The Oral Cavity Contains Abundant Known and Novel Human Papillomaviruses From the *Betapapillomavirus* and *Gammapapillomavirus* Genera

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Background. Human papillomaviruses (HPVs) primarily sort into 3 genera: *Alphapapillomavirus* (α-HPV), predominantly isolated from mucosa, and *Betapapillomavirus* (β-HPV) and *Gammapapillomavirus* (γ-HPV), predominantly isolated from skin. HPV types might infect body sites that are different from those from which they were originally isolated.

Methods. We investigated the spectrum of HPV type distribution in oral rinse samples from 2 populations: 52 human immunodeficiency virus (HIV)–positive men and women and 317 men who provided a sample for genomic DNA for a prostate cancer study. HPV types were detected with the MY09/MY11 and FAP59/64 primer systems and identified by dot blot hybridization and/or direct sequencing.

Results. Oral rinse specimens from 35 (67%) of 52 HIV-positive individuals and 117 (37%) of 317 older male participants tested positive for HPV DNA. We found 117 type-specific HPV infections from the HIV-positive individuals, including 73 α-HPV, 33 β-HPV, and 11 γ-HPV infections; whereas, the distribution was 46 α-HPV, 108 β-HPV, and 14 γ-HPV infections from 168 type-specific infections from the 317 male participants.

Conclusions. The oral cavity contains a wide spectrum of HPV types predominantly from the β-HPV and γ-HPV genera, which were previously considered to be cutaneous types. These results could have significant implications for understanding the biology of HPV and the epidemiological associations of HPV with oral and skin neoplasia.

Human papillomaviruses (HPVs) are a heterogeneous group of closed-circular, double-stranded DNA viruses ∼8 kb in size that are established as the etiological agents of invasive cervical, anogenital, and oropharyngeal cancers [1, 2]. Currently, >140 HPV types have been fully characterized; the majority cluster into 3 genera: *Alphapapillomavirus* (α-HPV), predominantly isolated from genital lesions; *Betapapillomavirus* (β-HPV), previously referred to as *Epidermodysplasia verruciformis*–related types; and *Gammapapillomavirus* (γ-HPV). The HPV types from the latter 2 genera have been mainly isolated from skin lesions [3, 4]. It has been assumed that HPV tissue tropisms reflect the sites from which the original types were isolated. Hence, the corresponding initial sites of isolation have led to the consequent classification of α-HPVs as mucosal or genital types and β- and γ-HPVs as cutaneous types. The genital high-risk oncogenic HPV types are all members of the α-HPV genus. The tissue tropism of a group of viruses is an important biological phenotype in understanding how viruses evolve in ecological niches and induce pathogenic consequences in their hosts.

Increasing evidence indicates that persistent HPV infection, particularly with certain high-risk oncogenic HPV types such as HPV type 16, is associated with some oral and/or oropharyngeal cancers [1, 5, 6]. However, previous oral HPV surveys mainly tested for α-HPV infections, possibly underestimating the overall prevalence of HPV infection in the oral cavity and in cancers of these sites [6, 7].

To evaluate the distribution of HPV in the oral cavity, we employed 2 polymerase chain reaction (PCR) systems using MY09/11 and FAP59/64 primer sets to detect α-, β-, and γ-HPV. The participants who provided oral rinse samples were part of 2 independent studies and included (1) human immunodeficiency virus (HIV)–positive men and women from an oral medicine clinic and (2) HIV-negative men of Ashkenazic descent participating in a case-control study of prostate cancer [8]. As a comparison group, a subset of cervical samples from a population-based study in Costa Rica was tested with both primer sets [9]. The HPV DNA types detected indicate that the oral cavity contains a wide spectrum of known and novel HPV types that phylogenetically cluster into the β- and γ-HPV genera, which were previously considered to be nearly exclusively skin types. The difference in the spectrum of HPV types detected in the oral cavity and exfoliated cervicovaginal cells has significant implications for our understanding of the anatomic tissue tropisms, the evolution of HPVs, and the epidemiological association of HPV with oral and skin neoplasia.

METHODS

Study Populations

Oral rinse samples were obtained from 2 studies: (1) the Cancer, Longevity, Ancestry, and Lifestyle study (CLAL), which collected oral rinse samples as a source of genomic DNA from men of Ashkenazi descent participating in a prostate cancer study [8]; and (2) a sampling study of the oral cavity in HIV-infected men and women attending an oral medicine clinic. The majority (94%) of participants in the latter study were receiving antiretroviral drugs; of the 46 participants with CD4 cell counts within 6 months of obtaining the oral rinse specimen, 7 had <200 cells/μL, 19 had 200–500 cells/μL, and 20 had >500 cells/μL. The cervical samples were from the population-based study of HPV natural history in Guanacaste, Costa Rica [9]. They represent a nonrandom subset of women whose specimens were retested as part of a study to evaluate the detection of HPV using FAP primers. The study protocols were approved by the appropriate institutional review boards, and all participants gave informed written consent.

Specimen Collection and DNA Isolation

Participants who provided an oral rinse sample were given a self-contained mouthwash collection kit consisting of a 44-mL bottle of Scope brand mouthwash and two 25-mL screw-top collection vials for self-sampling. All self-collection kits included detailed instructions about collection of specimens as well as prepaid and return-addressed mailers. Participants returned their mouthwash samples by postal service. Cervical cells for HPV detection were collected by a Dacron swab placed into a preservative buffer, as described elsewhere [9, 10].

All samples were processed in a BioSafety Cabinet in a laboratory that was physically separated from where the PCR amplifications were performed. One water blank was processed with 19 regular samples to monitor contamination. Genomic DNA was isolated from the mouthwash samples as described elsewhere [8]. Briefly, exfoliated cells from the oral cavity rinse were pelleted by centrifugation and rinsed with TE buffer (10 mmol/L Tris HCl and 1.0 mmol/L ethylenediaminetetraacetic acid [EDTA]; pH, 8.0), and the cell pellets were incubated in 1.5 mL of Buccal Cell Lysis solution (10 mmol/L Tris HCl, 10 mmol/L EDTA, 0.1 M of NaCl, 2% sodium dodecyl sulfate (SDS), and 1.5 mg of proteinase K [Roche, Indianapolis, IN]; pH, 8.0) at 55°C overnight and then treated with RNase A (Gentra Systems), followed by phenol-chloroform extraction using a Phase Lock Gel Tube protocol (Eppendorf, Westbury, NY). The DNA was precipitated, resuspended in 200 μL of TE buffer, and stored at −20°C. For cervical specimens, an aliquot of the specimen was lysed, and the DNA was precipitated by ammonium acetate–ethanol solution, pelleted by centrifugation, and resuspended in 100 μL of TE buffer as described elsewhere [11].

PCR Amplification and Genotyping

HPV DNA was detected from 5 μL of purified DNA from clinical material by means of either MY09/MY11 [11] or FAP59/64 [12] L1 degenerate primer PCR systems with Gold Taq polymerase (Applied Biosystems, Foster City, CA). Both HPV PCR assays included a control primer set (PC04/GH20), which simultaneously amplified a 268-bp cellular β-globin DNA fragment and served as an internal control for amplification. In addition, for every 48 specimens tested, a 100-cell copy and a 2-cell copy of SiHa DNA served as the HPV-positive controls, and a 100-cell copy of HuH7 DNA served as an HPV-negative control. All PCR assays were performed in an Applied Biosystems 9700 thermocycler, and the PCR products were screened for HPV by low-stringent Southern blot hybridization using a generic radioactive probe mix (ie, HPV types 11, 16, 18, 51, 73, and 81) that covered the major α-HPV species, as described elsewhere [11, 13, 14].

HPV-positive PCR products underwent dot blot hybridization using biotinylated type-specific oligonucleotide probes that recognized type-specific sequences within the MY or FAP fragments. The MY hybridization assay included probes specific for 47 HPV types (types 2, 6, 11, 13, 16, 18, 26, 31–35, 39, 40, 42–45, 51–59, 61, 62, 64, 66–74, 81–85, 89, 90, 97, 102, and 106), and the FAP hybridization assay included probes specific for 46 HPV types (types 2, 3, 5–8, 10–11, 15–19, 21, 23–32, 38–40, 42–43, 45, 48–54, 56–59, 60, 65, 77, 91, and 93) [11, 13, 14]. The numeric

Table 1. Distribution of Human Papillomavirus (HPV) Types and Genera in Oral and Cervical Samples

Anatomic site, HIV status	No. (%) of samples tested		No. (%) of samples with HPV types within each genus[a]			No. of unique types detected within each genus				Cumulative no. (%) of HPV types detected within each genus			
	Total	HPV-positive	α	β	γ	α	β	γ	Total	α	β	γ	Total[b]
Oral cavity													
Positive	52	35 (67)	21 (60)	20 (57)	7 (20)	30	14	9	53	73 (62)	33 (28)	11 (10)	117 (3.3)
Negative	317	117 (37)	29 (25)	87 (74)	14 (12)	24	27	8	59	46 (28)	108 (64)	14 (8)	168 (1.4)
Cervix													
Negative	1,807	257 (14)	248 (96)	6 (2)	9 (4)	43	4	6	53	366 (96)	6 (1)	10 (3)	382 (1.5)

NOTE. HIV, human immunodeficiency virus.

[a] Samples with HPV infection from >1 genus are counted for each genus.

[b] Mean numbers of types per HPV-positive sample are indicated in the parentheses.

measure of signal strength (1–5) was utilized as a validated semiqualitative measure of viral load [15].

Products that were HPV-positive but tested negative by all type-specific probes were considered to tentatively represent uncharacterized HPV types and were sequenced at the Einstein Genomics Core Facility (Bronx, NY). Sequence results were searched against GenBank and the Burk Laboratory papillomavirus database, using BLAST for classification. Although cloning was not performed prior to sequencing, chromatograms were carefully examined to screen for possible multiple infections. HPV types were classified according to the method of Bernard et al [4]. Potential novel types were cloned, sequenced, and submitted to the Human Papillomavirus Reference Laboratory (Heidelberg, Germany) for official designation.

RESULTS

Prevalence of HPV Infection in the Oral Cavity

To characterize the full spectrum of HPV types from the α-, β-, and γ-HPV genera that might be missed because of the limited spectrum of any 1 type of HPV PCR primer combination, we tested samples with 2 PCR primer systems that amplify a broad spectrum of HPV types from these genera. The study was conceived as an ecological investigation to characterize multiple samples from the oral cavity and cervicovaginal area. Samples from 3 different populations were utilized. Unexpectedly, oral rinse samples from 117 (37%) of 317 men who donated a specimen for a prostate cancer study were positive for HPV DNA, of which 30% had ≥2 HPV types detected (Table 1). The identification of HPV DNA in oral rinse specimens was exceptionally high in HIV-positive male and female participants (35 of 52 specimens [67%]); of the positive samples, 77% had multiple HPV types detected.

Diversity of HPV Types and Genera in the Oral Cavity

Of the HIV-negative participants who provided an HPV-positive oral rinse sample (n = 117), 29 samples (25%) were infected with an α-HPV type, 87 samples (74%) with a β-HPV type, and 14 samples (12%) with a γ-HPV type. When considering the cumulative number of HPV types in single-type and multiple-type infections, β-HPV types were detected most frequently and represented 64% (n = 108) of total HPV types detected, followed by 28% α-HPV types (n = 46) and 8% γ-HPV types (n = 14) (Table 1). HPV type 5 was the most common type and was observed in 17 samples (Figure 1; Supplementary Table 1).

Among the HPV-containing oral rinse samples from the HIV-positive individuals (n = 35), 21 samples (60%) were infected with at least 1 α-HPV type, 20 samples (57%) with at least 1 β-HPV type, and 7 samples (20%) with at least 1 γ-HPV type (Table 1). However, the HPV distribution within genera differed slightly when the total number of HPV types detected (n = 117) was considered: 73 α-HPV infections (62%), 33 β-HPV infections (28%), and 11 γ-HPV infections (10%). HPV type 58 was the most common single type detected in this set of samples from HIV-positive participants (8 of 52 infections). There was no statistically significant association between CD4 cell count and HPV positivity.

To contrast the difference between HPV infections in the oral cavity and cervical sites, 1807 cervical samples from HIV-negative Costa Rican women were tested for HPV infection by means of the same MY09/11 and FAP59/64 PCR systems. These samples were originally selected from different groups of women and are not representative of women in the study but serve to evaluate the detection of β- and γ-HPV types in cervicovaginal cells. Fourteen percent (n = 257) of samples were positive for HPV infection. The cumulative number of HPV types within each genus detected from sampling the cervix was as follows: 366 α-HPV types (96%), 6 β-HPV types (1%), and 10 γ-HPV types (3%). HPV type 16 was the most prevalent with a total of 37 infections (2.0%). Seventy-three of 257 samples (28%) were infected with multiple HPV types. Thus, samples from the cervix were predominantly infected with α-HPV types, whereas the majority of HPV-positive oral rinse specimens contained β- and γ-HPV types.

Figure 1. Prevalence of individual human papillomavirus (HPV) type infections in oral and cervical sites. The *y*-axis represents numbers of infections of each type. A2, degenerated FAP probe for HPV types 3, 10, 28, and 77; A3, mixed FAP probes for HPV types 61, 62, 71, 72, 84, 86, 87, 89, 90, 102, and 106; A5/6, mixed FAP probes for HPV types 26, 51, 53, 56, 66, 69, and 82; A7, mixed FAP probes for HPV types 18, 39, 45, 59, 70, 85, and 97; A8, mixed FAP probes for HPV types 7, 40, 43, and 91; A9, mixed FAP probes for HPV types 31, 33, 35, 52, and 67; B1, degenerated FAP probe for HPV types 19, 21, 24, 25, and 93; B2, degenerated FAP probe for HPV types 15, 17, 22, 23, and 38; Ga, degenerated FAP probe for HPV types 48, 50, 60, and 65; HIV, human immunodeficiency virus; HIV+, HIV-positive participants; HIV−, HIV-negative participants.

Table 2. Novel Human Papillomavirus (HPV) Types Detected in the Oral Cavity

Novel type name	Total no. of isolates	Previous name	HPV Genus	NCBI accession no.[a]
HPV-119	1	FA155	γ	GQ845441
HPV-120	3	FA16	β	GQ845442
HPV-121	2		γ	GQ845443
HPV-122	1	vs92-1	β	GQ845444
HPV-123	1	FA136	γ	GQ845445
HPV-124	4	FA23	β	GQ845446
HPV-134	2	FA1.2	γ	
HPV-135	1	FA28	γ	HM999987
HPV-136	1	FA8	γ	HM999988
HPV-137	1		γ	HM999989
HPV-140	1		γ	HM999992
HPV-141	1	FA73	γ	HM999993
HPV-143	1		β	HM999995
HPV-144	1	FA83	γ	HM999996
HPV-145	2	IA16	β	HM999997
FA14	1		β	
FA22	1		β	
FA27	1		γ	
FA150	1		γ	
FAIMvs6.2	1		β	

NOTE. [a] Noveltypes without a National Center for Biotechnology Information (NCBI) accession number were classified from the sequence of the FAP polymerase chain reaction product.

Detection of Novel HPV Types in the Oral Cavity

On the basis of partial sequence information, a large number of novel HPV types were detected in the oral specimens. In total, 12 novel γ-HPV types (60%) and 8 novel β-HPV types (40%) were identified, whereas no novel α-HPV types were found. The complete genomes of 15 novel HPV types were cloned and characterized (Table 2) (Z. Chen et al, unpublished data). A BLAST search against GenBank revealed that most types have been previously reported as partial FAP sequences obtained from skin lesions and samples [12, 16–21].

Novel types accounted for 28 infections in the oral samples. Among the novel types, 2 β-HPV types, HPV-124 and HPV-120, were the most prevalent, being detected in 4 and 3 individuals, respectively. In addition, 1 β-HPV type (HPV-145) and 2 γ-HPV types (HPV-121 and HPV-134) were each detected twice. There was insufficient information to define the potential pathogenicity of these novel types, since the studies were not designed to assess oral pathology.

DISCUSSION

The present study investigated the detection of HPV DNA in oral rinse samples using PCR primers that efficiently amplify α-, β-, and γ-HPV types. Because the oral cavity has not been studied as extensively as the cervical region, detection of oral and

cervical HPV infections using identical methods in one experienced laboratory indicated that the oral cavity contains a large number of HPV types that were not previously recognized. The HPV types detected in the oral cavity were predominantly from the β- and γ-HPV genera, which were previously considered nearly exclusively skin types. The HPV types identified in the oral cavity were unlikely to be contaminants, since they were detected with relatively high signal strength (data not shown) and encompassed many novel types. Former surveys of oral HPV infection mainly focused on high-risk genital α-HPV type infections (eg, HPV type 16) that are associated with oral and oropharyngeal squamous cell carcinoma [6, 22–24]. However, use of the FAP PCR system allowed us to detect a broader spectrum of HPV types, particularly viruses that are more commonly isolated from cutaneous cancers and skin lesions [12]. The different spectrum of HPV types detected in the oral cavity and cervicovaginal region provides an insight into a wider tissue distribution of β- and γ-HPV types than was previously recognized and supports the notion that the oral cavity consists of a complex biological niche [25]. In addition to certain types of sexual behaviors that increase the risk of HPV infection, direct mouth-to-mouth and/or skin-to-mouth contact may be involved in the transmission of skin types to the oral cavity.

The high prevalence of oral HPV infection in HIV-positive patients is consistent with a number of studies demonstrating that HPV has a higher prevalence in the oral cavity of HIV-positive individuals compared with HIV-negative individuals [26–30]. Moreover, the observation that the majority of HPV types detected in the oral rinse specimens from HIV-positive individuals was from the α-HPV genus supports the findings in these other reports. Nevertheless, there was also an abundance of β- and γ-HPV types detected in these samples that have not been widely recognized.

This study demonstrates the broad spectrum of HPV types detected within the oral cavity, although the pathological consequence of these infections requires further investigation. The fact that HPV types associated with skin cancer (eg, HPV-5 and HPV-8) were detected raises the question of whether there is another spectrum of oral or oropharyngeal tumors related to β- and γ-HPV type infections. Moreover, these results have significant implications for understanding the biology of HPV and the epidemiological association of HPV with oral and skin neoplasia. One possibility is that different variants of a given type infect predominantly the skin or the oral cavity. This would imply a relatively recent adaptation of a large number of HPV types to the oral cavity, given the well-established tropism of the β- and γ-HPV types for the skin. Alternatively, it is possible that the preferred site of infection for β- and γ-HPV types might be the oral cavity, and the skin could represent a satellite site of infection arising from hand-to-mouth transmission. Finally, serologic assays used to evaluate total body β- and γ-HPV type

prevalence in association with skin cancer risk need to consider the role of oral HPV colonization.

This study has limitations. This analysis was conceived as a molecular virology investigation to identify a very broad spectrum of HPV types in samples from the oral cavity and was not meant to be a direct comparison between populations or samples. Thus, we are not able to compare risk factors for the different genera of HPV types detected in the oral cavity between populations, nor are these populations meant to be representative of a general HIV-negative or HIV-positive population. Therefore, we have not performed statistical analyses between populations. We contrast HPV types detected in oral rinse samples and cervical samples, since we used the same methods at the same time. Nevertheless, the identification of large numbers of oral samples from 2 different populations containing β- and γ-HPV types, many of which are novel, provides a new observation to be followed up in well-designed epidemiological studies.

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