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Concordance of human papillomavirus types detected on the surface and in the tissue of genital lesions in men

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Summary

Swabbing the surface of a genital lesion to obtain a sample for HPV DNA testing is less invasive than a biopsy, but may not represent HPV types present in the lesion tissue. The objective of this study was to examine the concordance of HPV types detected in swab and biopsy samples from 165 genital lesions from men ages 18-70. Lesions included 90 condyloma, 10 penile intraepithelial neoplasia (PeIN), 23 non-condyloma with a known histology, and 42 lesions with an undetermined histology. All lesions were sampled by swabbing the surface of the lesion with a pre-wetted Dacron swab and taking a shave biopsy. HPV genotyping was performed using Linear Array for swab samples and INNO-LiPA for biopsy samples. The kappa and McNemar statistics were used to compare the concordance of detecting HPV types in swab and biopsy samples. Both sampling methods had high agreement for detection of HPV DNA in condyloma (87.8% agreement) and PeIN (100% agreement). There was also high concordance for detection of HPV16 (kappa = 1.00) and HPV18 (kappa = 1.00) in PeIN, however, agreement was low to moderate for detecting HPV6 (kappa = 0.31) and HPV11 (kappa = 0.56) in condyloma. Low to moderate agreement was also observed between sampling methods for detecting individual HPV types in the non-condyloma and lesions with an indefinite histology. The results suggest that obtaining a biopsy in addition to swabbing the surface of a lesion may provide additional information about specific HVP types associated with male genital lesions.

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The authors declare that there are no conflicts of interest.

Keywords

HPV; condyloma; penile intraepithelial neoplasia; kappa

INTRODUCTION

Genital condyloma are the most common clinical manifestation of human papillomavirus (HPV) infection [Lacey et al., 2006]. Current standard practice is to diagnose condyloma by visual inspection, and diagnosis is rarely confirmed by biopsy [Wiley et al., 2002]. Thus, many clinic-based HPV prevalence studies sample the surface of condyloma to determine the HPV types associated with genital lesions and estimate the prevalence of HPV genotypes present in the lesion tissue [Greer et al., 1995; Aubin et al., 2008; Chan et al., 2009]. It is possible however that the HPV types detected on the surface of genital lesions may not represent the types present in the lesions themselves. Accurate estimates of the distribution of HPV types in condyloma and other genital lesions are important to model the efficacy of the quadrivalent HPV vaccine that protects against HPV 6, 11, 16 and 18 and for use in the development of future vaccines that protect against additional HPV types. Given that biopsying condyloma and other genital lesions is invasive and may deter individuals from participating in studies, it is important to determine if HPV types detected on the surface of a lesion is representative of the types present within the lesion tissue. High concordance between these sampling methods would suggest that obtaining a swab without a biopsy provides an accurate and non-invasive way to characterize the HPV types associated with lesions. However, if the HPV types in the lesion tissue are significantly different than what is detected on the surface of the lesion, a tissue biopsy may provide valuable additional information needed to accurately characterize the HPV types associated with that type of lesion. The objective of this study was to examine the concordance of HPV DNA types detected in genital lesions in men by swabbing the surface of a lesion and obtaining a tissue biopsying.

MATERIALS AND METHODS

Study participants were enrolled in the prospective HPV in Men (HIM) Study that examined the natural history of HPV infection in men. A detailed description of study participants and procedures in the HIM Study has been published previously [Giuliano et al., 2008; Giuliano et al., 2009; Giuliano et al., 2011]. Briefly, men were between 18-70 years old and resided in Tampa, Florida, Sao Paulo, Brazil or the state of Morelos, Mexico. At each clinic visit men were examined by a trained clinician for the presence of external genital lesions. Lesions were first sampled for the presence of HPV DNA by swabbing the surface of the lesion with a pre-wetted Dacron swab. A tissue sample was also obtained from the lesion by shave excision. Excised tissue was placed in 10% buffered formalin and processed at the University of South Florida Dermatopathology Laboratory for histologic diagnosis by the study dermatopathologist, followed by DNA extraction for HPV genotyping. All lesions that appeared to be HPV related (i.e., condyloma and penile intraepithelial neoplasia (PeIN)) or had an unknown etiology based on visual inspection alone were sampled for HPV testing. Only lesions that were clearly not HPV related, and had distinct features of other types of lesions such as Herpes Simplex Virus, pearly penile papules, Molluscum Contagiosum, and skin tags, were not sampled. All participants provided written informed consent and study protocols were approved by Institutional Review Boards at each study site.

A total of 165 genital lesions that had HPV DNA laboratory results for both swab and shave biopsy samples were available for this analysis. Histologic review by a dermatopathologist determined that the lesions included 90 condyloma, 10 PeIN, 23 non-condyloma lesions

with a known histology, and 42 lesions with an undetermined histology. A lesion was diagnosed as condyloma if it had koilocytes, papillomatosis, hypergranulosis, parakeratosis, and dilated blood vessels. When a lesion lacked koilocytes but had one or two of the other features associated with being a condyloma, it was considered to have an undetermined histology and diagnosed as squamous keratosis or benign squamous papilloma, both non-specific diagnoses that signifies abnormal growth on the skin. The lesions that were categorized as having an indefinite histology were likely very early condyloma that did not yet exhibit all the histological features of a fully developed condyloma. The non-condyloma lesions that had an unknown etiology based on visual inspection, but had a definite histology upon pathologic review, included Molluscum Contagiosum, intradermal nevus, Fibroepithelial polyp (skin tag), chronic balanitis, genital melanotic macule, psoriasiform dermatitis, lichenoid tissue reaction, and acute mucositis.

The QIAamp Mini kit (Qiagen, Valencia, CA) was used to extract DNA from samples obtained by swabbing the surface of a lesion. The polymerase chain reaction consensus primer system PGMY 09/11 was then utilized to amplify a fragment of the HPV L1 gene and test for the presence of HPV DNA. Linear Array HPV Genotyping was used to test for the presence of 37 HPV genotypes in swab samples, including 13 oncogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) and 24 non-oncogenic types (6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 67-73, 81–84, IS39, and CP6108). To test for the presence of HPV DNA in biopsied tissue, thin section microtomy specimens were cut from formalin-fixed paraffin-embedded tissue samples. DNA was extracted from the tissue slice, after removal of paraffin by boiling and digestion with proteinase K, followed by precipitation of DNA with isopropanol using the QIAamp DNA FFPE Tissue procedure (Qiagen Inc – USA). The Linear Array assay used to detect HPV in the swab specimens utilizes a long primer that may not work as efficiently in formalin fixed tissue where DNA is more likely to be fragmented. To overcome this methodological problem, the INNO LiPA system that utilizes a much shorter primer set proven to amplify and detect HPV efficiently in formalin fixed tissue was employed for the biopsy samples. INNO-LiPA tested for the presence of 24 HPV genotypes including 13 oncogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) and 11 non-oncogenic types (6, 11, 40, 42, 43, 44, 53, 54, 68, 70, and 74). For both genotyping methods, a sample was considered HPV positive if it tested positive for one or more of the HPV types tested for by each assay.

HPV prevalence was calculated as the proportion of lesions that tested positive for a specific HPV type. Corresponding exact binomial 95% confidence intervals were calculated for the prevalence of any HPV infection and specific HPV types. McNemar's chi-squared test for matched pairs was used to test if there was a significant difference in the distribution of discordant pairs between sampling methods and the unweighted kappa statistic was used to determine the agreement of HPV types detected between the two sampling methods. All analyses were conducted using SAS 9.1.

RESULTS

The prevalence of HPV types detected in each category of lesion is presented in Table 1. Among condyloma lesions, no significant difference was observed between biopsy and swab samples for the detection of any HPV DNA ($p = 0.55$), HPV 16 ($p = 0.07$), and HPV 18 ($p = 0.22$). There was a high prevalence of HPV DNA in biopsy (96%) and swab (92%) samples and a low prevalence of HPV 16 and HPV 18 in biopsies (2%, 1%) and swabs (9%, 6%). Sampling methods differed for the detection of HPV 6 ($p = 0.007$) and HPV 11 ($p = 0.0005$) in condyloma; HPV 6 was less commonly detected in biopsy (44%) than swab (62%) samples, while HPV 11 was more commonly detected in biopsies (34%) compared to swabs (19%). Though there were differences in the prevalence of HPV 6 and 11 as individual types

in condyloma, the prevalence of detecting at least one of the two types (6 and/or 11) was not significantly different between biopsies (77%) and swabs (79%) (p = 0.85) (data not shown). There were no differences in the frequency of detecting HPV in PeIN, with HPV DNA observed in 100% of both biopsy and swab samples. With regard to specific HPV types in PeIN, HPV 6 and 11 were detected in 30% of biopsies and 20% of swabs, while HPV 16 was prevalent in 60% of all samples and HPV 18 was prevalent in 10% of each sample type.

Among lesions with an indefinite histology, there was a high prevalence of HPV DNA in both biopsies (86%) and swabs (70%) (p = 0.15). The prevalence of HPV 6 was the same in biopsy (40%) and swab samples (43%) (p = 1.00), however, HPV 11 was more common in biopsies (29%) than swabs (14%) (p = 0.03). HPV 16 was only present in the biopsy samples (10%) and HPV 18 was present in less than 10% of both sample types (p = 0.63). For the non-condyloma lesions, biopsy samples had a higher prevalence of any HPV DNA in biopsies (91%) compared to swabs (61%), though the difference was not statistically significant (p = 0.06). There were not significant differences in the prevalence of HPV 6 (43% vs. 26%; p = 0.29) or HPV 11 (20% vs. 9%; p = 0.38) in biopsies and swabs. For these lesions, HPV 16 was only present in biopsies (9%) and HPV 18 was not detected using either sampling method.

When restricting to the 16 HPV types other than 6, 11, 16, and 18 that were tested for in both the Linear Array and INNO LiPA assays (31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 56, 58, 59, 66, and 68), the prevalence of having one or more of these HPV types did not differ between sampling methods for PeIN (p = 0.25), lesions with an indefinite histology (p = 0.77), or non-condyloma (p = 1.00). Among condyloma however, other HPV types were more commonly detected in swab (21%) than biopsy samples (6%) (p = 0.0026). Other HPV types detected in condyloma biopsies included HPV 31, 39, 51, 52, 54, and 66, with a prevalence of less than 3% for each type. In the condyloma swab samples, HPV 39, 40, 42, 45, 51, 52, 53, 54, 56, 58, 59, and 66, were detected, though prevalence for each type was 5% or less. For lesions with an indefinite histology, other HPV types detected in biopsies were HPV 31, 33, 39, 40, 51, 52, 53, 58, and 66, all with a prevalence of less then 5%. The swab samples from the indefinite lesions contained HPV 31, 35, 39, 42, 53, 54, 58, 59, and 66 with a prevalence of less than 5% for each type. For the non-condyloma lesions, the other HPV types present in biopsy tissue were HPV 31 (8.7%), 33 (4.4%), 51 (17.4%), 52 (13.0%), 54 (8.7%), and 66 (4.4%), and the other HPV types in the swabs were HPV 31 (4.4%), 39 (4.4%), 40 (8.7%), 54 (13.0%), and 58 (4.4%). For PeIN, HPV 51, 52, and 66 were each detected in 10% of biopsy samples. PeIN swab samples had HPV 51 (10.0%) and 52 (40.0%). No lesion of any type was positive for HPV 35, 42, 45, 56, 59, or 68.

Table 2 presents percent agreement and kappa statistics for concordance between sampling methods. For condyloma, there is a high percent agreement for HPV DNA detection (87.8%), with both methods detecting HPV in more than 90% of samples. Though the kappa was low, likely due to the very high prevalence of HPV in these lesions, there was no difference in the prevalence of HPV detected for each sampling method (Table 1). For individual HPV types, concordance was low to moderate for other HPV types (kappa = 0.09), HPV 16 (kappa = 0.17), HPV 6 (kappa = 0.31) and HPV 11 (kappa = 0.56). The kappa for HPV 18 was very low (kappa = -0.02), likely due to the low prevalence of HPV 18 in condyloma. For lesions with an indefinite histology, the percent agreement was high for detection of any HPV (71.4%), HPV 16 (90.5%) and 18 (90.5%). Kappa values were lower for these HPV types due to the high prevalence of any HPV and very low prevalence of HPV 16 and 18 in this lesion type. Low to moderate concordance was observed for detection of HPV 6 (kappa = 0.26) and HPV 11 (kappa = 0.59). Agreement between sampling methods was also lower among non-condyloma lesions for individual HPV types including HPV 6 (kappa = 0.26), HPV 11 (kappa = 0.18), and other HPV types (kappa =

0.16). For PeIN, agreement was moderate for detecting other HPV types (kappa = 0.40), and high for detecting HPV 6 and 11 (kappa = 0.74) and HPV 16, 18 and any HPV (kappa = 1.00).

DISCUSSION

This study examined the concordance of HPV types detected in male genital lesions by swabbing the surface of the lesion and obtaining a shave biopsy. Both sampling methods detected a high prevalence of HPV DNA in condyloma and PeIN, however, there was less agreement between sampling methods for detection of specific HPV types in those lesions. Low to moderate agreement was observed between sampling methods for detecting individual HPV types in the non-condyloma and lesions with an indefinite histology.

The prevalence of HPV types for both sampling methods was consistent with previous studies for condyloma and PeIN. In the current study HPV DNA was detected in 96% of condyloma biopsies, in line with previous reports where HPV was detected in 91% of biopsied condyloma among women in the placebo arm of a vaccine trial [Garland et al., 2009] and 100% of condyloma biopsies among men and women seeking treatment for condyloma in a standard clinic setting [Brown et al., 1999]. Likewise, the prevalence of HPV in the condyloma swab samples from our study (92%) is similar to studies that also swabbed the surface of a condyloma and found HPV in 95%-100% of the lesions [Greer et al., 1995; Aubin et al., 2008; Chan et al., 2009]. In agreement with our results, HPV 6 and HPV 11 were the most common types detected in condyloma in past studies [Greer et al., 1995; Brown et al., 1999; Aubin et al., 2008; Chan et al., 2009; Garland et al., 2009; Ball et al., 2011]. HPV 16, the third most common type in condyloma in the present study, was also commonly detected in several other studies [Brown et al., 1999; Garland et al., 2009; Ball et al., 2011]. Also in line with our findings, previous studies of biopsied PeIN found 88%-90% of samples positive for HPV DNA, approximately 40% of PeIN positive for HPV 16, and about 20% positive for HPV 6/11 [Aynaud et al., 1994; Rubin et al., 2001; Krustrup et al., 2009].

The prevalence of HPV types in non-condyloma genital lesions has not been well characterized in men. A strength of this study was that men were examined for genital lesions every 6 months, therefore, the clinician was able to detect very early lesions that would likely be missed in a traditional clinical setting. The high prevalence of HPV observed in the tissue of lesions with an indefinite histology supports the idea that some of these lesions were actually very early condyloma. A significant number of these lesions were given the diagnosis of benign squamous keratosis, a relatively non-specific pathologic diagnosis for lesions that show some but not all of the diagnostic criteria for HPV infection. It is compelling that swabs from these lesions were less likely to be HPV positive than the lesion tissue, a phenomenon which may relate to low viral load of these pathologically subtle lesions. HPV DNA was also detected in the majority of the non-condyloma lesions with a definite histology, using both sampling methods. Given that these benign male genital lesions are common, future research is warranted to investigate whether HPV plays a role in the development and progression of these lesions.

Several HPV types had a negative kappa for the concordance between sampling methods. The kappa statistic is influenced by the prevalence of a trait, and a prevalence close to 0% or 100% will cause kappa to decrease because the probability of expected agreement between sampling methods is high by chance [Sim and Wright, 2005]. A negative kappa was observed for HPV types where the prevalence was very high (e.g., any HPV in condyloma) or very low (e.g., HPV 18 in condyloma). In these cases, the McNemar statistic is a more appropriate way to look at agreement between sampling methods. For instance, the kappa

for detection of HPV DNA in condyloma was -0.06, however there was no difference in the prevalence of HPV in condyloma between sampling methods (McNemar p = 0.55), with both methods detecting HPV in more than 90% of samples.

Small sample size was a limitation in this analysis. Given that most HPV types other than 6, 11, 16, and 18 were present in less than 5% of lesions, the sample size was not large enough to assess concordance for these less frequent types. There was also a small number of specific lesion types, such as PeIN (n=10), therefore, a larger sample size may provide a more precise estimate of the concordance of HPV types between sampling methods. Though the majority of lesions identified by visual inspection were sampled for HPV testing, it is possible that some of the lesions that did not appear to be HPV related, and were subsequently not sampled, may have been a true condyloma or PeIN. However, the number of potentially missed HPV related lesions would be small given that a lesion was sampled whenever there was uncertainty about the histology. If lesions were missed, this should not bias the observed associations, as it is unlikely that the concordance of HPV detection in swab and biopsy samples would be different in lesions that were not sampled.

In summary, both tissue biopsies and swab samples were able to detect a high prevalence of HPV DNA in condyloma and PeIN. However, the agreement between sampling methods was low to moderate for detecting most individual HPV types, suggesting that obtaining a tissue biopsy in addition to swabbing the surface of a lesion may provide additional information about the HPV types associated with male genital lesions.

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Table 1

Prevalence estimates and associated 95% confidence intervals for HPV types according to lesion histology.

HPV Type	Biopsy % positive (95% CI)	Swab % positive (95% CI)	Exact McNemar's p-value
Condyloma (N=90)			
Any HPV	96 (91, 100)	92 (87, 98)	0.55
HPV 6	44 (34, 55)	62 (51,72)	0.007
HPV 11	34 (25, 45)	19 (11, 29)	0.0005
HPV 16	2 (0, 8)	9 (4, 17)	0.07
HPV 18	1 (0, 6)	6 (2, 12)	0.22
HPV other[a]	6 (2, 12)	21 (13, 31)	0.0026
Lesions with indefinite histology (N=42)[b]			
Any HPV	86 (75, 96)	70 (57, 85)	0.15
HPV 6	40 (26, 57)	43 (28, 59)	1.00
HPV 11	29 (16, 45)	14 (5, 29)	0.03
HPV 16	10 (3, 23)	0	na
HPV 18	2 (0, 13)	7 (1, 19)	0.63
HPV other[a]	14 (5, 29)	19 (9, 34)	0.77
Non-condyloma (N=23)[c]			
Any HPV	91 (80, 100)	61 (41, 81)	0.06
HPV 6	43 (23, 66)	26 (1, 48)	0.29
HPV 11	20 (7, 44)	9 (1, 28)	0.38
HPV 16	9 (1, 28)	0	na
HPV 18	0	0	na
HPV other[a]	22 (5, 39)	26 (8, 44)	1.00
PeIN (N=10)			
Any HPV	100 (69, 100)	100 (69, 100)	na
HPV 6	30 (7, 65)	20 (3, 56)	1.00
HPV 11	30 (7, 65)	20 (3, 56)	1.00
HPV 16	60 (26, 88)	60 (26, 88)	na
HPV 18	10 (0, 45)	10 (0, 45)	na
HPV other[a]	20 (0, 45)	50 (19, 81)	0.25

CI = confidence interval, PeIN = penile intraepithelial neoplasia.

[a] Positive for at least one of the 16 HPV types other than 6/11/16/18 that were tested for in both assays used to genotype the swab and biopsy samples (31, 33, 35, 39, 40, 42, 45, 51-54, 56, 58, 59, 66, and 68).

[b] Includes squamous keratosis and benign squamous papilloma.

[c] Includes seborrheic keratosis, Molluscum Contagiosum, intradermal nevus, Fibroepithelial polyp (skin tag), chronic balanitis, genital melanotic macule, psoriasiform dermatitis, lichenoid tissue reaction, and acute mucositis.

Table 2

Concordance of HPV DNA types detected by swabbing the surface of a lesion and obtaining a shave biopsy.

HPV type	HPV positive in biopsy only	HPV positive in swab only	Biopsy and swab HPV positive	Biopsy and swab HPV negative	(%) Agreement	Kappa (95% CI)
Condyloma (N=90)						
Any HPV	7	4	79	0	87.8	-0.06 (-0.02 - -0.10)
HPV 6	8	24	32	26	64.4	0.31 (0.13 - 0.49)
HPV 11	15	1	16	58	82.2	0.56 (0.38 - 0.74)
HPV 16	1	7	1	81	91.1	0.17 (-0.15 - 0.50)
HPV 18	1	5	0	84	93.3	-0.02 (-0.05 - 0.01)
HPV other	3	17	2	68	77.8	0.09 (-0.11 – 0.28)
Lesions with indefinite histology (N=42)						
Any HPV	9	3	27	3	71.4	0.18 (-0.13 - 0.48)
HPV 6	7	8	10	17	64.3	0.26 (-0.03 - 0.56)
HPV 11	6	0	6	30	85.7	0.59 (0.31 - 0.87)
HPV 16	4	0	0	38	90.5	na
HPV 18	1	3	0	38	90.5	0.04 (-0.09 - 0.02)
HPV other	5	7	1	29	71.4	-0.02 (-0.31, 0.26
Non-condyloma (N=23)						
Any HPV	9	2	12	0	52.2	-0.16 (-0.37 - 0.04)
HPV 6	6	2	4	11	65.2	0.26 (-0.12 - 0.64)
HPV 11	4	1	1	17	78.3	0.18 (-0.26 - 0.63)
HPV 16	2	0	0	21	91.3	na
HPV 18	0	0	0	23	100.0	na
HPV other	3	4	14	2	69.6	0.16 (-0.27 - 0.60)
PeIN (N=10)						
Any HPV	0	0	0	10	100.0	1.00 (1.00 - 1.00)
HPV 6	1	0	2	7	90.0	0.74 (0.26 – 1.00)
HPV 11	1	0	2	7	90.0	0.74 (0.26 – 1.00)
HPV 16	0	0	6	4	100.0	1.00 (1.00 - 1.00)
HPV 18	0	0	1	9	100.0	1.00 (1.00 - 1.00)
HPV other	0	3	2	5	70.0	0.40 (-0.05, 0.85)