Role of HPV in Oropharyngeal Carcinoma in Japan

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Abstract

While HPV has emerged as a driving cause of head and neck cancer especially in the oropharynx in western countries, there has been limited investigation of the etiology of head and neck cancer in other world regions, especially Asia. The objective of this study was to investigate HPV rates of head and neck cancer in Japan.

Introduction

Head and neck cancers are the sixth most common cancer. [1,2] Over the past two decades, there have been important changes in the incidence, etiologic factors and demographics of head and neck squamous cell carcinoma (HNSCC).[3,4] While traditional risk factors for these cancers have been tobacco use and alcohol consumption, human papillomavirus (HPV) has been demonstrated to be an important etiologic cause of some head and neck cancers, especially those arising in the oropharynx and the tonsil.[3,5-9]

Over the last decade in particular, it has been noted that the incidence of oropharyngeal cancer has had a sharp increase, compared to other head and neck cancers, and this increase has been attributed to HPV as there has been a concomitant decrease in tobacco related head and neck cancers with decreasing tobacco use.[2-4,10-16] Although HPV infection is thought to act synergistically with traditional risk factors, 20%-30% of patients with oropharyngeal cancer will not have a history of tobacco or alcohol use.[5,11]

The prevalence of HPV in HNSCC differs over geographical region. In Western Europe, Canada and the US, HPV rates in oropharyngeal cancers rates ranged from 40-90% and these rates appear to be increasing over time.[12,14,17,18] However, the majority of published data regarding HPV related oropharyngeal cancer is from North America or Western Europe and data are limited from other world regions.[8] In Asian countries, investigation of oropharyngeal cancers either showed no evidence of HPV on pathologic examination or very low rates while rates of traditional head and neck cancers remain high.[3,19-21] However, one recently conducted study in Japan did show an incidence of HPV positivity of 51.9%.[22]

Given these apparent differences in HPV prevalence with geographical location, and to further investigate the role of HPV in the etiology of head and neck cancers in Asia, pathology specimens from oropharyngeal cancer from 2 universities located in opposing geographic locations of Japan were examined for the presence of HPV via p16 immunohistochemisty.

Methods and Materials

The charts and pathology from 59 patients diagnosed with oropharyngeal carcinoma from Nihon University located on Honshu Island and Kurume University located on Kyushu Island in Japan from the past five years (2010-2015) were examined. Demographics were collected of patient's age, gender, smoking history, stage of presentation and mortality.

The pathologic specimens were obtained and examined for p16 positivity by the Department of Pathology at Yale New Haven Hospital. p16 is a cyclin dependent kinase inhibitor and is induced as a result of inhibition of pRb activity by the HPV E7 oncoprotein. This is in contrast to most other head and neck cancers where p16 is downreguated.[12] Immunohistochemistry for p16 is a widely used surrogate biomarker for active HPV and is commonly used for detection of HPV in head and neck cancer.[23] In situ HPV DNA examination could not be conducted due to the fixation method used on the original specimens.

Statistical analysis comparing the two groups of p16 positive and p16 negative with regards to age, gender, smoking years via pack year history, stage of cancer at presentation and mortality was conducted using Microsoft ® Excel program.

Results

Of the included patient samples, the rate of p16 positivity was 29.5%. p16 positive and p16 negative groups were then compared. The patients with p16 positive tumors tended to be younger (p 0.05). (Figure 1) There was a higher percentage of women with p16 positive than p16 negative tumors. (Figure 2) Smoking showed a trend for fewer pack years in the p16 positive group but the difference was not statistically significant (p 0.43). (Figure 3) p16 positive patients had a mortality rate of 38% while the rate was 68% in the p16 negative group (p 0.064). (Figure 4) The majority of cases in both groups were Stage 3 or 4 (p 0.34). (Figure 5)

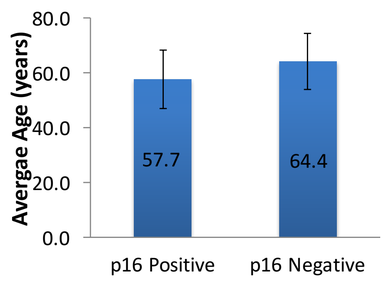

Figure 1. Patient Age

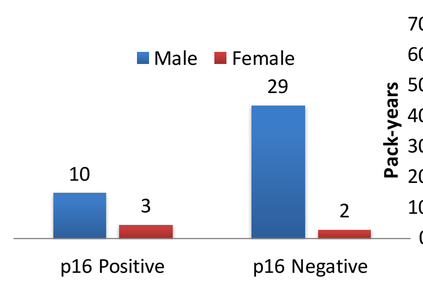

Figure 2. Patient Gender

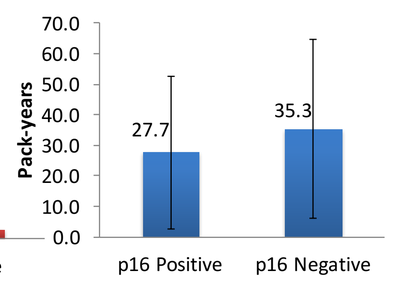

Figure 3. Number of Pack-years

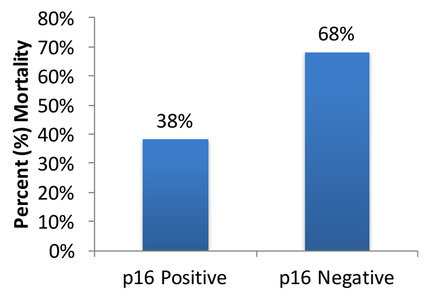

Figure 4. Rates of Mortality

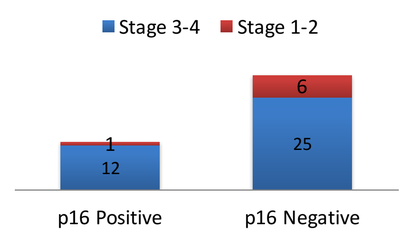

Figure 5. Stage of Presentation

Discussion

The role of HPV in the development of oropharyngeal cancer has been suggested to vary based on geographic location. This difference has been attributed to cultural or social factors, which influence high-risk behavior, including sexual practices.[20] In Asian countries, widespread tobacco use is a more recent phenomenon and continues to be widespread when compared to Western Europe and the US.[3,20] In fact, while head and neck cancer incidence rates have been mostly declining worldwide with decrease tobacco use, the incidence of head and neck cancer in Taiwan has continued to increase which is thought to be due to continued increase in betel quid.[19] In Korea while smoking rates have been declining since the 1980s, this is still 20 years later than in the US.[3]

In this study we found a rate of 29% HPV positivity, which is much lower both than the 40-90% commonly presented in the literature from the western world, as well as lower than the one initial study conducted in Japan. [12,14,17,18,22] However, it is higher than the rates reported in previous study out of other countries in the region. [3,19-21]

The mortality compared between the groups approached significance with improved survival in the p16 positive group (P 0.06). However, no statistically significant difference was observed in terms of stage at which patients presented. This is in keeping with the known biology of HPV positive oropharyngeal cancers, which tend to have improved survival and the difference in survival does not appear to be due to difference of extent of disease at presentation but instead is due to other factors.[9,24]

Limitations of this study included small sample size and determination of HPV positivity based solely on p16, which is a surrogate marker for HPV status.[23] p16 also has a high sensitivity leading to a higher false positive rate which may cause an over estimation of HPV positivity in this study.[25]

Conclusions

There appears to be a geographical difference in HPV rates of oropharyngeal cancers with persistently lower rates in Asian countries when compared to Western Europe and the US. This report serves to remind us that HPV expression in western countries may not be generalizable across the globe at this time.

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