** A literature review was undertaken through MEDLINE/PubMED/Ovid databases. The terms "HPV," "HNSCC," "carcinogenesis," "treatment," "prognosis" and "vaccine" were searched. Only studies published in English were considered with 65 articles selected and analysed. Preference was given to studies published in the last ten years. **Results:** The incidence of HPV-positive HNSCC is increasing. Infection with HPV can result in cancer through the expression of oncogenic proteins which disrupt normal cellular turnover. Aggressive treatment is often undertaken causing significant morbidity in many patients. A proportion of patients die from this disease, suggesting that these cancers have a considerable impact on society. **Conclusion:** Human papillomavirus is an infectious agent that is likely transmitted through skin-to-skin contact. The virus integrates into the DNA of the host with the high oncogenic risk genotypes, HPV 16 and 18 being strongly linked to HPV-positive HNSCC development. Prevention through vaccination against these genotypes is currently an option for all individuals. The cervical cancer vaccines immunise non-exposed females against HPV 16 and 18. Vaccination of both males and females will prevent HPV-positive HNSCC.

Introduction

Cancers of the head and neck are diagnosed annually in more than half a million people worldwide. These cancers represent the fifth leading cause of cancer by incidence and sixth leading cause of cancer mortality. [1,2] More than 90 percent of head and neck cancers (HNC), which are defined as those cancers arising from the upper aerodigestive tract, are pathologically identified as squamous cell carcinoma (SCC). [3,4] Whilst the carcinogenesis of head and neck squamous cell carcinoma (HNSCC) has primarily been attributed to environmental factors such as tobacco and alcohol, evidence has implicated a subset of these cancers are directly resultant from infection with human papillomavirus (HPV). [5-7]

Considerable research has been conducted in recent years to understand HPV-positive HNSCC as well as other HPV-associated cancers. Studies have suggested that HPV is a sexually acquired infection, with the virus resulting in an oncogenic mechanism which causes cancer in some individuals. [8] Epidemiological data of HPV-positive HNSCC has revealed a recent increase in the incidence of these cancers as well as a reduction in the median age of presentation. [8-11] Additionally, the treatment of these cancers is challenging and often results in disfigurement, physical disability and psychosocial morbidity in patients whom are fortunate enough to survive. [1,12]

The opportunity to decrease the incidence of HPV-associated cancers such as HNSCC has been highlighted by political and public attention generated since the introduction of HPV vaccination programs throughout the world to prevent cervical cancer. [13,14] As these programs target young women, the purpose of this review is to discuss



the role of HPV in HNSCC so as to educate healthcare workers on the importance of the announcement in Australia that young males will also be vaccinated against HPV.

Body

Background

Human papillomaviruses were first described as having a carcinogenic effect in a seminal study by Orth *et al.* in 1979. [15] However, it was not until 1983 that Syrjänen and colleagues suggested HPV as having a specific role in the pathogenesis of HNC. [16] From this research, studies have investigated the link between HPV infection and subsequent HNC, with SCC of the oral cavity, [6] pharynx, [9] and larynx [17] all being described. These findings, as well as other research implicating HPV in cancer of the penis, [18] cervix, vagina, vulva and anus have allowed significant insight into understanding HPV. [19,20]

Human Papillomavirus Virology

The virology of HPVs has uncovered that they are small, non-enveloped, double-stranded DNA viruses belonging to the Papillomaviridae family, with more than 120 different genotypes being described. [21] Research has categorised these HPVs into those which have a high carcinogenic risk associated with invasive cancer, whilst another group has been termed low risk or non-oncogenic. [4,22,23] Infections with the high risk genotypes, HPV 16 and 18, have become an increasing focus in head and neck carcinogenesis research.

Human Papillomavirus genotypes in head and neck squamous cell carcinoma

Studies investigating the exact role HPV infection plays in the development of HNSCC have consistently found that, overall, approximately 25 percent of HNSCC cases are associated with infection. [3,4,24] Furthermore, the degree of participation each individual genotype has in developing HNSCC has recently been reported in a large meta-analysis encompassing more than 5,000 cases. The high risk genotypes HPV 16 and 18 were found to be strongly implicated in HPV-positive HNSCC, with the authors uncovering that HPV 16 was responsible for the majority of cases. [4] This finding has been repeatedly demonstrated within the literature with studies reporting that HPV 16 is involved in 85 to 95 percent of HPV-positive specimens. The remaining cases comprising HPV-positive HNSCC have been found almost exclusively to be caused by infection with HPV 18. [1,22,24]

Infection

Understanding the exact route of transmission of these high risk HPVs

to the upper aerodigestive tract has lead to the knowledge that HPV is a sexually acquired infection. [8] One study conducted found that of 15.4 million cases of sexually transmitted infections, 5.5 million of these cases were from HPV. [25] Behaviours such as increasing numbers of lifetime vaginal or oral sex partners, a history of other sexually transmitted diseases, a history of casual sex, early age of sexual debut and the lack of using barriers during vaginal or oral sex have all being associated with HPV infection and HPV-positive HNSCC. [7,26] Research has suggested that HPV is only able to survive in certain epithelial sites, including lymphoid tissue, and this tissue may represent a reservoir for HPV infection. In regards to the upper aerodigestive tract, tonsillar tissue has been proposed to harbour HPV which has the possibility of inoculating sexual partners. [27]

Carcinogenesis

Whilst the vast majority of infections with the high risk HPVs are eliminated by the immune system and are therefore asymptomatic, studies have revealed that in some cases persistent infection can lead to cancer development. [28] The current carcinogenesis model that has been proposed suggests that HPV results in the initiation of cancer development, with a multitude of steps being involved in the progression to HPV-positive HNSCC. [29]

The commencing step in HPV-positive HNSCC development is viral infection of basal epithelial cells through wounds or abrasions by invading the actively dividing cells in the area. [22] In the vast majority of cases the HPV DNA is then integrated into the host cell genome which causes two viral genes to be expressed. The two viral genes are known as E6 and E7 with research implicating their expression with mutations from a proliferative perspective. [29]

It has been found that the expression of E6 and E7 in humans is sufficient and necessary for immortal transformation of keratinocytes. [30] The E6 protein is known to bind to, and induce, the degradation of the p53 tumour suppressor protein. [22,31] This protein plays a critical role in controlling cell growth by regulating cell cycle progression and responds to stress via apoptosis. [31] Meanwhile, the E7 protein has been found to have a role in disrupting the retinoblastoma (Rb) pathway. [22] The HPV E7 oncoprotein binds to and causes destabilisation of the Rb protein and the transcription factor E2F complex. This results in the release of E2F which is then able to act on cellular proliferation genes and thus increase the level of cellular division. [32]

Furthermore, research has also discussed the fact that genetic influences play a role in the development of HPV-positive HNSCC. One recent study by Chen *et al.* described that genetically susceptible individuals may be at increased risk of HPV 16-positive HNSCC. [33] The article suggests that alteration in vitamin C metabolism, manifested by the altered transporter SLC23A2, modifies the likelihood of HPV 16 infection and subsequent HNSCC development. [33]

In addition to host genetic susceptibility there is also a relationship between extrinsic factors and HPV infection. Although this issue remains somewhat controversial, [6] research has reported that HPV-positive individuals whom are smokers have a greater risk of developing HPV 16-positive HNSCC. [34,35] The complexity of the carcinogenesis is also complicated by the impact of alcohol consumption. In those people who drink, there is an increased tendency for collagenase activity thus leading to increased likelihood of invasive cancer. [36,37] It is therefore apparent that although the cellular proliferation of HPV-positive HNSCC has been well described, other influences may be involved in the carcinogenesis of HPV-positive HNSCC and this suggests that the disease may be multi-factorial. [38]

Presentation

The sites of presentation of HPV-positive HNSCC development are varied, with all areas of the upper aerodigestive tract being observed in the clinical context. [1] Due to the large variation of cancer sites affected, a range of clinical presentations are evident in patients. One principal aspect of HNC that requires particular consideration by primary care physicians is that of the presence of a painless enlarging neck mass. [39,40] This requires attention and work-up by specialist practitioners involving physical examination and diagnostic imaging which generally includes a combination of computerised tomography (CT), magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (PET) focusing on the area of interest. [40-43] Additionally, a panendoscopy under general anaesthesia is often performed with biopsy samples taken. [44]

Regardless of the site of origin that HPV-positive HNSCC develops, a number of common trends have been uncovered using the tumour-node-metastasis (TMN) staging system for HNC. In one study by Paz *et al.*, 83 percent of HPV-positive HNSCC were reported as having positive lymph nodes, whilst only 44 percent of HPV-negative HNSCC had positive lymph nodes.[41,44] Furthermore, it has also been uncovered that patients diagnosed with HPV-positive HNSCC often present with tumours of a larger size. [1] Considering these facts, it is clear that HPV-positive HNSCC presents at higher stages of disease.

Treatment

The overall complex vital anatomy and functional processes that occur in the head and neck area, as well as advanced stages of presentation of HPV-positive HNSCC make the management and treatment of these cancers difficult. [45] Numerous medical specialities and allied health professionals, including clinical psychologists provide input into the care of people diagnosed with HPV-positive HNSCC. The primary goal of all healthcare professionals involved is to improve the survival of the patient, as well as preserving organ function. [45]

Following the initial cancer diagnosis, patients are staged according to the TMN system. In individuals that present in early stages, which include stages 1 and 2, the treatment aim is curative and employs radiation therapy or surgery as a single modality. However, in those patients that present in stages 3 or 4, the management is challenging and based on assessing functional outcomes and competing morbidities. [1,46]

Treatment of advanced HNC, which has been noted to be more prevalent in HPV-positive HNSCC, previously employed surgical resection followed by radiation therapy. [46] However, this approach has been altered in recent times with one of two approaches being employed. The first option involves undertaking surgery and the patient receiving post-operative chemoradiation; whilst the second option is that of the patient receiving chemoradiation initially with surgical salvage being performed only if required. [46,47]

There has also been the more recent suggestion within the literature that transoral robotic surgery particularly in the management of oropharyngeal SCC may offer improved clinical outcomes. In one study by Moore *et al.*, [48] 45 patients with oropharyngeal SCC underwent transoral robotic surgery, with the study describing no major complications or no need to abort the surgery. Suggestions have been made that this surgery is a safer and more efficacious method of surgical treatment with very low estimated blood loss, decreased length of hospital stay and the enhanced ability of patients to retain or rapidly regain oropharyngeal function. [48,49] These results are suggestive of a shift in the management of oropharyngeal SCC and have implications for those patients diagnosed with HPV-positive HNSCC. [50]

In addition to these therapies, treatment targeting epidermal growth factor receptors (EGFR) has emerged in protocols of locally advanced HNSCC. [1] A monoclonal antibody against the EGFR called cetuximab has been developed and has proven effective in improving locoregional control and overall survival in combination with radiation therapy. [51] It should also be noted that in those patients that present with metastatic disease and are too advanced for curative action to be undertaken, palliation of symptoms and prolongation of life is generally achieved by using chemotherapeutic agents. [39,46]

Prognosis

The numerous treatment options that are currently available have all been associated with significant psychological and physical morbidities. Problems such as mucositis, xerostomia, dysphagia, voice alterations and trismus have all been linked to the various modalities involved in treatment. [46,52,53] Additionally, the risk of recurrence as well as cosmetic effects related to aggressive treatments can have negative mental implications and lead to decreased quality of life. [1,53]

Despite the negative effects of treatment, research has shown HPV-positive HNSCC as having an improved survival when matched with HPV-negative HNSCC. [54,55] This has been primarily attributed to an increased sensitivity of HPV-positive carcinomas to all treatment options, especially radiation therapy. [45,47] In one recent study by Charfi *et al.*, [56] it was found that HPV-positive tonsillar SCC had a five year survival rate of 71 percent, compared to HPV-negative tonsillar SCC which had a five year survival rate of 36 percent. Nonetheless, it is important to keep this in perspective with many patients fortunate enough to survive this cancer often having to deal with life-long side effects from aggressive treatment. [53]

Prevention

The overall seriousness of HPV-positive HNSCC has resulted in methods of reducing the burden of these cancers to be explored. There exists a distinct need to educate the population regarding the risk of exposure to HPV associated with sexual activities. Further, the public needs to acknowledge the importance of barrier contraception for penetrative intercourse as a possible means of avoiding HPV infection, in light of research remaining unconvincing regarding the route of infection. Moreover, the utilisation of prophylactic vaccines against HPV as a primary prevention health strategy in women to prevent a proportion of cervical cancers offers a way in which to prevent HPV infection in males. [14]

Specific immune responses can be generated against HPV 16 and 18 with reports of the efficacy of these vaccines being described as between 90 and 100 percent. [13,14] The vaccine induces immunity against HPV 16 and 18 with high levels of titres of antibodies being reported 6.4 years post-vaccination. [57] Females are currently receiving these vaccines through subsidised programs, and a subsidised program has recently been announced in Australia for males. [13,58] It is expected HPV-positive HNSCC incidence will dramatically decrease in future years with the vaccination programs.

Integrated Discussion

Current literature reports that HPV is a highly infectious agent. Whilst there does not appear to be a body of evidence that refutes this finding, the exact route of transmission has yet to be confirmed. Orogenital sex has emerged as one recent theory regarding infection, [59-61] however, this view has been questioned with the finding that open-mouth kissing may explain transmission. [26] From this, it appears that this variation in studies may be explained by the fact that sexual behaviours are difficult to study. Future research should accept that skin-to-skin contact of intimate nature is the route of transmission and instead focus on developing sex education programs. This is particularly important considering the increased acceptance of discussion regarding sexual practices.

With an expected increase in the incidence of HPV-positive HNSCC into the foreseeable future, it is critical that practitioners are educated regarding the presentation of HPV-positive HNSCC. Whilst various clinical presentations have been described, it is also important to acknowledge that a younger population will likely present as people experimental with sex earlier in life, thus leading to increased possibility of HNSCC development, [1,22] as well as other HPV-associated cancers. [18,19] The current viewpoint of research has highlighted the need to fully investigate a painless enlarging neck mass and has accepted that the presentation of HNC is clinically challenging. There has been a calling for the development of non-invasive screening tools. [62] This is one area of research that is actively being undertaken and may prove advantageous in future years.

Additionally, it is well established that HPV-positive HNSCC responds more favourably to the current treatment options when compared to HPV-negative HNSCC. [55] Subsequently, there has been an appeal from the medical and scientific communities to decrease the aggressive nature of treatment for HPV-positive HNSCC in order to avoid unnecessary morbidity. [45] Current studies are focusing on this fact, with researchers requesting HPV-positive HNSCC to be classified as a separate disease entity. [1,7] The variation between treatment sensitivity is being investigated through efforts to understand the mechanisms behind increased response, as well as research to uncover optimal stratification of treatment. [22,63]

Indications of the future of HPV-positive HNSCC suggest that prophylactic vaccination against high risk genotypes of HPV will decrease the incidence of HPV-positive HNSCC; however, this will not be demonstrated for many years. [57] Current investigations are being conducted regarding the cost-effectiveness of vaccinating males. Some studies have suggested that vaccination would be beneficial, [64] whilst others have disputed this finding. [65] There exists a need to fully investigate this point. A large scale study is required and whilst it was not considered in the scope of this review, anal and penile cancers as well as the opportunity to reduce the incidence of benign HPV disease associated with HPV 6 and 11 need to be included in the economic evaluation. [14] Additionally, it may be useful to include the positive effect of herd immunity that vaccinating males would have, especially considering that some females will have sub-optimal immune responses. [57] Homosexual males also need to be considered in the evaluation. This study, which could be conducted in Australia, needs to be fully reported so that developing countries can assess HPV vaccination programs in males and females.

Conclusion

Much research has been conducted since the initial description of HPV and associated HNC development. The identification of the HPV oncoproteins E6 and E7 has allowed for the subsequent recognition of alteration in cellular pathways. The current treatment of patients diagnosed with HPV-positive HNSCC involves multi-disciplinary teams that often manage advanced disease with a positive prognostic status. Nonetheless, significant life-long treatment side-effects have been noted.

Future research is likely to focus on trials investigating the increased susceptibility of HPV-positive HNSCC to different treatment regimens and may include a classification of HPV-positive HNSCC as a distinct subclass of HNSCC with less aggressive treatment protocols. Prophylactic vaccination protection against high risk genotypes associated with HNSCC is expected to be fully investigated. This may include investigations of alternative methods of delivery.

It is essential that we capitalise on the current scientific development of prophylactic vaccines developed against HPV and actively educate parents of young children to vaccinate their children in order to avoid the complexities of HPV-positive HNSCC.

Conflict of Interest

None declared.

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