Determinants of Type-Specific HPV Concordance Across Anatomic Sites in Young Men Who Have Sex with Men

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Abstract

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Men who have sex with men (MSM) are at high risk for HPV infection and HPV associated cancers. The dynamics of HPV infections at different anatomical sites and whether type-specific HPV infections are detected simultaneously at these sites in this population is not well understood. Information on HPV type concordance can be useful in determining the biological relationship between anatomic sites, the extent of auto-inoculation between sites, and susceptibility of different anatomic areas to specific HPV types. The aim of this study is to describe the concordance of HPV genotypes across anal, oral, and genital samples and to assess factors that predict concordance. We enrolled MSM participants aged between 18 and 26 years attending sexual health clinics or community centers in three US cities. Samples were obtained from oral, genital, and/or anal sites of 1876 study participants for type-specific HPV DNA testing. Clinical record details and data from a patient filled questionnaire were used to assess for risk factors associated with concordant infections. Concordance of type-specific HPV detection across anatomic sites was described with kappa statistics based on percent positive agreement (kappa +). Generalized estimating equations were used to measure the univariate

and multivariate associations for the correlates of type-specific concordant HPV detection at oral-anal and anal-genital sample pairs. The median age of the participants was 23 years, 8% were HIV positive and 39.6% received HPV vaccine. The prevalence of any HPV type was highest at the anal site (69%) followed by the penile site (49%) and the oral sites (7.4%). Concurrent detection of any HPV type was most prevalent in anal-genital sample pairs (40%) and was uncommon in pairings involving oral samples. There was little to no genotypic agreement across all sites with poor concordance noted across all sample pairings (kappa + <0.20). Nevertheless, participants who were younger and those who reported an older age of first sex were significantly more likely to have type concordant anal-genital infections while sexual behavior characteristics were not significant correlates of concordance. Lack of oral and anogenital HPV type concordance suggests that direct transmission of HPV infection from anogenital sites to oral sites is rare. Nonetheless, there is some degree of concurrence and concordance observed between anal and genital sites that were not found to be associated with sexual characteristics, suggesting that bidirectional transmission could be occurring between these two sites. However, large longitudinal studies are necessary in order to better demonstrate this mechanism of transmission.

INTRODUCTION

Human papillomavirus (HPV) infections are etiologically linked to anogenital warts and cancers, including cancers of the genitals, anus, and oropharynx. High-risk HPV types are well established as the primary cause of most cervical cancers in women[1]. High-risk HPV also contributes to a significant proportion of oropharyngeal, genital, and anal cancers in men[2-4].

Men who have sex with men (MSM) are at high risk for HPV infection and HPV-associated disease. The seroprevalence of HPV is approximately 2 to 6 times higher among MSM compared to heterosexual men[5]. Among MSM the prevalence of anal HPV infection ranges from 40% to 90%, with a higher likelihood of having an anal infection among HIV-positive MSM[6]. In some studies, the incidence of anal cancer in MSM has been estimated to be 37 cases per 100,000 person-years – a rate that is comparable to the incidence of cervical cancer prior to routine Pap screening[7, 8]. Moreover, over the last few decades there has been a pronounced increase in HPV-associated oropharyngeal cancers among males[9-11].

Despite evidence of increased risk of HPV infections and HPV-associated disease among MSM than the general male population[12], the epidemiology of HPV infections and risk factors associated with developing infections in this population is not fully understood. There are only limited data available about the relationship between HPV infections at the different anatomical regions in this population and moreover it remains unclear whether type specific HPV infections are detected simultaneously at anal, and genital sites in men[13].

A limited number of studies have evaluated the presence and positive concordance of HPV DNA at anal, genital, and/or oropharyngeal sites in men. Studies that have reported on the general

male population have found the prevalence of concurrent HPV infections in the oral cavity and the genitals to be between 1.9% and 3.2%[14-16], while those reporting on concurrent detection between oral and anal sites have reported a range from no concurrent detection to 6.9%[17, 18]. In these studies, smoking, higher lifetime numbers of sex partners and recent sex partners were associated with having higher likelihood of genotype-concordant HPV infections at multiple anatomic sites[14, 15].

Studies in MSM that have reported on positive concordant HPV infections have similarly reported varying results. In a 2018 study, conducted predominantly among MSM in Greece, the authors reported that a genotype-specific concordance rate of 7% of participants had a type-concordant HPV infection between the genital site and anal canal. However, the prevalence of a concordant HPV infection between the anal and oral sites in these participants was lower at 2%, and there were no concordant infections noted between the oral and genital sites[19]. Comparably, a 2017 study of young MSM in the US reported that the proportion with the same HPV type detected between anal and oral specimens was 3.4%, with HIV and smoking found to be associated with a higher likelihood of having a concordant infection[20]. In another US study of MSM with anal squamous intraepithelial lesions, concurrent oral–anal any-type HPV infection was found in 26% of participants and among these participants only 20% of them had a concordant infection at the two sites[21]. However, in a study of HIV-infected MSM in the US and another study of MSM attending a sexual health clinic in the UK, there was no HPV concordance reported between oral and anogenital sites among participants[11, 22]. The wide range and low prevalence of concordance reported in these studies may be due to the variability in sampling methods and the number of different anatomic sites included. Differences in sensitivity of the detection methods

may also have contributed to some disparity in HPV detection and the low concordance observed between anatomical sites. Additionally, some of the studies were not exclusively of an MSM population and included either a small number of MSM, or no MSM.

Studies of HPV at multiple anatomic sites with detailed sexual behavior data in men are needed to accurately describe the concordance of HPV infections and risk factors associated with concordance. The relatively high prevalence of HPV infections in MSM provides an opportunity to investigate the correlation of anal, genital and oral HPV types. Information on HPV concordance will provide information on the biological relationship between anatomic sites, the extent of auto-inoculation between sites, and susceptibility of different anatomic areas to specific HPV types.

We therefore conducted a cross-sectional study among young MSM to describe the concordance of HPV genotypes across anal, oral, and genital samples in young MSM, and to assess factors that predict concordance.

METHODS

We conducted a cross-sectional analysis of young men who have sex with men nested within a larger study evaluating the impact of HPV vaccine in young MSM in the US. Study procedures were already integrated in the completed study[23] for the cohort of young MSM including collection of samples for HPV DNA and collection of data on potential correlates of HPV infection.

The study enrolled young MSM between February 2016 and September 2018 from three U.S. cities: Seattle, Chicago, and Los Angeles. Enrolment occurred at a sexual health clinic and a community STD/HIV testing site in Seattle, a community center serving LGBT persons in Chicago,

and an LGBT clinic in Los Angeles. Participants attending these sites who reported having been assigned male sex at birth, with either a history of anal or oral sex with a male partner, identified as gay/homosexual or bisexual, or intended to have sex with a male partner in the future and were between 18 to 26 years of age were eligible to be included in the study.

Health care providers or research coordinators at the study sites pre-screened each participant for eligibility based on the patient's routine clinical history intake form. Potential subjects found to be eligible would receive further explanation regarding the study from the health care provider or research coordinator. If the patient agreed to participate, the health care provider or research coordinator administered written informed consent to each participant. Participants received compensation of nominal value and were enrolled and completed all study elements on the same day. Each participant was assigned a unique study ID code and no personally identifiable information was collected. Study procedures were reviewed and approved by the institutional review boards at all participating institutions.

Each participant was required to submit at least two specimens for HPV DNA testing: an anal swab and an oral rinse specimen. Additionally, participants from Seattle sites were also required to submit a genital-swab. Participants were provided with verbal and written instructions on how to self-collect clinical specimens and details of this have been reported previously.[6, 24, 25] Participant samples were then stored in a biohazard bag and shipped frozen to the CDC Research laboratory in Atlanta, Georgia, for batch processing. Specimens unless being processed were kept in a -80^{o}C freezer for storage.

Health care providers or research coordinators at the study sites requested study participants to complete a survey providing demographic characteristics, sexual behaviors, and health

information including HIV status and HPV vaccination history. Additional data were extracted from clinic computer-assisted self-interview data for subjects enrolled at the Seattle sites.

At the CDC laboratory, type-specific HPV DNA genotype testing was performed on the anal, genital and oropharyngeal samples using the Roche Linear Array test (Roche Diagnostics, Pleasanton, CA) which can detect 37 HPV DNA types i.e., types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, 89, and IS39. High risk HPV types are defined as HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 & 68. HPV types included in the quadrivalent (4-valent) HPV vaccine are HPV 6, 11, 16 & 18 while HPV types included in the nonavalent (9-valent) HPV vaccine are 6, 11, 16, 18, 31, 33, 45, 52 & 58 (https://www.cdc.gov/vaccines/pubs/pinkbook/hpv.html). Specimens were considered inadequate if they were negative for the human β-globin gene and all 37 types of HPV.

Prevalence was calculated for the following groups: any HPV type, any high-risk type, any 4-valent type, and any 9-valent type. We obtained separate estimates of prevalence for each anatomic site (anal, genital and oropharynx), and for detecting HPV concurrently at two anatomic sites (oral/anal, oral/penile, and anal/penile), and at all three anatomic sites. For each anatomic site grouping, we also described the proportion with full, partial, and no agreement in the HPV types detected between sites. Anatomic site-specific analyses were restricted to those with an adequate sample at the specific site(s).

Type-specific HPV concordance was determined by comparing detection between anatomic site pairings. Pooled positive type-specific concordance was calculated for any HPV, any high-risk HPV, any 9-valent-type HPV, and any 4-valent-type HPV, HPV 6 and/or 11, and HPV 16 and/or 18. The observed proportion positive agreement (PPA) between these sites was calculated by

obtaining the paired samples positive in both sites divided by the number of paired samples with any positive test at either site. The expected PPA between these sites was calculated based on the product of the marginal probabilities of obtaining positive samples at the sites divided by the probability of obtaining a positive at either site. To adjust for the PPA caused by chance for each pair, the unweighted PPA kappa statistic (kappa +) and 95% CI was calculated using percentile bootstraps (where the bootstrap resampled individuals to account for the correlation between samples within an individual).

We then conducted generalized estimating equations logistic regression to measure the effect of individual risk factors associated with type-specific concordance of HPV infections across oral-anal and genital-anal sample pairings (separate models). We did not assess for factors associated with concordance across oral-genital sample pairs due to the low number of concordant pairs. We estimated odds ratios and 95% confidence intervals based on robust variance estimates using a generalized estimating equation approach, clustering on the individual. Variables that were assessed included: age (18-21 years or 22-26 years), sexual orientation (gay/homosexual, straight/heterosexual or other/unknown), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander, other (includes either American Indian, Alaskan Native, more than one race, or other) or unknown), smoking status (never smoked or ever smoked), HIV status (positive or negative/unknown), history of ever taking PrEP (yes or no/unknown), self-reported HPV vaccination status (vaccinated, unvaccinated or unknown), age at first HPV vaccine dose (<19 years, >=19 years or unvaccinated/unknown), age at first sex with any partner (< 16 years or ≥ 16 years), lifetime number of sex partners (any gender) (≤ 5, 6 to 10, 11 to 20, or ≥21), male sex partners in the last 12 months (zero, 1, 2 to 4, 5 to 9, or ≥10), male sex partners in the

last 2 months (zero, 1, 2 to 4, 5 to 9, or ≥10), new male sex partner in the last 2 months (yes or no), gave oral sex to male partners in the last 2 months (yes or no), received oral sex from male partners in the last 2 months (yes or no), was a bottom in anal sex in the last 12 months (yes or no), engaged in condomless anal sex as a bottom in the last 12 months (yes or no), was a top in anal sex in the last 12 months (yes or no), engaged in condomless anal sex as a top in the last 12 months (yes or no), history of ever having anogenital warts (yes or no), history of ever having genital herpes (yes or no), history of having gonorrhea or chlamydia in the last 12 months (yes or no), and history of having syphilis in the last 12 months (yes or no). The following variables were not collected from the Gay City site in Seattle: received oral sex in the last 2 months, history of ever having anogenital warts and history of ever having genital herpes. In order to determine which variables to include in the multivariate logistic regression model, we selected variables that were found to be of statistical significance in the univariate analysis ($P<0.10$). When a variable was found to be significant in the univariate analysis and had greater than 5% missing data, we added a category for the missing data and performed the multivariate analysis with the missing category included for that particular variable.

RESULTS

A total of 1881 participants were enrolled in the study, of whom 1876 submitted at least one adequate biologic specimen and were included in the analysis.

Demographics, sexual behavior, and health history characteristics

The median age of participants in this study was 23 years and the median age of first sex with any partner was reported as 16 years (Table 1). The majority of the participants in this study

(76.5%) reported being gay or homosexual, while the rest were either bisexual, heterosexual or other. The most commonly stated race was non-Hispanic white (34.1%), followed by Hispanic (33.2%), non-Hispanic black (15.4%) and Asian/Pacific Islander (8.6%). Only 143 (8.0%) participants reported being HIV-positive. 742 (50%) participants reported that they were vaccinated against HPV, with the median age of receiving the first HPV vaccine dose being 19 years. More than half the participants reported having greater than 20 sexual partners in their lifetime (of any gender) and about three quarters reported having a new male partner in the last two months.

Prevalence and concordance of HPV detection among study participants

Most participants (71.2%) had HPV detected from at least one anatomic site, with more than half (52.5%) having a high-risk type HPV infection (Table 2). HPV was most likely to be detected from anal specimens (69.9%), followed by genital specimens (48.6%), and oral specimens (7.4%). This pattern of detection was similar across the different HPV type groups evaluated, including high risk HPV, 4-valent HPV vaccine types, and 9-valent HPV vaccine types. Among participants who had HPV detected in anal samples, the mean (standard deviation [SD]) and median (interquartile range [IQR]) number of HPV types detected was 3.1 (2.3) and 2 (1-4) respectively. The mean (SD) and median (IQR) number of HPV types detected was 2.0 (1.5) and 1 (1-2) for genital samples, and 1.3 (0.6) and 1 (1-1) for oral samples.

Concurrent detection of any HPV at more than one anatomic site was most common in anal-genital sample pairs (40.9%) followed by oral-anal sample pairs (6.5%) and oral-genital samples (3.4%) (Table 2). Among participants with samples from all three sites, 3.0% had at least one HPV

type detected at all three sites, and 0.9% had at least one high-risk type detected in all three sites. Of participants with concurrent anal and genital infections, 39.2% had complete concordance of the HPV types detected at both sites. The proportion of concurrently positive pairs with complete concordance was lower at both the oral and anal sites and at the oral and genital sites at 25.9% and 33.3% respectively. Of participants with concurrent detection at all three sites, 20.0% had complete concordance.

Type-specific HPV concordance was highest for genital/anal sample pairs (percent positive agreement=16.7%, kappa + =0.15, 95% CI 0.13 – 0.17) (Table 3). The percent positive agreement among both oral/anal sample pairs and oral/genital sample pairs was considerably lower at 1.2% (kappa + =0.01, 95% CI 0.01 – 0.02) and 1.4% (kappa + =0.01, 95% CI = 0.00 – 0.02) respectively. Similar patterns for comparisons of agreement across sample pairs were observed for all HPV type groups evaluated.

Factors associated with type-specific HPV concordance across oral-anal sample pairings

In univariate analyses, the likelihood of detecting the same HPV type in paired oral and anal samples was significantly higher among participants who had ever smoked compared to those who had never smoked (OR 2.27; 95% CI, 1.17 – 4.40). Participants who were 16 years or older at sexual debut were less likely to have a concordant oral-anal infection than those who were 15 years or younger at sexual debut (OR 0.48, 95% CI, 0.26 – 0.91) (Table 4). Borderline statistically significant associations were observed for lifetime number of sex partners and reporting being a top in anal sex in the past 12 months.

In the multivariate model including smoking status, age of sexual debut, lifetime number of sex partners and being a top in anal sex in the last 12 months, age at sexual debut remained significantly associated with type-specific HPV concordance (adjusted OR (aOR) 0.50, 95% CI, 0.27 – 0.93). The association between smoking status and concordance was attenuated and borderline statistically significant (aOR 1.90, 95% CI, 0.96 – 3.76). Associations for lifetime number of sex partners and being a top in anal sex in the last 12 months were not statistically significant in the multivariate model (Table 4).

Factors associated with type specific HPV concordance across genital-anal sample pairings

In the univariate analysis, the odds of having a concordant genital-anal HPV infection were significantly lower in those who were aged 22-26 years compared to those who were aged 18-21 years (OR 0.66, 95% CI, 0.47 – 0.93) (Table 5). On the other hand, the chance of detecting the same HPV type in paired genital-anal samples was higher among participants who reported that their age at first sex was 16 years or older than in those who reported a younger age at first sex (OR 1.43, 95% CI, 1.02 – 2.00). Self-reporting being HIV positive also trended towards having a significant association with a concordant HPV genital-anal infection (OR 1.95, 95% CI, 0.88 – 4.29).

After including age at enrolment, age at first sex and HIV status in the multivariate model, the likelihood of a concordant HPV infection was even lower in those who were 22-26 years old compared to those who were younger than 22 years (aOR 0.62; 95% CI, 0.44 – 0.87). Older age at first sex also continued to be significantly associated with having a higher odds of the same HPV type detected across paired anal and genital samples (aOR 1.46; 95% CI, 1.04 – 2.05). Moreover, the magnitude of association between concordance and HIV status was slightly larger

in the multivariate model, but was only borderline significant (aOR 2.13, 95% CI, 0.96 – 4.74) (Table 5).

DISCUSSION

In this population of young MSM, HPV prevalence was highest at the anal site with 70% of participants having at least one HPV type detected. Almost half (49%) had genital HPV and only 7.4% had oral HPV. Also, among those who had HPV detected in either the anal or genital site, the majority had multiple HPV types detected in the same sample. In a recent systematic review and meta-analysis, the pooled prevalence of anal HPV infection in HIV-negative MSM was comparable (64%), but genital HPV prevalence was considerably lower (29%) and oral HPV prevalence higher (14.5%) [26]. Of note, there was substantial between-study heterogeneity in this review article that might explain some of the observed variance to our study[26].

Concurrent detection of any HPV at multiple sites was highest for paired anal and genital samples, with over 40% of participants having concurrent HPV detected. This is higher than what has been observed in other studies reporting on MSM in which the prevalence of concurrent anal-genital HPV infection ranged between 15% and 23% [27-29]. Besides differences in sampling techniques, this disparity could be due to the fact that our study population was younger compared to these other studies which meant they may have been more likely to have had more recently acquired infections at the time of the study.

The concurrent detection of HPV in oral and anogenital samples was uncommon in our population of young MSM, and only a third of those with concurrent oral and anogenital HPV infection had the same type detected at both sites. The low concurrence and concordance

involving the oral site is likely due to the low prevalence of oral HPV infection in our study population. Among those who had an oral HPV infection we observed that the concurrent detection of HPV was much more likely from an anal sample (84%) than from a genital sample (17%), which is likely attributable to both the high prevalence of anal HPV infection and having multiple HPV types detected in anal samples. A comparable study in the US also reported a similarly low level of concurrent anal-oral HPV infection (8%) in young MSM, but unlike our study they observed that among those who had an oral HPV infection only 34% had a concurrent anal HPV infection[20]. Other studies among MSM reported a slightly higher prevalence of concurrent oral and genital HPV infection (7% - 8%) than what we observed, as well as a higher proportion of genital HPV infection among those with an oral HPV infection (66%)[11, 27]. These differences could be explained by the higher prevalence of oral HPV infection (14% and 16%) in their study populations, or differences in participant characteristics.

In our study, there was also little overall agreement at a genotypic level between the various sample pairings analyzed which as expected was lower than the HPV agreement observed at the subject level. The HPV genotypic agreement was only low for anal and genital sample pairings, and there was little to no agreement observed in pairings that involved an oral sample.

In our analysis of the correlates of concordance, we found that younger age was positively associated with genital-anal concordance. However, studies in MSM and the general male population, do not report any association of age with concordant HPV type infections across different anatomic sites[15, 20, 30, 31]. However, there are some studies in women that have demonstrated increasing age to be associated with a lower likelihood of detecting type concordant HPV DNA in anal-genital infections[32] and oral-genital infections[33]. This inverse

relationship probably reflects the higher likelihood of detecting concurrent HPV infections at the different sites in those who are younger as these are likely to be new infections, whereas in older persons the infection may be more likely to have cleared from at least one site. On the other hand, we did not observe any association of age with oral-anal concordance in our study and this is possibly due to the low prevalence of oral HPV infection in our study population.

We also observed smoking to be significantly associated with a twofold higher likelihood of oral and anal HPV type concordant infection in our population of young MSM. Other studies in both MSM and MSW have also reported smoking to be associated with concordant oral and anogenital infections[15, 20]. Smoking is generally thought to increase the persistence and reactivation of HPV infections in the oral cavity and is therefore associated with a higher prevalence of oral HPV infections[34, 35]. The higher prevalence of concordant oral-anal HPV infections among smokers is probably related to higher oral HPV prevalence in this group. In contrast, smoking was not found to be associated with anal-genital type concordance in our study.

Furthermore, HIV status was borderline significantly associated with a twofold higher likelihood of genital-anal concordance. Similarly, we also noted a non-statistically significant higher likelihood of a concordant oral-anal infection among those who were HIV positive. The proportion of HIV positivity in our study population was low, reducing the power to detect significant associations. Other studies have shown HIV to be positively associated with HPV concordance at different anatomic sites, and in a recent study of MSM, HPV concordance at anal and oral sites was significantly higher in those who were HIV-positive compared to others (10% vs 3.4%; $p < 0.001$) [20]. Moreover, the prevalence of HPV infection is known to be significantly higher among HIV-positive persons compared to the general population[36-38] and this is

thought to be due to an increased risk of reactivation of latent infections, as well as increased persistence of HPV infection due to immune system dysregulation[39]. It is therefore possible that the frequency of concordance detected could be mostly attributable to the higher prevalence and persistence of HPV among HIV-positive persons.

In our study, the only sexual characteristic that was found to be significantly associated with type concordance was age at first sexual encounter. Oral-anal HPV genotypic concordance was significantly lower among participants who reported an older age of first sex (16 years or older) compared with those who were younger at their first sexual encounter. Contrary to this, in the inverse was observed for anal-genital samples. It is unclear why we observed this difference, but potential explanations include different dynamics in HPV DNA acquisition at the oral site, as well as significant variances in clearance and persistence of HPV infections in the oral site compared to the anogenital sites[21, 40]. In the only other study among MSM that reported on the association of age of first sex with HPV concordance, those who reported an older age of first sex were more likely to have a concordant infection at both sites, compared to those who had a younger age, but this was not statistically significant[30]. On the other hand, studies among women have observed that those reporting a younger age of sexual debut were more likely to have a concordant oral-genital HPV infection[32, 33] as seen in our study population. Nevertheless, their findings failed to achieve statistical significance in the multivariate model.

Although sexual behaviors are independent risk factors for infection at individual anatomical sites, we did not find that condom use, being a bottom, oral sex history, recent sex partners, or history of warts and STIs, to have a significant association with either genital-anal or oral-anal concordance. We did observe lifetime number of sex partners and being a top in anal sex in the

last one year to be associated with a higher likelihood of oral-anal HPV type concordance, but we did not find these associations to be significant after adjusting for age, smoking and age of sexual debut. Other studies among men and women have however observed certain sexual characteristics (e.g. recent sex partner, number of oral sex partners, marital status and history of chlamydia infection) to be significantly associated with type concordant oral-genital HPV infections[15, 31, 33]. The lack of statistical significance with some of these sexual behavior characteristics in our study may be attributed to the relatively low prevalence of concordance as well as the high prevalence of most sexual behaviors among study participants.

The lack of type-concordance between oral and anogenital HPV infections seen in our study and other similar studies suggest that oral HPV infections are acquired independently of anogenital infections and are less likely to reactivate from latency compared to anogenital infections [11]. In addition, self-inoculation between oral and anogenital sites may be uncommon and there are likely different pathways or timing of infection at the oral site compared to the anogenital sites[40]. Faster clearance from oral epithelia and latent infections remaining undetected due to limitations of exfoliated cell sampling might also explain the low prevalence of concordant infections involving the oral site[20]. Moreover, the lack of concordance at the different sites can also be explained by differences in the duration of infection at the different sites[41], varying limitations of specimen collection from the three sites, and difference in tissue structure and virus tropism between the different sites[29].

On the other hand, we observed that there was some level of type-concordance between genital and anal HPV infections in our population of young MSM, but that this was not found to be associated with sexual behavior characteristics. This suggests that nonpenetrative sexual

behaviors and auto-inoculation might therefore still play a role in transmission of HPV infections. This theory is also supported by the high prevalence of anal HPV infections in the absence of anal sex in studies of both men and women[32, 42-47]. Although the mechanism of transport between these anatomic sites is unclear, some data suggest that HPV infection at either site can serve as a reservoir for infection at the other site[48]and there is a potential for transmission of HPV via hand carriage[49, 50] and objects,[51] which may facilitate HPV inoculation between the anal canal and genitals. Nonetheless, as our study is cross-sectional it limits the ability to distinguish between newly acquired versus persistent infections and therefore longitudinal studies are needed to elucidate HPV transmission dynamics.

A strength of our study was that it was conducted at three sites with access to a large source population which allowed us to conduct the largest study to date evaluating the concordance of HPV DNA at three anatomic sites in young MSM. In addition, the study efficiently enrolled participants at minimal costs while still having access to a wide range of racially and ethnically diverse MSM. Another strength of our study is that we used the gold standard method of collecting HPV specimens from the various sites and all samples were tested in one laboratory using a genotyping PCR assay that allowed us to detect 37 different HPV DNA types. Lastly, we had access to a rich array of demographic data, medical information and sexual behavior data through the clinical CASI tool, medical records and survey tools allowing us to study a wide range of potential covariates.

Nevertheless, out study had some limitations which need to be considered when interpreting our findings. First, participants were enrolled from clinics serving MSM which resulted in a convenience sample that may not be broadly representative of MSM and transgender women in

general. Another limitation is that self-reported characteristics, such as sexually transmitted infections, were likely to be underreported due to social desirability and recall bias and we also observed a relatively high proportion of missing data for these variables. However, self-report was the only way to obtain this data and is considered a standard practice. Although we used the gold standard method for collecting HPV specimens, it is unclear whether the sensitivity of HPV DNA testing is similar across the three different sites and different sample types. In addition, as we tested each of the 23 variables for a statistically significant association between oral-anal and anal-genital HPV concordant infections there is a possibility that some our findings could have occurred due to chance alone. Lastly, our findings pertain to young MSM and they might not generalize to older MSM, men who have sex with women, women, or immuno-compromised persons.

In summary, genotype-specific concordance of oral and anogenital sites was rare in our population of young MSM. It is likely that the initial exposure at these sites occurred in separate events, and/or that the oral mucosa has significantly different susceptibility to HPV infection[11, 40]. Although, we observed some degree of concordance between anal and genital HPV infections, our findings do not support the role of sexual behavior as a determinant of concordant HPV infections in MSM. The acquisition of the same HPV genotype at the anal and genital sites might therefore be occurring from nonsexual transmission such as autoinoculation from one site to the other or from contiguous spread[48, 49]. However, large longitudinal studies that investigate multiple anatomic sites at the same time are necessary to better understand the mechanism of non-sexual transmission.

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Table 1 - Baseline demographics and sexual characteristics of young MSM enrolled in 3 US cities from 2015 to 2017

Characteristic		No. (%)[†] (N = 1876)[ǂ]
City	Chicago	664 (35.4%)
	Los Angeles	462 (24.6%)
	Seattle	750 (40%)
Age (years)	Mean (SD), N = 1876	22.6 (2.4)
	Median (IQR), N = 1876	23 (21 - 25)
	18 – 21	661 (35.2%)
	22 – 26	1215 (64.8%)
Gender identity	Male	1772 (94.6%)
	Female/transgender female	55 (2.9%)
	Other	47 (2.5%)
Sexual orientation missing = 100[^]	Gay/homosexual	1358 (76.5%)
	Straight/heterosexual	32 (1.8%)
	Other/unknown[†]	386 (21.7%)
Race/Ethnicity missing = 160[^]	Non-Hispanic White	585 (34.1%)
	Non-Hispanic Black	265 (15.4%)
	Hispanic	569 (33.2%)
	Asian/Pacific Islander	147 (8.6%)
	Other*/unknown[†]	150 (8.7%)
Smoking status	Ever smoked	789 (42.4%)
	Never smoked or Unknown[†]	1074 (57.6%)
Most recent HIV test result	Positive	143 (8.0%)
	Negative or unknown[†]	1634 (92.0%)
History of PrEP for HIV prevention missing = 195[^]	Yes	397 (23.6%)
	No or unknown[†]	1284 (76.4%)
HPV Vaccination status missing = 225[^]	Vaccinated	742 (39.6%)
	Unvaccinated	741 (39.5%)
	Unknown[†]	168 (9.0%)
Age at 1st HPV Vaccine dose (restricted to 742 participants self-reporting HPV vaccination) missing = 52[^]	Mean (SD), N = 690	18.7 (4.5)
	Median (IQR), N = 690	19 (16 - 22)
	< 19 years	311 (45.1%)
	>=19 years	379 (54.9%)
Age at first sex with any partner	Mean (SD), N = 1863	16.2 (2.9)

	Median (IQR), N = 1863	16 (15 - 18)
	<16 years	663 (35.6%)
	>= 16 years	1197 (64.4%)
Lifetime no. of sex partners of any sex	Mean (SD), N = 1814	41.9 (63.3)
	Median (IQR), N = 1814	21 (10 - 50)
	<=5	190 (10.5%)
	6 - 10	273 (15.0%)
	11 - 20	404 (22.3%)
	>20	947 (52.2%)
Number of male sexual partners in the last 12 months missing = 124^	Mean (SD), N = 1752	10.6 (17.4)
	Median (IQR), N = 1752	5 (2 - 12)
	None	62 (3.5%)
	1	198 (11.3%)
	2 - 4	482 (27.5%)
	5 - 9	438 (25.0%)
	>=10	572 (32.7%)
Number of male sexual partners in the last 2 months missing = 118^	Mean (SD), N = 1758	3.7 (4.6)
	Median (IQR), N = 1758	2 (1-5)
	None	168 (9.5%)
	1	443 (25.2%)
	2 - 4	701 (39.9%)
	5 - 9	283 (16.1%)
	>=10	163 (9.3%)
Any new male sexual partners in the last 2 months missing = 278^	Yes	1155 (72.3%)
	No	443 (27.7%)
Recently gave oral sex in the last 2 months missing = 119^	Yes	1457 (82.9%)
	No	300 (17.1%)
Recently got oral sex in the last 2 months^^ missing = 266^	Yes	1365 (84.8%)
	No	245 (15.2%)
Last 12 months was a bottom in anal sex missing = 128^	Yes	1369 (78.3%)
	No	379 (21.7%)
In the last 12 months engaged in condomless bottom anal sex missing = 152^	Always	324 (18.8%)
	Not always	1017 (59.0%)
	Not a bottom in the last 12 months	383 (22.2%)

Last 12 months was a top in anal sex missing = 127^	Yes	1343 (76.8%)
	No	406 (23.2%)
In the last 12 months engaged in condomless top anal sex missing = 149^	Always	342 (19.8%)
	Not always	975 (56.5%)
	Not a top in the last 12 months	410 (23.7%)
Ever had anogenital warts^^ missing = 430^	Yes	90 (6.2%)
	No	1356 (93.8%)
Ever had genital herpes^^ missing = 425^	Yes	60 (4.1%)
	No	1391 (95.9%)
History of chlamydia or gonorrhea in the last 12 months missing = 117^	Yes	538 (30.6%)
	No	1221 (69.4%)
History of syphilis in the last 12 months missing = 129^	Yes	150 (8.6%)
	No	1597 (91.4%)

†Presented as number (%) unless otherwise specified

‡N includes total number of participants enrolled in the study unless otherwise specified

†Unknown includes whenever a participant responded to a question with "Don't know/Not sure" *Other includes those who reported their race as American Indian, Alaskan Native, more than one race or other

^^This data was not available for participants from the Gay City site in Seattle

^Missing data has been included for variables where more than 5% of data was missing

Table 2 - Prevalence of HPV genotype detection at various anatomic sites among participants enrolled in the study[‡]

	Any HPV type		Any high-risk HPV type		Any 4-valent HPV type		Any 9-valent HPV type	
	no.	%	no.	%	no.	%	no.	%
Any site* (n = 1876)	1336	71.2%	985	52.5%	520	27.7%	728	38.8%
Oral Site (n = 1868)	138	7.4%	58	3.1%	34	1.8%	41	2.2%
Anal Site (n = 1787)	1250	69.9%	916	51.3%	470	26.3%	667	37.3%
Genital Site (n = 701)	341	48.6%	207	29.5%	96	13.7%	136	19.4%
Oral & Anal sites^ (n = 1779)	116	6.5%	45	2.5%	23	1.3%	29	1.6%
No concordance[a]	74	63.8%	24	53.3%	5	21.7%	9	31.0%
Complete concordance[b]	30	25.9%	20	44.5%	18	78.3%	19	65.5%
Partial concordance[c]	12	10.3%	1	2.2%	0	0.0%	1	3.5%
Oral & Genital sites^ (n = 700)	24	3.4%	9	1.3%	3	0.4%	3	0.4%
No concordance[a]	16	66.7%	6	66.7%	0	0.0%	0	0.0%
Complete concordance[b]	8	33.3%	3	33.3%	3	100.0%	3	100.0%
Partial concordance[c]	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Anal & Genital sites^ (n = 668)	273	40.9%	150	22.5%	56	8.4%	87	13.0%
No concordance[a]	77	28.2%	39	26.0%	6	10.7%	19	21.8%
Complete concordance[b]	107	39.2%	79	52.7%	46	82.1%	52	59.8%
Partial concordance[c]	89	32.6%	32	21.3%	4	7.2%	16	18.4%
All 3 sites^ (n = 668)	20	3.0%	8	1.2%	2	0.3%	3	0.5%
No concordance[a]	15	75.0%	5	62.5%	0	0.0%	1	33.3%
Complete concordance[b]	4	20.0%	2	25.0%	2	100.0%	2	66.7%
Partial concordance[c]	1	5.0%	1	12.5%	0	0.0%	0	0.0%

[‡]These analyses are restricted to having an adequate sample at the site specified

*HPV detected at either one of the three sites (oral, anal or penile)

^HPV genotype(s) detected at both all or three of the sites specified

[a]Among those with HPV detected at both or all three sites, no similar HPV genotype(s) detected

[b]Among those with HPV detected at both or all three sites, all the HPV genotypes detected were the same

[c]Among those with HPV detected at both or all three sites, some of the HPV genotypes detected were the same

Table 3. Genotype level comparison of concordance of HPV infections between oral, anal and genital sites

	No. of pairs*				PPA (%)	Kappa +⸸	(95% CI)
	+/+	+/-	-/+	-/-			
Any HPV type							
Oral/Anal	50	123	3851	61799	1.2%	0.01	0.01 - 0.01
Oral/Genital	10	31	682	25177	1.4%	0.01	0.00 - 0.02
Anal/Genital	299	1125	362	22930	16.7%	0.15	0.13 - 0.17
Any HR-HPV type							
Oral/Anal	24	39	1762	23081	1.3%	0.01	0.01 - 0.02
Oral/Genital	4	12	299	9485	1.3%	0.01	0.00 - 0.03
Anal/Genital	145	488	151	8568	18.5%	0.17	0.14 - 0.20
Any 4-valent HPV type							
Oral/Anal	18	15	561	6522	3.0%	0.03	0.01 - 0.04
Oral/Genital	3	5	104	2688	2.7%	0.02	0.00 - 0.01
Anal/Genital	53	164	51	2404	19.8%	0.18	0.13 - 0.23
HPV 6 &/OR 11 type							
Oral/Anal	10	9	309	3230	3.0%	0.03	0.01 - 0.05
Oral/Genital	2	1	54	1343	3.5%	0.03	0.00 - 0.08
Anal/Genital	32	86	22	1196	22.9%	0.21	0.14 - 0.28
HPV 16 &/OR 18 type							
Oral/Anal	8	6	252	3292	3.0%	0.03	0.01 - 0.05
Oral/Genital	1	4	50	1345	1.8%	0.02	0.00 - 0.05
Anal/Genital	21	78	29	1208	16.4%	0.14	0.08 - 0.21

*Represents the number of participants multiplied by the number of HPV types evaluated per participant multiplied by the number of valid samples evaluated per participant

⸸Kappa + is calculated based on the percent positive agreement

Table 4. Correlates of genotype level concordance for any HPV type detected among paired oral-anal samples

Characteristic		Crude (N= 4024)				Adjusted (N = 3842)			
		N	n	OR	95% CI	N	n	AOR	95% CI
Age (years)	18 – 21	1091	14	Ref	0.48 - 1.89				
	22 – 26	2933	36	0.96					
Sexual orientation missing = 238[†]	Straight, bisexual or other	701	9	Ref	0.44 - 2.21				
	Homosexual or gay	3085	39	0.98					
Race missing = 365[†]	Non-Hispanic White	1037	15	Ref	Ref				
	Non-Hispanic Black	771	9	0.8	0.32 - 2.02				
	Hispanic	1241	19	1.06	0.48 - 2.36				
	Other/Unknown*	610	5	0.56	0.17 - 1.86				
Smoking status[‡]	Never smoked or unknown	2140	17	Ref	1.17 - 4.40	2058	17	Ref	0.96 - 3.76
	Ever smoked	1851	33	2.27		1784	32	1.90	
HIV status missing = 242[†]	Negative or unknown	3101	36	Ref	0.68 - 3.32				
	Positive	681	12	1.53					
Ever taken HIV PrEP missing = 704[†]	No or unknown	2149	27	Ref	0.44 - 2.05				
	Yes	1171	14	0.95					
HPV Vaccination status missing = 455[†]	Unvaccinated or unknown	1947	27	Ref	0.43 - 1.66				
	Vaccinated	1622	19	0.84					
Age of 1st HPV Vaccine dose missing = 569[†]	<19	497	3	Ref	Ref				
	>=19	1011	14	2.31	0.64 - 8.33				
	Unvaccinated or unknown	1947	27	2.32	0.69 - 7.74				
Age of sexual debut[‡]	<=15	1610	29	Ref	0.26 - 0.91	1536	29	Ref	0.27 - 0.93
	>=16	2395	21	0.48		2306	20	0.50	
Lifetime number of sexual partners[‡]	<=10	662	2	0.22	0.05 - 0.93	636	2	0.30	0.07 - 1.36
	11 - 20	701	13	1.37	0.62 - 3.07	700	13	1.57	0.71 - 3.49
	>20	2508	34	Ref	-	2506	34	Ref	Ref
Male sexual partners in the last 12 months missing = 285[†]	<=1	400	9	1.73	0.67 - 4.50				
	2-4	868	10	0.88	0.36 - 2.11				
	5-9	868	8	0.70	0.28 - 1.75				
	>=10	1603	21	Ref	Ref				
Male sexual partners in last 2 months missing = 278[†]	<=1	1089	16	Ref	Ref				
	2-4	1480	16	0.73	0.33 - 1.63				

	5-9	710	12	1.15	0.49 - 2.72				
	>=10	467	4	0.58	0.11 - 3.03				
New male sex partner (last 2 months) missing = 566†	No	786	15	Ref	0.30 - 1.36				
	Yes	2672	33	0.64					
In the last 2 months gave oral sex missing = 277†	No	473	4	Ref	0.46 - 5.58				
	Yes	3274	44	1.6					
In the last 2 months got oral sex^ missing = 553†	No	516	7	Ref	0.38 - 2.76				
	Yes	2955	41	1.02					
Was a bottom in anal sex in the last 12 months; missing = 302†	No	420	7	Ref	0.30 - 1.83				
	Yes	3302	41	0.74					
In the last 12 months engaged in condomless bottom anal sex missing = 769†	Always	541	7	Ref	Ref				
	Not always	2714	33	0.94	0.37 -2.39				
	Not a bottom	426	7	1.27	0.39 - 4.14				
Last 12 months was a top in anal sex‡	No	929	6	Ref	Ref	902	6	Ref	Ref
	Yes	2800	42	2.34	0.87 - 6.28	2667	41	1.98	0.72 - 5.40
	Missing**	295	2	1.05	0.20 - 5.56	273	2	0.99	0.18 - 5.36
In the last 12 months engaged in condomless top anal sex missing = 1290†	Always	581	8	Ref	Ref				
	Not always	2153	30	1.01	0.42 - 2.42				
	Not a top	944	6	0.46	0.14 - 1.52				
Ever had anogenital warts^ missing = 949†	No	2779	32	Ref	0.25 - 5.52				
	Yes	296	4	1.18					
Ever had genital herpes^ missing = 937†	No	2890	36	Ref	0 - 1.57				
	Yes	197	0	0					
History of chlamydia or gonorrhea in the last 12 months; missing = 274†	No	2124	27	Ref	0.49 - 1.92				
	Yes	1626	20	0.97					
History of syphilis in the last 12 months missing = 321†	No	3184	38	Ref	0.52 - 4.12				
	Yes	519	9	1.46					

† Missing data is presented for variables where there was more than 5% missing data

*Other includes those who reported their race as either Asian, Pacific Islander, American Indian, Alaskan Native, more than one race or other

^This data was not available for participants from the Gay City site in Seattle

‡$p < 0.1$

**Missing has been included as a category for variables found to be both significant in the univariate analysis and with substantial missing data (i.e., >= 5%)

Table 5. Correlates of genotype level concordance for any HPV type detected among paired anal-genital samples

Characteristic		Crude (N= 1786)				Adjusted (N = 1778)			
		N	n	OR	95% CI	N	n	AOR	95% CI
Age (years)‡	18 – 21	423	91	Ref	0.47 - 0.93	421	91	Ref	0.44 - 0.87
	22 – 26	1363	208	0.66		1357	208	0.62	
Sexual orientation missing = 260†	Straight, bisexual or other	254	44	Ref	0.63 - 1.55				
	Homosexual or gay	1272	219	0.99					
Race	Non-Hispanic White	854	142	Ref	-				
	Non-Hispanic Black	139	24	1.05	0.48 - 2.29				
	Hispanic	394	58	0.87	0.57 - 1.31				
	Other/Unknown*	344	64	1.15	0.79 - 1.67				
Smoking status	Never smoked or unknown	1238	211	Ref	0.67 - 1.35				
	Ever smoked	513	84	0.95					
HIV status‡ missing = 259	Negative or unknown	1456	244	Ref	Ref	1448	244	Ref	Ref
	Positive	71	20	1.95	0.88 - 4.29	71	20	2.13	0.96 - 4.74
	Missing**	259	35	0.8	0.49 - 1.23	259	35	0.78	0.49 - 1.24
Ever taken HIV PrEP missing = 343†	No or unknown	891	145	Ref	0.81 - 1.56				
	Yes	552	99	1.12					
HPV Vaccination status	Unvaccinated or unknown	873	147	Ref	0.72 - 1.32				
	Vaccinated	886	146	0.97					
Age of 1st HPV Vaccine dose missing = 141†	<19	163	20	Ref	Ref				
	>=19	609	104	1.47	0.74 - 2.93				
	Unvaccinated or unknown	873	147	1.45	0.74 - 2.83				
Age of sexual debut‡	<=15	573	78	Ref	1.02 - 2.00	573	78	Ref	1.04 - 2.05
	>=16	1205	221	1.43		1205	221	1.46	
Lifetime number of sexual partners missing = 136†	<=10	203	36	1.04	0.66 - 1.66				
	11 - 20	307	43	0.79	0.53 - 1.18				
	>20	1140	195	Ref	Ref				
Male sexual partners in the last 12 months missing = 323†	<=1	36	1	0.14	0..02 - 1.11				
	2-4	283	57	1.26	0.79 - 2.00				
	5-9	382	71	1.14	0.80 - 1.64				
	>=10	762	127	Ref	Ref				

Male sexual partners in last 2 months missing = 323†	<=1	197	27	Ref	Ref	
	2-4	689	123	1.37	0.75 - 2.50	
	5-9	364	71	1.53	0.82 - 2.84	
	>=10	213	35	1.24	0.62 - 2.47	
Any new male sexual partners in the last 2 months; missing = 606†	No	193	24	Ref	0.82 - 3.43	
	Yes	987	190	1.68	0.77 - 2.67	
Recently gave oral sex missing = 323†	No	99	13	Ref	0.77 - 2.67	
	Yes	1364	243	1.43		
Recently got oral sex^ missing = 597†	No	77	22	Ref	0.23 - 1.20	
	Yes	1112	193	0.53		
A bottom in anal sex (in last 12 mos.) missing = 326†	No	117	15	Ref	0.84 - 2.60	
	Yes	1343	240	1.48		
In the last 12 months engaged in condomless bottom anal sex missing = 384†	Always	144	27	Ref	Ref	
	Not always	1141	196	0.9	0.56 - 1.45	
	Not a bottom	117	15	0.64	0.32 - 1.28	
A top in anal sex (in last 12 mos.) missing = 334†	No	282	50	Ref	0.65 - 1.49	
	Yes	1170	205	0.99		
In the last 12 months engaged in condomless top anal sex missing = 372†	Always	156	20	Ref	Ref	
	Not always	976	175	1.49	0.90 - 2.44	
	Not a top	282	50	1.47	0.81 - 2.65	
Ever had anogenital warts^ missing = 534†	No	1152	200	Ref	0.82 - 2.21	
	Yes	100	22	1.34		
Ever had genital herpes^ missing = 534†	No	1166	209	Ref	0.37 - 1.81	
	Yes	86	13	0.82		
History of chlamydia or gonorrhea in the last 12 months; missing = 259†	No	810	138	Ref	0.75 - 1.43	
	Yes	717	126	1.04		
History of syphilis in the last 12 months missing = 259†	No	1326	226	Ref	0.67 - 1.93	
	Yes	201	38	1.13		

†Missing data is presented for variables where there was more than 5% missing data

*Other includes those who reported their race as either Asian, Pacific Islander, American Indian, Alaskan Native, more than one race or other

^This data was not available for participants from the Gay City site in Seattle

‡$p < 0.1$

**Missing has been included as a category for variables found to be both significant in the univariate analysis and with substantial missing data (i.e., >= 5%)