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Genetic polymorphisms and HPV infection in oral squamous cell carcinomas

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Despite declining smoking rates in the United States, the incidence of oral squamous cell carcinomas (OSCC, including oral cavity and oropharynx) is rising in young adults. The reasons have been attributed to changes in sexual behaviors and the increasingly prevalent infection of oncogenic subtypes of human papillomavirus (HPV), principally type16 and occasionally type18. However, only small proportion of individuals who have contracted HPV infection will develop OSCC, suggesting that there is an inter-individual variation in susceptibility to HPV infection and related OSCC. Identification of susceptible biomarkers for HPV status would be useful to identify those individuals who are susceptible to HPV infection, to refine the prognostication of HPV associated OSCC, and ultimately to improve prevention efforts for OSCC and potentially other HPV-associated diseases. Our public health OSCC prevention paradigm will need to expand beyond tobacco and alcohol control.

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Introduction

Only small proportion of individuals who have contracted HPV16/18 infection will develop OSCC, suggesting that there is an inter-individual variation in susceptibility to HPV16/18 infection and related OSCC. Given that HPV-positive and HPV-negative OSCC patients appear to have different etiology and prognosis, it is important to identify susceptible markers for both HPV status and HPV-associated outcome among OSCC patients in order to optimize therapeutic management. Therefore, in this paper, we summarize and present our pilot data on genetic polymorphisms of genes in cell cycle/apoptosis and inflammation/immune response pathways which contribute to HPV16/18-associated OSCC. Furthermore, we selected genes in several molecular pathways to assess the combined effects of a panel of polymorphisms within the same pathway, since such combined analysis may amplify the effects of the individual association of each polymorphism with the risk of HPV infection and related outcome among OSCC patients. By knowing the HPV infection status of OSCC patients or other HPV-associated cancer patients, there may be important prognostic implications and potential influences on current and future treatment and prevention strategies for an improved survival and a better quality of life.

Epidemiology of oral squamous cell carcinoma (OSCC) and trends in OSCC incidence

OSCC, which constitutes the majority of head and neck cancers, is common worldwide. In the United States, it is estimated that approximately 35 000 new OSCC cases will be diagnosed and 7600 deaths will occur from these cancers in 2008 [1]. The leading known risk factors for these cancers are tobacco use and alcohol consumption. However, despite declining smoking rates in the United States, the overall incidence of OSCC show little change and even is increasing in young adults in the last several decades, and this increasing trend has been related to changes in sexual practices and the increasing prevalence of human papillomavirus (HPV) infection [2••,3]. Studies show that oral cavity, laryngeal and hypopharyngeal cancers are ALL in significant declines in incidence which mirror the declines in smoking prevalence in the U.S. [2••,4,5]; however, the incidence of oropharyngeal cancer and young oral tongue cancer has been stagnant or increasing for the last three decades [2••,4]. This may be due to an increase of HPV infection, which is supported

by rising HPV seroprevalence in Western populations over the last 30 years [6] and changing sexual practices in these populations [7,8]. It is possible that OSCC is evolving from primarily a cancer of middle-aged to elderly smokers and drinkers to one of younger to middle aged nonsmokers who have been exposed to HPV. Understanding susceptibility for and modifying factors of HPV carcinogenic process will facilitate individualized treatment for OSCC. Of the 120 known types of HPV, the high-risk oncogenic HPV16 is the most frequent type, accounting for approximately 90–95% of HPV-positive OSCC [9,10]. Although HPV infection may be a major risk factor for OSCC [9,11•], only a small fraction of individuals with a long period of high-risk HPV exposure develop OSCC, implying that host genetic factors may modify the association between HPV infection and risk of OSCC.

Prevalence of HPV in OSCC

While only 10–25% of SCCHN are associated with high-risk, oncogenic HPV types, these HPV-associated cases represent a distinct subset of tumors, chiefly young oral cavity and oropharyngeal cancer with distinct epidemiologic, clinical, and molecular characteristics. Oropharyngeal cancers were significantly more likely to be HPV positive (35.6%; 95% confidence interval [CI] = 32.6–38.7) than 23.5% (95% CI = 21.9–25.1) of oral cavity cancers [12]. Almost half of the oral cavity cancers were from Asian studies with particularly high rates of HPV positive tumors (33%) as compared to Western countries where only 16% of oral cavity cancers were HPV positive [12]. With the progress in molecular techniques, oncogenic HPV DNA has been consistently detected in approximately 50% of oropharyngeal cancer and this may be much higher in certain groups of oropharyngeal cancer, such as those lacking significant tobacco exposures [11•,13,14]. While the prevalence of detecting HPV in OSCC was 46.5% in a total of 4680 samples from 94 studies [12], we found that among MD Anderson head and neck cancer cases, HPV16 was detected in approximately 25% of the tumors in the oral cavity, and 80% in oropharynx [15]. For HPV-positive tumors, HPV16 has been identified in 90–95% of the tumors followed by HPV31, 33 and 18 [16••]. It has been suggested that certain subgroups of OSCC patients are more likely to be HPV16-positive due to effect of potential genetic variants on HPV infection rates.

Association of HPV with risk of OSCC

The strongest evidence of an association of HPV16 with risk of oropharyngeal cancer has been, from molecular epidemiologic (HPV16 serologic or tumor DNA status) studies with a case–control design, showing a range of odds ratios from 3 to 60 [11•,16••,17–21]. A nested case–control study of 292 cases and 1568 controls within a prospective Scandinavian cohort of almost 900 000 subjects found that HPV16 seropositivity was significantly associated with a 14.4-fold increased risk of oropharyngeal cancer [21]. A case–control study in Mexican population identified HPV as risk for OSCC (OR = 3.4) after adjustment for other confounding factors including age, smoking, and drinking [22]. The estimate of association of HPV with OSCC (OR = 3.4) in our study [23] was consistent with these results. In addition, other studies also have demonstrated that HPV infection, particularly HPV16, was associated with an increased risk of OSCC, independent of exposure to alcohol and tobacco [20,24]. In a multi-institutional international study of 1670 cases and 1732 controls, Herrero and colleagues found that HPV16 L1, E6, and E7 seropositivity was a significant risk for OSCC [16••]. In our matched pair analysis at our institution, we found 40.8% of 120 patients with squamous carcinoma of the head and neck to be HPV-16 seropositive but only 9.2% of matched cancer-free controls (adjusted OR = 6.7, 95% CI = 3.0–14.9) [17].

Cell cycle control polymorphisms and HPV infection

Cell cycle related genes play a role in modulating cellular DNA repair, cell-cycle control, cell growth and apoptosis to maintain genome stability. *p53* and *Rb* are chief among many critical cell cycle regulatory tumor suppressor genes. Inactivation of both p53 and Rb by E6 and E7 allows the cell to escape normal cell cycle checkpoints, with resulting cell transformation and immortalization [25].

Simultaneous analysis of genetic polymorphism in both *p53* and *Rb* pathways may aid in understanding the distinct mechanisms involved with HPV-associated OSCC. The alteration of genes in the *p53* (e.g., *MDM2*, *p73*, *p21*, *p27* or *p53*) and *Rb* pathways (e.g., *Rb*, *CCND1*, *E2F*, or *p16*) can lead to loss of appropriate tumor suppressor functions. A common single nucleotide polymorphism (SNP) of *p53* at codon 72 in exon 4 results in a substitution of Pro for Arg in the transactivation domain [26]. The common Arg variant allele may alter the susceptibility of p53 to oncogenic HPV E6-mediated degradation [27], and this allele has been associated with oncogenic HPV infection [28,29,30•]. Furthermore, in case–control analyses, the homozygous Arg/Arg genotype has been significantly associated with an increased risk of HPV-associated cancer [27,31]. p73, a member of the p53 family, activates the promoters of several p53-responsive genes participating in cell-cycle control, DNA repair, and apoptosis. The two linked non-coding exon 2 polymorphisms of *p73* at positions 4 (G > A) and 14 (C > T) are thought to affect p73 function by altering gene expression, perhaps by altering the efficiency of translational initiation [32]. This polymorphism has been reported to significantly modify the risk of HPV-associated OSCC individually or in combination with *p53* codon 72 SNP [23]. MDM2 negatively regulates p53 levels by modulating p53 cellular activity [33]. A SNP G2580Tof *MDM2*, at