Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas

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Introduction

Human papillomavirus (HPV) infection is the principal cause of a subset of oropharyngeal squamous cell carcinomas (OPSCC). Epidemiological associations with sexual behavior and HPV exposure are strong and consistent for OPSCC, but less so for oral cavity squamous cell carcinoma (OCSCC). A role for HPV in the pathogenesis of OCSCC therefore remains somewhat controversial.

In a systematic review by Kreimer and colleagues, HPV DNA was detected in 24% of OCSCC worldwide. However, the presence of HPV DNA alone is insufficient evidence for a causal association from a molecular perspective. Expression of HPV oncogenes E6 and E7 remains a gold standard for classification of an HPV-caused cancer and is necessary for tumor initiation and maintenance of the malignant phenotype in model systems of oral cancer. While case reports have provided compelling evidence of HPV E6/E7 expression in some cases of OCSCC, comprehensive analyses of large series have not been reported.

A recent analysis of OPSCC collected as part of the Surveillance, Epidemiology and End Results (SEERs) program in the United States (US) estimated that the proportion of OPSCC attributable to HPV infection increased from 16% to 72% between 1988 and 2004. An analogous fourfold increase in the HPV-attributable fraction for OCSCC could elevate even a negligible fraction to a significant fraction at the population level. We therefore evaluated a large series of consecutive cases of OCSCC diagnosed in North America from 2005 to 2011 for high-risk (HR)-HPV E6/E7 oncogene expression.
Methods

Study population and design

A four-institution, retrospective case-series was designed to estimate the etiologic fraction for HPV in OCSCC and was powered to detect a prevalence of as low as 0% with precision. Zero positives among 400 cases would provide a one-sided 97.5% CI of 0–0.92%. Adjusted for an estimated 7.5% in-evaluable samples, a total of 430 cases were included in the analysis.

Eligible tumor specimens included consecutive, newly diagnosed cases of formalin-fixed, paraffin-embedded, pathologically-confirmed, in situ or invasive squamous cell carcinoma of the oral cavity (inclusive of lip, ventricle of mouth, gingiva, alveolar process, tongue, buccal mucosa, hard palate, floor of mouth and retromolar trigone) diagnosed at four academic medical centers in North America, including: The Ohio State University, Columbus, OH; Princess Margaret Hospital, Toronto, CA; University of Chicago, Chicago, IL; and The University of California, San Francisco (UCSF), CA. Consecutive cases were identified from pathology archives retrospective from a diagnosis on December 31, 2011 until a total of 430 were obtained. Anatomic site of tumor origin was determined by the operating physician and confirmed by the pathologist. Subject age, gender and AJCC TNM stage were extracted from pathology reports, but stage was not available for some cases from a biopsy referral service at UCSF. Institutional Review Board approval was obtained from all participating sites.

Histopathological analysis

Histopathological interpretation was performed by pathologists (AS, ML) masked to laboratory analysis. Hematoxylin and eosin stained slides were used to confirm presence and estimate the proportion of in situ or invasive squamous cell carcinoma in the specimen as well as to classify histopathological features, including differentiation status (well, moderate, poor) and histopathological variants of squamous cell carcinoma. Tumors were categorized into variants of squamous cell carcinoma based upon the presence of specific histopathological features as previously described for acantholytic, adenosquamous, basaloid, carcinoma cuniculatum, verrucous carcinoma, papillary, spindle cell, and lymphoepithelial-like variants. All tumors were evaluated for expression of a surrogate biomarker of HPV E7 oncoprotein function, the cdk inhibitor p16, by means of an immunohistochemical analysis with a mouse monoclonal antibody (MTM Laboratories, City State) visualized with the use of an autostainer and a cone-view secondary detection kit. Positive p16 expression was defined as an H score of 60 or greater as previously described, where the H score was derived from the cross product of intensity of staining (0, 1, 2, 3+) and percent of tumor staining at maximum intensity.

The specificity of HPV to tumor cell nuclei was evaluated for all tumors positive for HPV DNA by use of the in situ hybridization-catalyzed signal amplification method for biotinylated probe (Genpoint, Dako, Carpinteria, CA) with either a biotinylated DNA probe that was specific for HPV16 (code Y1407, Dako) or a wide spectrum probe for detection of HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82, three potentially high-risk types (6, 11, 40, 43, 44, 54, 69, 71, 70, 74) by consensus primer PCR amplification by use of the SFF.10 primer system designed to amplify a 65 bp fragment of the conserved L1 region of the genome, followed by reverse line blot hybridization for HPV type specification (The Inno-LiPA assay, Innogenetics, Gent, Belgium). Samples positive for H(human)DNA control were considered evaluable as indicated by the manufacturer.

HPV type-specific TaqMan quantitative real-time PCR assays designed to amplify a 60–136 bp fragment of the E6 or E7 region (depending on type) of the 15 HPV types classified as high-risk as per Munoz and colleagues noted above were used: (1) to analyze all tumors for HPV16 E6 DNA; (2) to confirm HPV type-specific detection in samples positive by the Inno-LiPA assay; and (3) to analyze samples in-evaluable by Inno-LiPA (human DNA control negative) but evaluable by ERV3 for 15 HR-HPV DNA types as previously described. Primer and probe sequences as well as reaction conditions are shown in Supplementary Table 1. Samples above the lower limit of reproducibility of the assays (for all, ≥3 copies) were considered positive. HPV viral load in tumors was estimated from the quotient of viral load and ERV-3, adjusted to the percent tumor present in the sample.

Purified tumor RNA was evaluated for HR-HPV E6/7 mRNA expression after reverse transcription to cDNA by use of HPV type-specific quantitative real-time TaqMan PCR assays noted above. All tumors were evaluated for HPV16 E6/7 expression. Additionally, all tumors positive for HPV DNA were evaluated for HPV E6/7 expression by qRT-PCR for the corresponding HPV type(s) detected. Results were reported as HPV E6/7 mRNA expression level.
All p16-positive tumors that were HPV-negative by the above analysis were further screened for HPV DNA sequences from HPV.
types other than the high-risk and low-risk types noted above by consensus primer PCR by use of GP5+/6+ primer sets followed by gel electrophoresis and DNA sequencing.

Statistical considerations

Differences between evaluable and in-evaluable cases as well as type-specific gold standard HPV-positive and -negative samples in demographic and clinical characteristics were analyzed using contingency table chi-square tests or Fisher’s exact test. Nonparametric Mann–Whitney or Kruskal–Wallis tests were used to determine equality of medians in age at diagnosis and laboratory testing values. Contingency tables were used to determine sensitivity, specificity, and positive and negative predictive values (and 95% confidence intervals [CI]) for p16 classification compared to HR-HPV E6/7 expression. All reported p values were two-sided. Statistical analyses were performed by use of Stata 10.1 software (Stata-Corp, College Station, TX).

Results

A flow diagram of the laboratory analysis performed is shown in Fig. 1. A total of 430 OCSCC were obtained for analysis, and 21 (4.7%) tumors were deemed in-evaluable due to inability to amplify a control gene (ERV-3) by PCR or absence of detectable expression of a control gene (RPLPO) by qRTPCR. The demographic and clinical characteristics of the 409 cases of OCSCC included in the final analysis are shown in Table 1. When evaluable and in-evaluable OCSCC were compared with regard to these factors, evaluable tumors were significantly more frequent among men and were more likely to be tongue cancers (Supplementary Tables 2 and 3).

The total yield and purity of DNA (median 1.95 ugs [interquartile range [IQR], 1.05–5.98], 260/280 ratio 1.63 [IQR 1.56–1.69]) extracted from paraffin-embedded tumors was very good, with a median yield of 1,068 (IQR 562–1860) human diploid genome equivalents per microliter of sample (total 50 l), as estimated by real-time PCR for a control gene (ERV-3). The RNA was of similarly high quantity and quality (median 2.70 ugs [IQR 1.38–6.36], 260/280 ratio 1.95 [IQR1.83–2.0]), with a median of 371 (IQR 167–878) RPLPO copies per microliter of sample, as estimated by qRT-PCR. The distribution of values for ERV3 and RPLPO among evaluable cases is shown in Fig. 2, stratified by calendar period of diagnosis. Although values declined significantly with calendar time, yield among older samples remained sufficient for analysis.

In our analysis, HR-HPV DNA was detected in 40 of 409 (9.8%, 95%CI 6.9–12.7) OCSCC. Neither possibly high-risk (26, 53, 66) nor low-risk (6, 11, 40, 43, 44, 54, 69, 71, 70, 74) HPV types were detected in any of the tumors. When evaluated by use of the Inno-LiPA assay, 31 of 409 OCSCC were negative for the human DNA control. However, all of these samples had high human DNA content when evaluated for a control gene (ERV-3) by quantitative real-time PCR (median 7327, IQR [3343, 12678]), consistent with the presence of an inhibitor of the Inno-LiPA assay. Therefore, these 31 samples were also evaluated for HPV DNA and mRNA by use of 15 different HR-HPV type-specific real-time PCR assays, and none were positive. Forty of 378 evaluable samples were positive in the Inno-LiPA assay [HPV16 (n = 27), HPV 18 (2), HPV31 (2), HPV33 (2), HPV35 (1), HPV39 (2), HPV45 (1), HPV51 (2), HPV52 (1)]. HPV16 DNA and mRNA were not detected in any additional cases when all 409 tumors were evaluated by real-time PCR and qRT-PCR.

Of the 40 samples positive for HR-HPV DNA by the Inno-LiPA assay, 27 were confirmed positive by type-specific real-time PCR for the corresponding HPV type. When evaluated for HR-HPV E6/7 expression, 24 cases (5.9%, 95%CI 3.6–8.2) were positive [HPV16 (n = 15), HPV 18 (2), HPV31 (2), HPV33 (2), HPV35 (1), HPV39 (1), HPV45 (1)]. The laboratory analysis for the 16 OCSCC that were HR-HPV positive by Inno-LiPA but negative for HPV E6/7 expression analysis is summarized in Supplementary Table 4. Of note, the HPV viral load among cases that were positive for HPV DNA but negative for E6/7 expression was significantly lower than for cases positive for E6/7 expression (0 [IQR 0.0–0.002] versus 9.8 [IQR 2.2–152.0] copies per cell, p < 0.001). The specificity of HPV DNA to tu-

Figure 1 Flow diagram of laboratory analysis of 430 oral cavity squamous cell carcinomas. See text for detailed methods. Abbreviations: SCC, squamous cell carcinoma; ERV3, endogenous retrovirus 3; RPLPO, human ribosomal protein large; IHC, immunohistochemistry; HR-HPV, high-risk human papillomavirus; RT-PCR, real-time polymerase chain reaction; ISH, in situ hybridization; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; WS, wide spectrum.
mor cell nuclei was confirmed by HPV in situ hybridization for 20 of 24 cases positive for HR-HPV E6/7 expression. Representative cases are shown in Fig. 3.

The characteristics of HR-HPV E6/7 expression positive and negative oral cavity cases are compared in Table 1. Median age of HPV-positive cases was similar to HPV negative cases (61 versus 64 years, \( p = 0.35 \)). A majority of HPV-positive cases were floor of mouth or tongue cancers, but the anatomic-site distribution did not differ from HPV-negative cases. HPV-positive cases were significantly more likely than HPV-negative cases to be diagnosed among men, to be of early tumor stage, to be poorly differentiated, basaloid histopathology.

When tumors were evaluated for p16 expression, 46 (11.2%, 95%CI 8.2%–14.3%) of 409 were positive by H score criteria, including 19 of 24 HR-HPV E6/7 positive tumors and 27 of 385 negative tumors. The sensitivity of p16 for HR-HPV E6/7 expression was 79.2% (95% CI: 57.9–92.9), specificity 93.0% (95% CI: 90.0–95.3), positive-predictive value 41.3% (95% CI: 27.0–56.8) and negative-predictive value 98.6% (95% CI: 96.8–99.6). When evaluated for the presence of additional HPV types by use of GP5+/6+ consensus primer PCR, no HPV DNA sequences were detected in the 27 p16-positive/HPV-negative cases. A summary of the clinical characteristics and HPV testing results for all 24 OCSCC positive for HR-HPV E6/7 expression is shown in Table 2.

Discussion

The incidence of HPV-positive oropharynx cancer increased by 225% from 1988 to 2004 in the United States, in contrast to a 50% decline in incidence of HPV-negative cancers. Presumably, the population-level changes over calendar time in tobacco smoking and sexual behaviors that are hypothesized to underlie this etiologic shift would similarly affect OCSCC. Given the consistently high estimates (> 70%) of the HPV-etiologic fraction in oropharyngeal cancers diagnosed in North America after 2000\(^{15,21}\), we specifically chose to investigate the etiologic fraction for HPV among a series of contemporaneously diagnosed cases of OCSCC from North America. To our knowledge, this is the largest and most comprehensive analysis of HR-HPV E6/7 expression specific to oral cavity cancers. We observed HR-HPV E6/7 expression in approximately 6% of OSCC. Analogous to oropharynx cancers, HPV-positive cancers were significantly associated with male gender, early tumor stage, and poorly differentiated, basaloid histopathology.

In contrast to the anatomic site specificity for the lingual and palatine tonsils in the oropharynx, HPV-positive and negative OCSCC had a similar anatomic site distribution. In this study, the small tumor size and the anatomic discontinuity of the HPV-positive OCSCC from the oropharynx indicate they are unlikely to represent misclassified oropharynx cancers. The oral region therefore appears analogous to the genital tract with regard to field effects of HPV infection, wherein the overwhelming majority of cancers arise from distinct anatomic sites with apparent increased susceptibility to HPV infection and/or transformation (e.g., the tonsil crypt and cervical transformation zone), with a minority sporadically arising from other anatomic sites (e.g., the oral cavity and the vagina, vulva).

Several recently published studies have identified a high proportion (35–55%) of OCSCC with detectable HPV DNA by sensitive PCR methods.\(^{22,23}\) Our data indicate that caution should be used in inferring HPV-causality based on DNA detection alone, as approximately half of HPV DNA-positive cases were confirmed as positive for HR-HPV E6/7 expression. Additionally, the viral load was markedly lower among HR-HPV-E6/7 expression-negative tumors, possibly consistent with the presence of a pathophysiologically unrelated oral HPV infection. In a recent population-based study in the US, gender, age and intensity of current tobacco smoking were strongly associated with prevalent oral HPV infection.\(^{24}\) In that study, oral HPV infection was detected in ~10% of men, ~11% of individuals aged 55–64 years and among 20% of current smokers of one or more packs per day. Given the gender and age distribution of our study population, approximately 10–20% would be expected to have an oral HPV infection. In a recent meta-analysis of case-control studies, oral HPV infection was associated with a fourfold increase in odds of oral cavity carcinoma (OR 3.98, 95%CI 2.62–6.02).\(^{25}\) However, the authors noted that their analysis did not account for the possible effects of tobacco smoking. Therefore, there is considerable potential for residual confounding of the association between oral HPV infection and OCSCC by tobacco smoking. Nevertheless, relatively strong associations have been observed between high-risk oral HPV infections overall and OCSCC.
in case-control studies after adjustment for tobacco exposure,\textsuperscript{26,27} in contrast to weak associations observed for serologic measures of HPV16 exposure.\textsuperscript{28–32} The HPV type distribution we observed in our series among OCSCC was significantly more diverse than for the corresponding series of oropharyngeal cancers (94.9% HPV16, 5.1% non-16),\textsuperscript{15} with approximately 38% of positive cases attributable to HR-HPV types other than 16. Studies that focus exclusively on HPV16 may therefore underestimate associations.

\textit{p16 IHC is an accepted surrogate diagnostic biomarker for HPV status for OPSCC, and in our recent analysis had a positive predictive value of \~93\% for HR-HPV E6/7 expression.\textsuperscript{15} However, the positive-predictive value of p16 for HPV in OCSCC is very poor...}

\textbf{Figure 3} Representative histopathology for oral cavity squamous cell carcinomas that were positive for HR-HPV E6/7 expression. Cases evaluated by hematoxylin and eosin staining (A, D, G, J), for expression of p16 by IHC (B, E, H, K), and for HPV presence by ISH (C, F, I, L). Panel A–C is an example of a poorly differentiated, basaloid squamous cell carcinoma of the alveolar process that was p16-positive (B) and HPV16 ISH-positive (C). The tumor was positive for HPV16 E6/7 expression. Note the hyperchromatic cells with scant cytoplasm, marked nuclear atypia, and high mitotic activity characteristic of basaloid carcinoma. Panel D–F is an example of a well differentiated squamous cell carcinoma in situ of the floor of mouth that was p16-positive (E) and HPV31 ISH-positive (F). The tumor was positive for HPV31 E6/7 expression. Panel G–I is an example of a well differentiated squamous cell carcinoma of the hard palate that was p16-positive (H) and HPV16 ISH-negative (I). The tumor was negative for HPV DNA and mRNA. Panel J–L is an example of a poorly differentiated, basaloid squamous cell carcinoma of the floor of mouth that was p16-negative (K) and HPV16 ISH-positive (L). The tumor was positive for HPV16 E6/7 expression.
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our study was not population based. we note, however, that the
the population-level HPV-attributable fraction in North America.
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the larynx will need to be evaluated.
HPV status in tumors arising from other anatomic sites such as
in OSCC. Whether or not p16 expression is predictive of tumor
cate that p16 IHC should not be used as a surrogate for HPV testing
Although constituting a low percentage of OSCC overall, the
of HPV in OSCC relative to OPSCC, this is not unexpected.
(41%), with the majority of p16-positive cancers being negative
for HR-HPV E6/7 expression. Given the lower overall prevalence of
HPV in OCSCC relative to OPSCC, this is not unexpected.
Although constituting a low percentage of OCSCC overall, the
p16-positive HPV-negative proportion (7.0%) exceeded that for
HR-HPV E6/7 expression-positive OCSCC. Our data therefore indicate
that p16 IHC should not be used as a surrogate for HPV testing
in OCSCC. Whether or not p16 expression is predictive of tumor
HPV status in tumors arising from other anatomic sites such as
the larynx will need to be evaluated.
our study has several potential limitations. Although our esti-
mate of the HPV-etiologic fraction was precise, it may not reflect
the population-level HPV-attributable fraction in North America.
Our study was not population based. we note, however, that the
HPV-etiologic fraction of 68% for oropharynx cancers in our series
of patients diagnosed after 2000 was quite similar to the 72% we
previously observed in a US population-based analysis with identi-
cal laboratory methods. A US population based analysis of HPV in
OCSCC currently being conducted by the US centers for Disease
Control and Prevention will address this issue. DNA and RNA deg-
radation in paraffin may decrease sensitivity of HPV detection, but
would result in an underestimate of the etiologic fraction. Addi-
tionally, our PCR assays are all specifically designed to yield small
amplons, as appropriate for degraded DNA. although we ob-
served a significant decline in DNA and RNA yield with increasing
time since diagnosis, the quality and quantity remained far above
that necessary for the specimen to be evaluable.
It is now clear that HPV-positive OPSCC constitutes a unique
epidemiological and clinical entity. Risk factor profiles and prog-
dictions between HPV status and cofactors (e.g. tobacco and alcohol
use) or survival outcomes for OCSCC, and therefore this will require
further study. Of particular interest will be the association of HPV
and p16 status in combination with survival of OCSCC and whether
or not the small subset of HR-HPV E6/7 positive OCSCC could be
reated with organ preservation therapy in lieu of surgical
resection.
Despite these limitations, our data may have important implica-
tions for the primary prevention of oral cavity carcinoma. The
International Agency for Research on Cancer (IARC) recently esti-
mated the HPV-attributable fraction for OPSCC to be 26% world-

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<td>Pathological</td>
<td>T4b</td>
<td>N3</td>
<td>16</td>
<td>6.7</td>
<td>1565045.0</td>
<td>Pos</td>
<td>Pos</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Lip</td>
<td>SCC, conventional</td>
<td>Well</td>
<td>Pathological</td>
<td>T4a</td>
<td>N0</td>
<td>39</td>
<td>309.2</td>
<td>3373.1</td>
<td>Pos</td>
<td>Pos</td>
</tr>
</tbody>
</table>
wide, accounting for approximately 22,500 incident cases of OPSCC each year. If as high as 5% of the 263,000 annual cases of OCSCC are also due to HPV infection, a total of 35,650 oral cancer cases worldwide might be preventable through HPV vaccination (assuming efficacy equivalent to that for genital infection). In the US for 2012, the corresponding number would be ~10,500 cases. The broader HPV type distribution for OCSCC than OPSCC might also have implications for potential benefits from newer generation HPV vaccines that may protect against a broader range of HPV types.

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Conflict of interest statement

None declared.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.oraloncology.2012.07.002.

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