The Growing Epidemic of HPV Associated Oropharyngeal Malignancy

Abstract:

Against the prevailing view during the 1970s, Harald zur Hausen postulated a role for human papilloma virus (HPV) in cervical cancer and subsequently won a nobel prize for his work in 2008[1]. The pathway by which the viral oncogene causes malignant transformation in the cervix has been well described in the literature. What is far less appreciated is the association between HPV and oropharyngeal malignancy. The extensive prevalence of HPV in humans and growing numbers of head and neck malignancies secondary to HPV suggest that if unchecked HPV has the potential to continue to be the oncogenic pathogen of the decade. We present the findings of a recent head and neck cancer education day held in the Mater University hospital. In preparation for the meeting and this paper an extensive literature search of Medline and Pubmed was conducted. The incidence of HPV associated oropharyngeal malignancy is increasing rapidly and is a preventable disease. It represents a distinct disease entity and treatment should be tailored accordingly. We recommend the vaccination of both boys and girls against HPV.

We present the discussion and conclusions from the 4th Mater University Hospital head and neck oncology meeting November 2011. The Human Papilloma Virus (HPV) is the most commonly diagnosed sexually transmitted viral infection and causes anogenital warts, respiratory papillomas and malignancy of both the cervix and oropharynx. They are sexual transmitted to the oropharynx and tonsil through oro-genital route, perinatal route or less commonly mouth to mouth kissing[2]. Conservative estimates suggest an annual HPV infection incidence of 5.5 million people in the United States alone. The American social health association estimates that up to 80% of Americans will be infected with HPV at some point during their lifetime[3]. The HPV virus is a ubiquitous virus with more that 100 strains. The high risk strains found in Ireland include HPV 16 and 18. The majority of infections clear within two years, the persistent infections can lead to dysplastic and ultimately neoplastic change.

Current HPV vaccination in Ireland
Current HSE recommendations for vaccination against HPV include vaccination of all females in 1st year of secondary school with a concurrent HPV catch up program for females in secondary school until 2013. In 2014 all females in 1st year will be targeted with an expected uptake rate of 80% through this school based program. The vaccine is delivered in three intramuscular doses at 0 months, 2 months and 6 months[4]. Presently it is not known if a booster may be required after 5 years. Unfortunately this program fails to tackle the HPV epidemics true impact by presuming it solely represent a health threat to females. In reality the current data suggested the disease burden of HPV associated oropharyngeal squamous cell cancer (OPSCC) will outweigh that of cervical cancer by 2020[5]. This fact has been recognised by the Centre of Disease Control in the United States who in October of this year recommended the vaccination of all males from 9-21 years.

Two Sub Types of OPSCC
We now have two subtypes of oropharyngeal malignancy[6]. The first are HPV negative malignancies found in an older population with a 6:1 male preponderance[7]. This traditional group behavioural risk factors include; cigarette smoking/ betnal nut/alcohol exposure over a long period which causes somatic mutations with subsequent interruption of normal cellular apoptosis. The second group are HPV positive malignancies. This group have distinct biological and clinical profiles[7,8]. They present in younger patients with a male preponderance[9]. It is persistent HPV infection with high risk strains 16 and 18 that are associated with cancer[8,10]. When over expressed the HPV viral oncogenes E6 and E7 inhibit normal tumour suppressor genes p53 and retinoblastoma protein (pRb) respectively thus giving rise to a malignant cell line[11,12]. At present we cannot predict when viral infection will persist or indeed when or if it will progress from oropharyngeal papilloma to squamous dysplasia and eventually squamous carcinoma.

Disease burden
There is strong evidence supporting the hypothesis that the increase in HPV prevalence has lead to an increase in HPV positive oropharyngeal squamous cell carcinoma (OPSCC). There is a global increase in the incidence of OPSCC.[5,9] Chaturvedi et al[5] tested this hypothesis by analyzing surgical specimens dating back to 1984 from the three United States oncology tissue repositories (SEER). The incidence of HPV positive OPSCC increases by 225% from 1988 to 2004 in the U.S. In addition the incidence of HPV-positive OPSCC in men from 1988-2004 increased at a staggering 7.5% per year from 20% to greater than 70% of OPSCC.

If this trend continues the annual number of oropharyngeal malignancies in men will exceed cervical malignancies in women by 2020[5]. These findings highlight the increasing disease burden of HPV OPSCC. We cannot predict whether this epidemic will continue along its current trend, level off, accelerate or decline secondary to uptake of the HPV vaccine. Certainly in the short term we are presented with increased frequency of OPSCC and a changing patient demographic in this group with associated implications for longer term management.

Impact on treatment
Several studies have found that HPV positive OPSCC responds better to radiation and chemotherapy. Falkry et al[6] suggested this is due to the presence of wild type p53 in tumours and the associated intact apoptotic pathway. The response rates and survival outcomes are clearly superior for HPV positive OSCC[13]. But these findings should be tempered as relative survival is independent of therapy and the absolute survival to therapy relationship is not yet known. Lymph node involvement in HPV positive OPSCC typically leads to high TNM staging that doesnâ t reflect disease risk relative to other head and neck squamous cell cancers[14,15]. These factors suggest that at present we are just beginning to elucidate the ideal treatment for HPV positive OPSCC and that HPV positive OPSCC are more sensitive to chemoradiation treatment[13]. Also the new younger and healthier patient demographic, often necessitate a more cautious treatment approach in an attempt to limit what can be severe co-morbidities.

Prognosis
HPV status predicts relative survival advantage which is independent of age, gender, tumour size and lymph node status. Several studies have found improved disease-specific survival in HPV positive OPSCC[16-18]. RTOG 0129 study found a 26 % improvement in 3 year survival when comparing HPV positive OPSCC to HPV negative OPSCC. The absolute survival difference between HPV positive and HPV negative cancers at 5 years is consistently e 30%[16].

At present the treatment protocols for HPV positive and negative OPSCC are similar but we are seeing improved treatment responses to HPV positive OPSCC. HPV oropharyngeal malignancy is a preventable disease. It represents a distinct disease subtype and future treatment of oropharyngeal malignancy will need to be tailored according to whether it is HPV positive. It also presents in a younger and healthier cohort of patients with improved prognosis and expected life span thus accentuating the need for lower intensity treatment to minimise therapy associated morbidities[19]. Our aim at this juncture apart from refining treatment methods for this malignancy should be the eradication of HPV OPSCC through a comprehensive vaccination program for both boys and girls.

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Comments: