ROLE OF HUMAN PAPILLOMAVIRUS IN THE ETIOLOGY OF HEAD AND NECK CANCER

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Abstract: Head and neck cancer is the world’s sixth most common cancer, but despite advances in treatment, there has been no significant decline in the mortality rate. In recent years, there has been mounting epidemiologic and experimental evidence of a role for human papillomavirus (HPV) as the etiologic agent of a subset of head and neck cancers. The association is strongest for oropharyngeal cancers, especially those of the tonsil. HPV 16 is invariably the predominant type. HPV-positive cancers have been shown to be biologically distinct, clustering among nonsmokers and light drinkers, and have been associated with a favorable prognosis. This review examines the current findings of HPV in head and neck cancers and discusses implications for developing new treatments.

Keywords: tonsil cancer; human papillomavirus; oropharyngeal cancer

Squamous cell carcinomas of the head and neck are a biologically heterogeneous group of cancers with a variable clinical course. Head and neck cancer ranks sixth among malignancies worldwide (GLOBALCAN 2002. http://www-dep.iarc.fr/). A summary of the global incidence rates of cancer at different sites within the head and neck is presented in Table 1. In 1990, the incidence of oropharyngeal cancer, where the association with HPV is strongest, was highest in Melanesia, Western Europe, and Australia, with rates of 20.2, 28.6, and 22.5 per 100,000 in males and 14.3, 5.2, and 7.5 per 100,000 in females, respectively.1 Lowest rates of approximately 4 per 100,000 in males and 2 per 100,000 in females were recorded in developing countries such as China.1

RISK FACTORS FOR HEAD AND NECK CANCERS

The main risk factors for head and neck cancer globally are tobacco and alcohol. Exposure to one or both accounts for more than 75% of oral cavity and pharyngeal cancers in developed countries.2 The combined effect is multiplicative rather than additive.3–5 These agents act by inducing mutations in key genetic pathways that govern normal cell turnover such as p53 and the product of the retinoblastoma gene (pRb).6 Both p53 and pRb are classical tumor suppressor genes, and the abrogation of their ac-
Activity permits the accumulation of genetic mutations leading to a carcinogenic phenotype (Figure 1). Other major players in the p53 and pRb pathways include the anti-proliferative proteins p16INK4A and p21CIP1/WAF1. Disruption or the altered expression of these proteins has been associated with many forms of human cancer. Diets lacking in essential micronutrients, exposure to agents such as radiation, and poor oral hygiene have also been associated with an increased risk of cancer, although the mechanisms remain unclear.

Approximately 20% of head and neck cancers occur in people lacking these established risk factors. There is strong epidemiologic and experimental evidence indicating that human papillomavirus (HPV) accounts at least partly for this subset of cancers. The role of HPV as an etiologic agent in cancer was first recognized in the uterine cervix. It has been estimated that HPV infections account for 6% of worldwide cancers; most HPV-related cancers are anogenital cancers.

The purpose of this review is to present a summary of the recent literature describing HPV and its role in head and neck cancer. Attention will focus mainly on the oropharynx and oral cavity.

**HUMAN PAPILLOMAVIRUS AND CANCER**

More than 118 HPVs have been completely described. This number is expected to increase with many presumed new types being discovered by preliminary data such as subgenomic amplicons. Approximately 50 HPVs infect surfaces within the anogenital region. Many of these types have also been identified in mucosal lesions in the head and neck. Mucosal HPVs can be categorized in 2 major groups based on oncogenic potential. HPV 6 and 11 are the 2 most common “low-risk” types accounting for the majority of genital warts, while HPV 16 and 18 are the major “high-risk” types, predominating in cervical cancers. Studies of cervical cancers have shown that the central components of HPV-induced malignant transformation are as follows: (1) inactivation of the cellular p53 gene by the E6 oncoprotein, and (2) inactivation of the pRb gene by the HPV E7 oncoprotein. Thus, HPV targets the same molecular pathways as the mutagens present in tobacco and alcohol (Figure 1).

**Table 1. Summary of the world incidence, mortality, and prevalence rates of head and neck cancers.**

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Incidence</th>
<th>Cases</th>
<th>Crude rate</th>
<th>ASR</th>
<th>Mortality</th>
<th>Deaths</th>
<th>Crude rate</th>
<th>ASR</th>
<th>Prevalence</th>
<th>1-year</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity (males/females)</td>
<td>More developed regions</td>
<td>64830/26311</td>
<td>11.2/4.3</td>
<td>7.9/2.4</td>
<td>22422/8259</td>
<td>3.9/1.4</td>
<td>2.7/0.7</td>
<td>53071/23092</td>
<td>185830/89453</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less developed regions</td>
<td>111011/72022</td>
<td>4.4/2.9</td>
<td>5.7/3.5</td>
<td>58282/38438</td>
<td>2.3/1.6</td>
<td>3.0/1.9</td>
<td>80922/52677</td>
<td>280853/183903</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharynx (males/females)</td>
<td>More developed regions</td>
<td>5168/2021</td>
<td>0.9/0.3</td>
<td>0.7/0.2</td>
<td>2394/973</td>
<td>0.4/0.2</td>
<td>0.3/0.1</td>
<td>4385/1738</td>
<td>15722/6377</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less developed regions</td>
<td>50456/22156</td>
<td>2.0/0.9</td>
<td>2.4/1.0</td>
<td>32408/14390</td>
<td>1.3/0.6</td>
<td>1.6/0.7</td>
<td>36449/16048</td>
<td>128555/56858</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Other pharynx (males/females)</td>
<td>More developed regions</td>
<td>41044/7415</td>
<td>7.1/1.2</td>
<td>5.1/0.8</td>
<td>20382/3807</td>
<td>3.5/0.6</td>
<td>2.5/0.4</td>
<td>30402/5905</td>
<td>93390/20712</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less developed regions</td>
<td>65144/16667</td>
<td>2.6/0.7</td>
<td>3.4/0.8</td>
<td>47555/12213</td>
<td>1.9/0.5</td>
<td>2.5/0.6</td>
<td>41580/10725</td>
<td>122367/32193</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larynx (males/females)</td>
<td>More developed regions</td>
<td>57504/7033</td>
<td>9.9/1.2</td>
<td>6.9/0.7</td>
<td>28182/2849</td>
<td>4.8/0.5</td>
<td>3.3/0.3</td>
<td>51210/6349</td>
<td>195889/25242</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less developed regions</td>
<td>81624/12965</td>
<td>3.2/0.5</td>
<td>4.3/0.6</td>
<td>50388/8471</td>
<td>2.0/0.3</td>
<td>2.7/0.4</td>
<td>57512/9114</td>
<td>200415/32702</td>
<td></td>
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</tbody>
</table>

*Estimates were derived from GLOBALCAN 2002 [http://www-dep.iarc.fr/] and are based on the most recent incidence, mortality, and survival data available at IARC. Abbreviations: ASR, age-standardized rate; IARC, International Agency for Research into Cancer. Incidence rates are presented as crude rates and ASR per 100,000.

Etiologic Role of Human Papillomavirus

reports of the conversion of recalcitrant laryngeal papillomas to malignancy after radiation therapy. A possible role for HPV in the etiology of cancers at other sites within the head and neck was first suggested by Lüning et al in 1985. There is now mounting epidemiologic and experimental evidence of an association between HPV and cancer at several mucosal sites within the head and neck. The association is strongest in the oropharynx, most notably the tonsil.

One of the most important studies establishing the causal relationship between HPV and head and neck cancer was a multi-center case control study conducted by the International Agency for Research into Cancer (IARC) involving 9 countries, including Australia. A total of 1670 case patients (1415 with cancer of the oral cavity and 255 with cancer of the oropharynx) and 1732 control subjects were recruited. Findings confirmed that HPV-positive tumors cluster among non-smokers and nondrinkers as reported in several smaller studies. The IARC concluded that HPV is highly likely to play an etiologic role in many cancers of the oropharynx and possibly a small subgroup of cancers of the oral cavity.

Mucosal cancer occurring in the younger age groups has long been thought to constitute an etiologically distinct group that is increasing in incidence. However, the relationship between HPV and age remains controversial. Some studies have reported an association with older age, and others have found no association. However, on balance, there appears to be a trend for HPV to be detected in the younger age groups. Even those studies that did not show a significant effect of age reported a lower mean and median age in their HPV-positive group. For example, Gillison et al studied 253 patients with squamous cell carcinoma of the head and neck and reported the median age among the HPV-positive group to be 60.5 years compared with 64 years in the HPV-negative group.
An elevated risk of oropharyngeal cancer has been associated with increasing numbers of sexual partners, younger age of first sexual intercourse, the practice of oral sex, and a history of genital warts.\textsuperscript{4,27,34–37} Further investigations will be needed to determine whether the links between HPV positivity and younger age reflect sexual practices (ie, orogenital sexual contact) or other factors, such as genetic predisposition.

**EXPERIMENTAL EVIDENCE OF AN ETIOLOGIC ROLE FOR HUMAN PAPILLOMAVIRUS IN HEAD AND NECK CANCER**

There has been wide variation in HPV positivity rates in cancers at different sites within the head and neck. Approximately 25\% of oropharyngeal cancers have tested HPV-positive,\textsuperscript{27} with rates in tonsillar cancer considerably higher. A recent review of the world literature showed that a cumulative total of 422 tonsillar carcinomas had been examined for the presence of HPV DNA.\textsuperscript{38} Of these, 51\% (216/422) were found to be HPV DNA-positive. HPV positivity rates varied from 20\% to 75\% across the various studies.\textsuperscript{12,38} HPV 16 was overwhelmingly the most frequent type at 84\%. Discrepancies in the proportion of cancers attributable to HPV can be partly explained by differences in sampling techniques and HPV detection methods. One major caveat with a polymerase chain reaction (PCR)-based approach for HPV testing is the possibility of false-positive results due to cross-contamination.\textsuperscript{38} There is a need to develop standardized molecular screening assays for the detection of HPV, avoiding the well-identified risk of contamination of samples being tested by PCR-based methods. However, our group has provided evidence of geographic variation in the proportion of tonsillar cancers induced by HPV. HPV positivity rates in tonsillar cancers from Australian patients (46\%) were consistent with reports from other western countries,\textsuperscript{39} but HPV was not detected in any of a small series from patients living in Northern China.\textsuperscript{40} The absence of HPV in tonsillar than in cervical cancers,\textsuperscript{50} but further studies are needed for confirmation. It is unknown whether the physical state of the virus influences tumor biology. However, in a recent study, patients with tumors harboring the episomal DNA were more likely to have large (T3–T4) tumors at diagnosis than those with integrated or mixed forms.\textsuperscript{51} Seroreactivity against the viral capsid proteins and oncoproteins has been consistently associated with an increased risk of head and neck cancer.\textsuperscript{26,27} Finally, molecular investigations have provided strong evidence linking specific patterns of expression of cell cycle markers to HPV-positive tonsillar cancers.\textsuperscript{52–54} The expression signatures of p53, pRb, p16, and cyclin D1 strongly support the proposition that tonsillar cancers can be classified as a distinct biologic group. This subset of cancers generally shows a loss of pRb and cyclin D1 expression and overexpression of p16.\textsuperscript{13} In comparison, HPV-negative tonsillar tumors frequently exhibit...
overexpression of pRb, cyclin D1 and loss of p16. p53 mutations have been reported in approximately 50% of head and neck cancers, but are uncommon in the HPV-positive subset. Similarly, mutated p53 has been rarely reported in uterine cervical cancers.

**CLINICAL IMPLICATIONS OF HUMAN PAPILLOMAVIRUS AS ETIOLOGIC AGENT OF HEAD AND NECK CANCER**

It has been consistently reported that patients with HPV-positive tonsillar cancer have a better prognosis than patients with HPV-negative tonsillar cancer. Patients with tonsillar cancers carrying a high viral load have been shown to have a better clinical outcome, including increased survival, compared with patients whose tumors have a lower load. The effect of HPV on clinical outcome at other sites in the head and neck has not been established, although several studies have supported the association. The reason for this underlying therapeutic benefit is unknown, but there is some evidence to suggest that it may be treatment related. One plausible explanation relates to the state of the p53 in the tumors. Previous studies have shown that the E6 oncoprotein does not completely inactivate all the endogenous p53 protein. Thus, residual functional p53 may mediate cellular apoptosis following radiotherapy. Nonetheless, the role of p53 in radiosensitivity remains controversial.

Recognition that HPV has an etiologic role in head and neck cancer has important implications for prognosis, treatment, and disease prevention. The prognosis for head and neck cancer has not improved appreciably over the past 2 decades, despite a better understanding of the patterns of spread of invasive tumors, advances in surgical reconstruction, and the increased use of combined-modality treatment. This highlights the need for more reliable markers to guide treatment and predict outcome. Various cellular proteins such as p53, cyclin D1, and p27 have been identified as prognostic markers in some surveys, but none has gained universal acceptance. Lack of stratification for HPV may account for some of the confusion. There are real prospects that HPV itself may provide a new generation of prognostic markers. Screening of head and neck cancers for HPV 16 by polymerase chain reaction or for p16 expression by immunohistochemistry, as a marker of HPV E7 oncogene activity, is now technically within the reach of routine pathology laboratories. Current evidence suggests that patients with HPV-negative tumors may benefit from closer than usual follow-up or additional therapy.

There is growing international acceptance for the screening of HPV DNA as an adjunct to cytology for the detection of uterine cervical cancer or its precursors. Cytologic screening of cells collected from the oral cavity by dentists or general practitioners could eventually play a similar public health role to the Papanicolaou smear in cervical cancer, but rational assessments of the value of this approach await insight into the natural history of HPV infection in the head and neck.

Confirmation that HPV has an etiologic role in head and neck cancers may have an important bearing on the strategy for using HPV vaccines. Prophylactic vaccines based on viral capsids of HPV 16 and 18, the major types in cervical cancers, and types 6 and 11, responsible for the majority of genital warts, have shown great promise in advanced clinical trials and are expected to become commercially available within 2 years. The lessons learned will lay the foundations for similar trials for head and neck cancer. Therapeutic vaccines based on the viral oncoproteins are still in the developmental stage, but they may eventually prove beneficial if used in association with conventional approaches for the management of advanced disease.

**CONCLUSIONS**

There is a growing international consensus supporting the role of HPV as an etiologic agent in a subset of head and neck cancers. The HPV detection rate of 50% in tonsillar carcinomas is among the highest of any extragenital human malignancy. Given this high rate of positivity, HPV must now be recognized as a tumorigenic factor for the development of head and neck cancers.

**REFERENCES**


