Dismissing links between HPV and aggressive tongue cancer in young patients

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Background: The objective of this study is to disprove and dismiss etiological links between human papillomavirus (HPV) and aggressive tongue cancer in young patients.

Methods: Review of available literature with focus on presenting the epidemiological, histological and immunohistochemical arguments against an association between HPV and aggressive glossal neoplasm in younger populations.

Conclusion: HPV is not associated with the recent surge in the incidence of biologically aggressive oral cavity cancer in young populations.

Key words: cancer, HPV, oral, oropharynx, tongue, young

Introduction

Although head and neck cancers account for only 3% of all new cancer cases and 2% of all cancer deaths in the United States annually, this group still constitutes the fifth most common malignancy worldwide [1]. Cigarette smoking and alcohol ingestion, which remain the two major predisposing factors associated with these lesions, have markedly decreased over the past 40 years [2]. Public awareness and support of tobacco control has translated in the United States into a growing population of Americans who classify themselves as never smokers than ever before [3]. None the less, in 2004, 20 010 new cases of oral cavity cancer, 8250 new cases of pharyngeal cancer and 10 270 new cases of laryngeal cancer were discovered nationwide [1].

The median age at diagnosis for head and neck squamous cell carcinoma (HNSCC) has classically and historically been set at ~60 years. The incidence of a subset of neoplasms originating from the oral cavity and the oropharynx, however, in young adults, age <40, has been steadily and rapidly increasing. Furthermore, carcinoma of the tongue appears to account for the majority of this increase in incidence [1] and has now become the second most common malignancy in the oral cavity [4]. Schantz and Yu [5] reported a sharply increasing trend in the incidence of tongue cancer in young Americans since the mid-1970s. Typically, and in resemblance to HNSCC, 95% of cases of tongue cancer occur after the age of 45 [6].

Early invasive oral disease has improved prognosis over advanced carcinoma, and at present, the 5-year survival for patients with T1 tongue lesions without nodal involvement is ~80% [4]. Disappointingly however, and despite improvements in both diagnosis and local management, the long-term survival rates in patients with head and neck cancer have not increased significantly over the past 40 years and stay behind among the lowest of the major cancers worldwide [1]. Although Shiboski et al. [7] report a higher percentage of localized oral tongue carcinoma in young adults as compared with patients >45 years, many practicing head and neck surgeons acclaim notoriously more aggressive biological behavior of glossal neoplasms in young populations.

The following review presents the arguments against a major role of human papillomavirus (HPV) in the biologically more aggressive oral tongue squamous cell carcinoma (SCC) in the young as opposed to the well-established link between this DNA virus and oropharyngeal squamous cell carcinoma (OPSCC).

The carcinogenic effect of HPV

HPVs of the high-risk types [e.g. human papillomavirus type 16 (HPV16), HPV18, HPV31, HPV33 and HPV45] have been consistently incriminated of inducing carcinogenesis. The genetic material of this DNA virus is divided into three regions: a long control region, an early region and a late region. Following integration of its genome with that of the host, two gene products come out evidently involved in carcinogenesis; the E6 protein which forms a complex leading to the degradation of p53 and therefore an inhibition of apoptosis and the E7 protein that disrupts the active retinoblastoma tumor suppressor gene (TSG), thereby leading to increased DNA synthesis and proliferation. The target cells for such complex interplay, in cervical epithelium, are the basal keratinocytes, their differentiation allowing HPV to replicate and assemble...
new virions, which are then released when the superficial cells flake off [8].

A similar process if not the exact one is presumptively claimed to be implicated in the etiology of head and neck cancer. The viral mechanism of carcinogenesis in OPSCC—in similarity to cervical carcinoma—is presumed to be due to chronic DNA damage, multistep TSG inactivation and oncogene activation. However, the demographics of patients developing HPV-associated HNSCC come forth to broach that such carcinogenic infection, might, in fact be the single event necessary for tumor induction. The characters of the population afflicted support this former statement, younger patients with no risk behaviors (typically nonsmokers/ nondrinkers) [9].

**the established role of HPV in OPSCC**

It has been proposed that the link between HPV and HNSCC is most specific to carcinoma of the tonsils [10, 11] and base of tongue with this association steadily and consistently confirmed through the molecular detection of HPV in oropharyngeal cancers using sensitive and specific techniques [9]. More broadly, HPV DNA was found in 32 of 52 (62%) cases of OPSCC in one series [12]. More specifically, HPV16 DNA was distinctively found in 94.7% of all HPV-positive lesions [13]. Almost half of all the tonsil cancer patients, in another study, had HPV in their tumors, again, with HPV16 as the dominant strain. Moreover, a tendency toward an increase in the proportion of HPV-positive tumors was observed when comparing the percentage of HPV-positive tumors collected from 1992 to 1998 with those collected from 2000 to 2007 [14]. The consistent detection of the papillomavirus in the nonsmoker/nondrinker (NS/ND), in addition, points out to the infectious nature of OPSCC in these patients [15].

Hence, HPV does appear to play a major etiologic role in many cancers of the oropharynx [13]. However, HPV is significantly more common in base of tongue tumors (40.0%) compared with tumors of the mobile tongue (2.3%) [16]. Likewise, other reports have demonstrated that the association between HPV16 and cancer appears strongest for tonsil [odds ratio (OR) = 15.1, 95% confidence interval (CI) 6.8–33.7], intermediate for oropharynx (OR = 4.3, 95% CI 2.1–8.9) and weakest for the oral cavity (OR = 2.0, 95% CI 1.2–3.4) [10].

**HPV and the improved survival in OPSCC**

It is overtly apparent and epidemiologically explicit that the oncogenic processes in the tonsils of nonsmokers differ greatly from those occurring in smokers, the former being mainly and principally related to HPV16 infection. Furthermore, the presence of HPV does appear to correlate significantly with low tobacco ($P = 0.002$), alcohol intake ($P = 0.011$) and a decreased locoregional recurrence rate ($P = 0.039$) [11]. Not only so, but even in smoking patients with HPV-containing tonsillar squamous cell carcinoma (TSCC), remarkably improved disease-specific survival was exhibited [11, 16, 17]. The 5-year figure for overall survival (OS) demonstrated was unvaryingly higher in HPV16-positive patients than in HPV-negative patients (71% versus 36%; $P = 0.023$) [12]. More veraciously, HPV-positive patients with the highest viral loads had more encouraging OS and favorable disease-free survival with recurrences significantly less likely to occur on increasing viral loads. This study, and in addition to the fairly frank observation mentioned earlier, further indicates that viral load might even serve as an independent prognostic indicator for patients with HPV16-associated TSCC [18].

Pathologically, tonsillar lesions related to HPV in younger patients tend to exhibit nonkeratinizing basaloid epithelium and a characteristic immunophenotype and thusly are considered a distinct subtype of HNSCC [19]. The nonkeratinizing epithelium evident with exceedingly more proportion among younger patients with TSCC provides more rigid foundation to the framework that distances this pathological process away from the emergence of a new, biologically more aggressive and characteristically keratinized epithelium of lesions arising from the oral cavity and the mobile tongue in young women.

**HPV and oral cavity cancer**

The detection of genomic material related to HPV in the oral cavity has been reported with various rates [20]. However, the incidence of HPV in oral tongue cancer is low and unlikely to play a major, significant or decisive role in the etiology, pathogenesis and clinical outcomes of this disease in young patients, respectively. The overall frequency of HPV detection in oral tongue cancer was set at 1.96% (1 in 51 cases) in one series [2]. Another report addressing the role of HPV in seven consecutive NS/ND patients from 2003 to 2006 with a SCC located at the oral/mobile tongue failed to detect viral genomes in any of the seven specimens examined [20]. These results, as well as other work, provide supplementary affirmation reinforcing that an etiologic link between HPV and intraoral carcinogenesis in the young is less unequivocal [21], than in the oropharynx, if not mistakable altogether.

**oral histology and cancer**

An important argument against a role of HPV in tongue cancer is cellular histology. Nonkeratinization is characteristic of the epithelia in both locations where HPV has been strongly linked to carcinogenesis, namely the cervix and the tonsils. The tonsils are coated by a stratified squamous nonkeratinized epithelium. The majority of cervical cancers arise in the transformation zone, which is also lined by metaplastic nonkeratinized squamous epithelium [22].

The anterior two-thirds of the dorsum of the tongue is lined by specialized mucosa, bound by connective tissue fibers to the underlying skeletal muscle of the tongue. This specialized mucosa is modified keratinized squamous epithelium covered with small papillae that are visible to the naked eye. According to shape, the papillae can be filiform, fungiform, foliciate or circumvallate. The great majority are filiform papillae, which break through as conical projections of the keratinized epithelium. Among these are scattered the fungiform papillae, which are rounded elevations above the surface of the tongue,
and their surface is nonkeratinized [23]. The turnover time (the transition of a cell from the basal layer to the outermost layer and desquamation) of the keratinized epithelium is ~30 days and that of the nonkeratinized epithelium 25 days [24]. The ventral and lateral surfaces of the tongue, on the other hand, are lined by stratified nonkeratinized epithelium [25].

The keratin layer on the surface of glosso epithelium, possibly, acts as a barrier against external environment invaders [24]. In light of the former statement, the prevalence of HPV was significantly reduced in lesions at keratinized sites (14.5%) compared with nonkeratinized sites (34.4%; P = 0.007; OR = 0.32; 95% CI 0.13–0.81) of the oral cavity in one study. Although this lower frequency might actually indicate that HPV detection by lesion brushing is affected by keratinization, there is growing consensus, however, indicating that the keratinized epithelium is truly less susceptible to HPV infection or, alternatively, the highly proliferative activity in nonkeratinized sites may predispose to HPV infection [26].

Furthermore, OSCCs of nonkeratinized sites were at a less advanced stage, upon presentation, and histologically well differentiated when compared with those originating from other types of epithelia. These patients, in addition, benefited from improved survivals over patients with tumors originating from the keratinized epithelium. On the other hand, 63% of the OSCCs originating from keratinized epithelium were identified as stage III and IV diseases, compared with 32% of nonkeratinized mucosa, and the recurrence rate was also higher in disease arising from keratinized oral linings [24].

Demographically, it has been established that women tend to have more OSCCs arising from keratinized epithelium than men. Moreover, women with no obvious risk behaviors were more commonly afflicted by OSCCs originating from the keratinized masticatory epithelium of the gingiva and hard palate [24].

It has therefore been concluded that these tumors are, most likely, accountable for the emergence of the new category of patients with biologically more aggressive glossal neoplasms upon presentation. And since the majority of such patients happen to harbor disease originating from keratinized epithelium, and as such type of epithelium appears more resilient to HPV infiltration, the DNA virus is unlikely to be considered implicated, at least, in the pathogenesis of many of these lesions.

**immunohistochemistry and oral cavity cancer**

It is clear that epidermal keratinocytes and keratinocytes in keratinizing oral epithelium appear to follow similar differentiation pathways, in contrast to keratinocytes in nonkeratinizing oral epithelium that follow different differentiation pathways. And since the presence of inflammation in some regions of the oral mucosa materializes, evidently, to have the ability to affect keratinocyte differentiation [25], it might well be that HPV is only capable and specific in inducing immortalization effects on the later type of cells explicitly in nonkeratinized epithelium.

More microscopically, keratins are a heterogeneous family of polypeptides that form a subclass of intermediate filaments and serve as excellent markers for various pathways of epithelial differentiation. Furthermore, they have been used to define discrete populations of keratinocytes within tongue epithelia. Cumulative data seemingly indicate that, in addition to the ubiquitous expression of the stratified epithelial-type keratins (K5 and K14), different regions of the tongue displayed distinct patterns of keratin expression. The nonkeratinized epithelium of the lateral and ventral surfaces of the tongue, as well as the epithelium covering the lateral aspects of filiform and fungiform papillae and the interpalatine mucosa of the dorsal tongue, express esophageal-type keratins (K4 and K13). In contrast, the orthokeratinized epithelium overlying the tips of filiform papillae makes skin-type keratins (K1 and K10), and the epithelium covering taste buds synthesizes simple epithelial-type keratins (K8, K18 and K19) [27].

Reports, in accession, indicate a differential effect of two cytokeratins (CKs): 7 and 19 on HPV16 E7 oncoprotein expression, where CK7 would function in protecting and storing the E7 transcript, whereas CK19 would assure the viral messenger RNA (mRNA) translation into the oncopgenic product. In molecular terms, CK19 might, in essence, free the viral E7 mRNA from the translational block exerted by CK7, thus leading to increased E7 protein level and, eventually, to the possibly related carcinogenic events. So and so, such data favor a possible association between HPV16 E7 protein level and CK19 [28]. The signification of this former statement essentially implies that HPV could possess ability to interact with and possibly immortalize keratinocytes only at sites where CK19 expression is evident, namely the nonkeratinized epithelium covering the taste buds on the lateral surface of the tongue. So and so, HPV, possibly, plays a role in the etiology of a subset of oral tongue neoplasms particularly those arising from nonkeratinized epithelium on the lateral border of the tongue. However, since the emergence of the aggressive breed of oral tongue cancer mainly relates to keratinized glossal lesions, HPV does not appear to be a major player in the carcinogenesis of these lesions.

**recent trends in aggressive tongue cancer against an association with HPV**

As stated earlier, oral cavity cancer typically afflicts elderly men during the fifth to eighth decade of life and rarely burdens young patients under the age of 40 [29]. In recent years, however, there has been an increase in the number of patients with SCC of the mobile tongue in the absence of previous alcohol and tobacco use [2, 6, 20]. And because this particularly applies to young women, this group of females, with habitually a less pronounced history of alcohol and smoke consumption, is now emerging as a new epidemiological category of patients [6].

Even though the etiology of invasive glossal lesions in these younger patients is most probably multifactorial [30], it is quite coherent that this younger group does indeed possess biologically more aggressive tumors than stage (tumor–node–metastasis), at presentation, would indicate. In cancer centers, this translates into more complex treatment strategies, frequently necessitating major resections plus irradiation for what apparently and intuitively is early disease [4].
Several studies, in addition, have successfully demonstrated a greater locoregional recurrence and decreased survival rates when compared with that of older patients indicating that lesions arising in younger patients may more accurately reflect a distinct disease entity [29]. This disappointing link between younger age and worsened prognosis is not, in any manner, new. In a study that was undertaken at the Regional Cancer Centre in India, from 1988 to 1990 on patients <35 years with oral SCC, noticeable early lymphatic spread was reported [31]. Likewise, clinicians have also acknowledged that a great majority of young patients present with locally advanced stage [6]. Other investigators revealed that young women with SCC of the anterior tongue had significantly higher rates of recurrent disease and the interval to recurrence was significantly shorter than in older patients [29, 32]. This might explain why in one report, nonsmokers had significantly worse prognoses as compared with the ‘typical’ high-risk elderly patients [33]. Some have taken this statement even further, indicating that in patients with SCC of tongue, young age is an independent predictor of worsened survival [29].

However, with all this said, it remains statistically unproven whether oral cancer in the young is inherently more aggressive with worse prognosis than the disease in older individuals [29].

On the other side of the spectrum, some argue that since it is so rare, when cases do occur, among younger patients, they are often misdiagnosed and inappropriately treated leading to delay in definitive therapy [29]. Additionally, and in context with this former statement, studies have demonstrated, in younger individuals, a local and regional control rate at 64.8%, a figure roughly identical to that of older patients in that series. Similarly, this article narrates that the prognosis of oral SCC in the young patient does not appear to be at variance from that in the older population [34]. A number of investigators were also able to channel the development of SCC at a young age to heavy smoking and drinking, demonstrating that the poor survival in many patients is actually due to self-neglect and failure to seek medical care early in the course of disease [35], rather than any inherent difference in disease process.

In either case, HPV is unlikely to constitute a significant factor in the rising trend of oral tongue cancer in the young population [2]. Tongue carcinoma in the young which is more or at least equally aggressive to glossal neoplasms in the old clearly defy HPV interplay in the demographics of head and neck cancer in general and thus deny HPV any major role in their pathogenesis.

conclusions

All previously described trends and tendencies and their underlying histological and immunohistochemical statements in oral squamous cell carcinoma (OSCC) contradict reciprocation to emerging HPV-associated neoplasms in nearby locations such as the oropharynx or tonsils. To independent observers, the DNA virus has been an active player in improving the overall prognosis and OS in OPSCC patients. The undeniable epidemiological effect of HPV on oropharyngeal cancer has been the emergence of a new category of patients with improved OS. Thus, the mere emergence of the new epidemiological entity, with worsened prognosis, in oral tongue cancer contradicts any major HPV involvement in carcinogenesis of these lesions inside the oral cavity. These tumors are notoriously more aggressive, in terms of biology, in young populations. Moreover, such lesions are more inclined to originate from keratinized epithelium, the type of epithelium proven to have heightened HPV-resistant capabilities. Yet, this does not deny a possible role of HPV in oral cavity carcinogenesis altogether; HPV might be implicated in premalignant lesions and in tumors arising from nonkeratinized epithelium of the lateral surface of the tongue.

And since such lesions are evidently less aggressive, this goes well in context with the effects of HPV on head and neck cancer prognosis and survival in general. Moreover, and with all this said, the papillomavirus might actually play a minor and perhaps secondary role in the etiology of more aggressive mobile tongue neoplasms. And since the herpes simplex (HSV) virus appears to have a higher association with cell keratinization patterns as compared with HPV [36], a coinfection theory of carcinogenesis engaging both DNA viruses in more aggressive OSCC occurring in young populations should be further cross-examined, with future research concentrating and more closely examining yet another possible relationship—HSV and mobile tongue cancer in the young.

references