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Incidence and clearance of oral and cervicogenital HPV infection: longitudinal analysis of the MHOC cohort study

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Abstract

Objectives: The Michigan HPV and Oropharyngeal Cancer (MHOC) Study aimed to evaluate patterns of oral and cervicogenital HPV infection prevalence, incidence, and clearance as well as their relationship to sexual behaviors.

Design: Cohort

Setting: General public in and around Ann Arbor, MI

Participants: 394 college-age and older-adult participants of both sexes provided oral samples, and 325 completed at least 2 visits. 130 who provided a cervicogenital samples, and 127 completed at least 2 visits.

Outcomes: Incidence and clearance rates as well as hazard ratios (HR) for oral and cervicogenital HPV.

Results: Oral HPV infections were transient, with only 16% of genotypes persisting to the next visit. The mean time to clearance of a genotype was 46 days (95% CI: 37–58). In contrast, cervicogenital infections were more persistent, with 56% of genotypes persisting to the next visit. The mean time to clearance of a genotype was 87 days (95% CI: 74–102). HPV vaccination was associated with reduced incidence of cervicogenital HPV infection (HR: 0.63; 95% CI: 0.47, 0.83) but not oral HPV infection. Incidence of oral HPV infection was associated with 2+ recent deep kissing partners (HR: 2.00; 95% CI: 1.13, 3.56). Incidence of both oral (HR: 1.70; 95% CI: 1.08, 2.68) and cervicogenital (HR: 2.46; 95% CI 1.69, 3.59) was associated with 2+ recent sexual partners.

Conclusions: Detection of oral HPV was highly transient, but incidence was associated with recent deep kissing and sexual partners. Detection of cervicogenital HPV was more persistent, and incidence was positively associated with recent sexual partners and negatively associated with HPV vaccination.

Article summary

Strengths and limitations of this study

- This study enrolled men and women and reports on both oral and cervicogenital HPV
- This study's longitudinal cohort design allowed for inference of HPV dynamics
- This study is limited by its comparatively small sample size and convenience sample design.

Introduction

The human papillomavirus (HPV) is the cause of virtually every cervical cancer and an increasing number and fraction of head and neck cancers [1–8]. Although vaccines are available that cover the most common cancer-causing genotypes, coverage is not complete among targeted age groups in the US [9], and there are oncogenic genotypes not covered by any of the available vaccines. In 2018, the US Preventive Services Task Force (USPSTF) updated its cervical cancer screening guidelines for women 21–65 to include an option of testing for high-risk HPV every five years, with or without cytology, in addition to the option of cervical cytology alone every three years [10]. While the USPSTF has concluded that the evidence for oral cancer screening in asymptomatic individuals is currently insufficient to recommend it, HPV testing could, in the future, be part of oral cancer screening either in the general population or in targeted, high-risk groups [2]. Because the most HPV infections clear without major consequences nor lead to cancer, it is essential that we understand the dynamics of cervicogenital and oral HPV infections, both to understand the implications of an oral HPV positive test and to understand the risk factors and transmission pathways associated with infection.

Cross-sectional studies, such as the National Health and Nutrition Examination Survey (NHANES) in the US, can identify risk factors associated with prevalence but are unable to assess those associated with infection dynamics—neither incidence nor clearance can be determined. Longitudinal studies of HPV, such as the HPV in Men (HIM) study [11], have provided estimates of site-specific incidence and clearance. However, most previous longitudinal studies have had a relatively long time period between follow-up, making it difficult to understand short-term infection and clearance dynamics.

The Michigan HPV and Oropharyngeal Cancer (MHOC) Study aims to evaluate patterns of oral HPV infection prevalence, incidence and clearance and their relationship to sexual history and sexual behaviors [12]. The epidemiological arm of the MHOC Study has tested a cohort of adults for oral and, in a substudy, cervicogenital HPV over 3 years, with follow-up visits every 3–4 months. This shorter follow-up time allows us to determine incidence and clearance rates in our participants with greater precision. Using a multistate transition model, we estimate the underlying rates of incidence and clearance for oral and cervicogenital HPV and the associations (hazard ratios) of demographic and behavioral characteristics on incidence at each site.

Methods

We previously published the full MHOC study protocol [12]. We briefly describe the main aspects of the study here.

Study subjects

Study participants were recruited in Ann Arbor, Michigan and the immediate surrounding areas. Participants were recruited at University of Michigan campus dormitories, through community fliers, and through the UM Health Research website. Volunteers over the age of 18 without a history of head and neck cancer who were willing to return every 3–4 months for 3 years for followup visits were invited to enroll. We enrolled 394 participants between April 2015 and December 2017. Participants completed between 1 and 12 visits, with a median of 6 visits; 325 participants completed at least 2 visits. A substudy focusing on cervicogenital HPV enrolled 130 participants. Documented informed consent was obtained from all participants. The University of Michigan IRB approved consent documents and study protocol (HUM00090236). Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Michigan [13, 14].

Surveys

A baseline questionnaire was administered to each participant at their initial visit. Participant ID numbers were assigned to ensure participant confidentiality. Follow-up surveys were administered at each subsequent visit. The surveys were designed to individually assess a variety of topics including demographics, vaccination and screening history, sexual health and behavior, and alcohol and drug use. Sexual behavior questions assessed current and past experiences of vaginal, oral, and anal sex. The baseline questionnaire collected a complete sexual behavior history, with the subsequent follow-up visits collecting more recent information and updates. Numbers of recent sexual partners were grouped into 0, 1, 2+ categories except for numbers of recent anal sex partners, which were grouped into 0 and 1+ because of smaller numbers.

HPV testing

All participants self-collected a saliva sample with Scope mouthwash (Proctor & Gamble; Cincinnati, OH) or an Oragene RE-100 kit (DNA Genotek; Kanata, Canada). Saliva samples were taken at each study visit.

Participants who had a vagina, were not pregnant, and were not menstruating at the time of a study visit were invited to self-collect a cervicogenital sample with a HerSwab (Eve Medical; Toronto, Canada). The cervicogenital substudy was rolled out after the main study, so most substudy participants had their first cervicogenital test at a follow-up visit rather than at their baseline visit. DNA was extracted from samples and genotyped using PCR Mass Array [15]. We tested for genotypes 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 90.

Statistical analysis

We used Markov multistate transition modeling to estimate the incidence and clearance rate for oral HPV and cervicogenital HPV. Markov state transitions models are continuous-time, finite-state stochastic processes that assume that the transition hazard rate depends on one's current state but not on one's history (i.e., we assume that previous infection does not increase the likelihood of future infection) [16]. Infection and clearance occur at any time, but we only observe individuals states at certain points in time (Figure 1). For a given rate of infection and clearance, we can calculate the probability of each individual's observed trajectory. By maximizing this probability as a function of the infection and clearance rates, we estimate best-fit rates. Data were analyzed in R 4.0 (R Foundation for Statistical Computing; Vienna, Austria) using the msm package [17], 2018–20. Participants with missing data were excluded from analyses involving those missing data. Participants lost to follow up were included if they had at least two visits.

For this analysis, we assumed that incidence and clearance of each HPV genotype occurs independently of the others and that hazard ratios are the same for all genotypes. We estimated hazard ratios for incidence for selected covariates in univariable models. We assumed there is no impact of covariates on clearance—both due to the lack of biological justification for the impact of most behavioral and demographic covariates on clearance and also due to potential issues of practical unidentifiability. That is, we want to avoid estimating increased incidence as reduced clearance if we are not observing at a sufficiently fine time scale. This will potentially neglect the impact of age on clearance, but we felt that the effect of age on incidence (e.g., via changes in risk, behavior, etc.) was more salient.

Patient and Public Involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Among the 325 participants who had at least two study visits, 317 had two or more valid oral HPV tests across any of their visits. The characteristics of these 317 participants are given in Table 1. An alluvial plot, which shows the number of participants in each state at each visit and the transition between statuses between subsequent visits, is shown in Figure 2a. Among these participants, we recorded 1,845 negative oral HPV tests and 148 positive oral HPV tests for at least one tested genotype. We observed 1,676 pairs of participant visits: 1,455 pairs of visits where the participant remained HPV negative, 94 pairs of visits where the participant transitioned from HPV negative to HPV positive, 107 pairs of visits where the participant transitioned from HPV positive to HPV negative, and 20 pairs of visits in which the participant remained positive for the same genotype. Only 16% of detected genotypes persisted to the next study visit. Through the multistate transition model, we estimated the average time to clearance of a previously detected genotype was 46 days (95% CI: 37–58 days).

Table 1: Baseline characteristics of participants in the MHOC Study with at least two study visits with valid HPV tests (data collected in Ann Arbor, MI, 2015-17, analyzed 2018-20). Note: percentages may not add up to 100% as participants could refuse to answer questions. *Other than HPV.

	Full cohort (N=317)		Cervicogenital substudy cohort (N= 115)	
	%	n	%	n
Age				
18	29%	91	25%	29
19-22	33%	104	32%	37
23-29	12%	38	11%	13
30-49	12%	37	16%	18
50+	15%	47	16%	18
Sex				
Female	68%	216	100%	115
Male	32%	101	0%	0
Race				

White	60%	189	64%	74
Asian	23%	73	18%	21
Black/Hispanic/multiracial/unknown	17%	55	17%	20
Marital/partner status				
Never married/partnered	77%	243	73%	84
Ever married/partnered	23%	72	27%	31
Circumcised (male only)				
Yes	68%	69	—	—
No	31%	31	—	—
Ever diagnosed with STI*				
No	93%	296	92%	106
Yes	7%	21	8%	9
HPV vaccination				
No	45%	142	45%	52
Yes	48%	152	50%	58
Alcohol use				
Never or non-current	31%	99	27%	31
Current	66%	210	71%	82
Ever cigarette use				
Never	77%	246	78%	90
Ever	21%	68	21%	24
Ever marijuana use				
Never	54%	171	53%	61
Ever	41%	130	44%	51
Deep kissing partners (6 months)				
0	42%	132	79%	91
1	34%	109	14%	16
2+	24%	76	7%	8
Vaginal, oral, or anal sex partners (6 months)				
0	39%	124	35%	40
1	43%	137	44%	51
2+	17%	54	21%	24
Vaginal sex partners (6 months)				
0	49%	154	43%	50
1	38%	120	38%	44

2+	13%	41	18%	21
Received oral sex partners (6 months)				
0	48%	152	42%	48
1	36%	112	39%	45
2+	16%	51	19%	22
Performed oral sex partners (6 months)				
0	52%	165	44%	51
1	35%	110	43%	49
2+	13%	40	13%	15
Anal sex partners (6 months)				
0	89%	279	89%	101
1+	11%	34	11%	12

Among the 127 participants who provided cervicogenital samples for at least two study visits, 115 had two or more valid cervicogenital HPV tests; the characteristics of this subcohort mirror those of the full cohort, with the exception that the subcohort is entirely female. The characteristics of these 115 participants are given in Table 1, and alluvial plots of participant statuses are shown in Figure 2b. Among these participants, we recorded 396 negative oral HPV tests and 166 positive oral HPV tests for at least one tested genotype. We observed 447 pairs of participant visits: 250 pairs of visits where the participant remained HPV negative, 74 pairs of visits where the participant transitioned from HPV negative to HPV positive, 54 pairs of visits where the participant transitioned from HPV positive to HPV negative, and 69 pairs of visits in which the participant remained positive for the same genotype. Unlike oral infections, cervicogenital infections were persistent, with 56% of detected genotypes persisting to the next study visit. Using the multistate transition model, we estimated the average time to clearance of a previously detected genotype was 87 days (95% CI: 74–102 days).

Hazard ratios for HPV incidence are given in Tables 2. In this population, participants ages 23–29 and 50+ were less likely to acquire an oral HPV infection. There were no significant differences in incidence of cervicogenital HPV by age. Sex, race, marital status, circumcision status, previous sexually transmitted infection (STI) diagnosis, current alcohol use, and ever cigarette use were not associated with incidence of either oral or cervicogenital HPV. Ever marijuana use was associated with greater incidence of

cervicogenital HPV. Being vaccinated for HPV was significantly associated with lower incidence of cervicogenital HPV but not associated with incidence of oral HPV.

Table 2: Hazard ratios for the incidence rate of oral and cervicogenital HPV in the MHOC Study (data collected in Ann Arbor, MI, 2015-17, analyzed 2018-20). *Other than HPV.

	Oral HPV incidence			Cervicogenital HPV incidence		
	N	Hazard ratio	95% CI	N	Hazard ratio	95% CI
Age						
18	91	1 (ref)	—	29	1 (ref)	—
19-22	104	0.73	(0.49, 1.1)	37	1.18	(0.82, 1.69)
23-29	38	**0.32**	(0.15, 0.68)	13	1.03	(0.63, 1.67)
30-49	37	0.77	(0.45, 1.29)	18	1.23	(0.78, 1.94)
50+	47	**0.46**	(0.27, 0.79)	18	0.92	(0.59, 1.41)
Sex						
Female	216	1 (ref)	—	115	1 (ref)	—
Male	101	0.85	(0.59, 1.23)	0	—	—
Race						
White	189	1 (ref)	—	74	1 (ref)	—
Asian	73	0.61	(0.37, 1.02)	21	0.91	(0.63, 1.32)
Black/Hispanic/multiracial/unknown	55	1.24	(0.83, 1.85)	20	1.33	(0.95, 1.87)
Marital/partner status						
Never married/partnered	243	1 (ref)	—	84	1 (ref)	—
Ever married/partnered	72	0.80	(0.54, 1.19)	31	0.82	(0.59, 1.14)
Circumcised (male only)						
Yes		1 (ref)	—	—	—	—
No		0.70	(0.33,1.47)	—	—	—
Ever diagnosed with STI*						
No	296	1 (ref)	—	106	1 (ref)	—
Yes	21	0.81	(0.41, 1.59)	9	1.20	(0.74, 1.92)

HPV vaccination						
No	142	1 (ref)	—	52	1 (ref)	—
Yes	152	1.22	(0.87, 1.71)	58	**0.63**	(0.47, 0.83)
Alcohol use						
Never or non-current	99	1 (ref)	—	31	1 (ref)	—
Current	210	1.32	(0.91, 1.94)	82	1.11	(0.82, 1.51)
Ever cigarette use						
Never	246	1 (ref)	—	90	1 (ref)	—
Ever	68	1.37	(0.71, 2.62)	24	0.92	(0.65, 1.29)
Ever marijuana use						
Never	171	1 (ref)	—	61	1 (ref)	—
Ever	130	1.05	(0.74, 1.47)	51	**1.48**	(1.12, 1.96)
Deep kissing partners (6 months)						
0	132	1 (ref)	—		1 (ref)	—
1	109	1.65	(0.96, 2.83)		0.87	(0.49, 1.52)
2+	76	**2.00**	(1.13, 3.56)		0.57	(0.25, 1.28)
Vaginal, oral, or anal sex partners (6 months)						
0	124	1 (ref)	—		1 (ref)	—
1	137	1.26	(0.87, 1.84)		**1.62**	(1.17, 2.26)
2+	54	**1.70**	(1.08, 2.68)		**2.46**	(1.69, 3.59)
Vaginal sex partners (6 months)						
0	154	1 (ref)	—		1 (ref)	—
1	120	1.24	(0.86, 1.78)		**1.44**	(1.05, 1.98)
2+	41	**1.96**	(1.23, 3.11)		**3.35**	(2.34, 4.78)
Received oral sex partners (6 months)						
0	152	1 (ref)	—		1 (ref)	—
1	112	1.22	(0.85, 1.74)		**1.60**	(1.18, 2.17)
2+	51	1.07	(0.65, 1.76)		**1.81**	(1.24, 2.65)

Performed oral sex partners (6 months)						
0	165	1 (ref)	—		1 (ref)	—
1	110	1.41	(1.00, 2.00)		**1.88**	(1.39, 2.53)
2+	40	0.93	(0.52, 1.69)		**1.97**	(1.31, 2.97)
Anal sex partners (6 months)						
0	279	1 (ref)	—		1 (ref)	—
1+	34	0.88	(0.50, 1.56)		1.33	(0.89, 1.99)

A greater number of deep kissing partners was associated with increased incidence of oral HPV but not significantly associated with cervicogenital HPV incidence. The number of recent (6 month) sexual partners (oral, vaginal, anal) and number of recent vaginal sex partners were each associated with greater incidence of both oral and cervicogenital HPV, with stronger associations for cervicogenital HPV. The number of recent sexual partners that one has received oral sex from or performed oral sex on were each associated with greater incidence of cervicogenital HPV but not associated with oral HPV incidence. Having at least one recent anal sex partner was not associated with either oral or cervicogenital HPV incidence.

Discussion

In this study, we assessed the longitudinal dynamics of oral and cervicogenital HPV using frequent (every 3-4 months) testing over 3 years. We found that oral HPV was highly transient, with only 16% of detected genotypes persisting to the next study visit and an estimated mean of 46 days (about 1.5 months) to clearance. In contrast, cervicogenital HPV was more persistent, with 56% of detected genotypes persisting to the next study visit and an estimated mean of 87 days (about 3 months) to clearance. Incidence of oral and cervicogenital HPV were also associated with different behavioral patterns.

Previous studies estimating oral HPV clearance, including the HPV in Men (HIM) Study [18], the Finnish Family Study [19–21], and the Persistent Oral Human Papillomavirus Study [22], among others [23, 24], have varied substantially in their populations of interest, their sample collection and testing methodology, and their frequency of follow up [25, 26]. Estimates of time to clearance were substantially greater in the previous literature, on the order of 6 months or more, compared to the 1.5 months estimated here. Many previous studies of cervicogenital clearance, including the Hawaii Cohort Study [27] and others [28–33] have estimated mean or median clearance times of about 6-12 months, with some evidence of low-risk

types clearing more quickly. In our study, we did not have the statistical power to differentiate between low- and high-risk genotypes, but we estimated a mean clearance time of about 3 months.

Most previous studies had comparatively long periods between follow-up, potentially obscuring underlying dynamics, particularly if clearance is fast but reinfection from a reservoir (either self or partner) is common. Other work has suggested that there may be substantial variation in short-term detectability of HPV DNA that may impact results of our and previous studies [34]. If detectability varies, then more frequent sampling is more likely to record an apparent break in infection persistence. This phenomenon could contribute to the overall shorter times to oral or cervicogenital HPV clearance in this study compared to previous studies with longer times between follow-up. We are also specifically tracking genotypes individually and not whether an individual has an infection of any HPV type, which would increase estimates of persistence. Further study of the optimal sampling frequency and methodology for oral HPV measurements is needed—if oral infection dynamics are more rapid and variable, more frequent measurements may be needed to fully assess clearance and reinfection patterns. Finally, regarding the very low persistence of oral HPV in particular, it may be that the HPV DNA we are detecting in our participants' oral cavities do not reflect true basal layer infections, per se, but rather more superficial infections. Given that PCR testing is highly sensitive and detects DNA rather than viable virions, it may also be that some of these transient detections are from non-viable virus. However, the same detection methods were used for the oral and cervicogenital samples, and we do not see the same transience in the cervicogential samples, which points to the results being driven by differences in the tissues or perhaps the collection methods.

In this analysis, HPV vaccination was associated with reduced incidence of cervicogenital HPV but not oral HPV. Previous work from us and others has indicated the HPV vaccination does reduce prevalence of oral HPV [35–37]. This result may give further credence to the hypothesis that we are detecting superficial infections. Cohort and age differences between our study sample and others could also explain the null effect found of vaccination on oral HPV infections.

Greater oral HPV incidence was associated with 2 or more recent deep kissing partners, vaginal sex partners, and any sex partners but was not associated with oral sex specifically. Previous literature has shown that oral HPV infection is most likely related to oral sex behaviors [22, 38, 39], so our lack of association may be due to confounding. Greater cervicogenital HPV incidence was not associated with recent deep kissing partners but was associated with 1 or 2 or more recent vaginal or oral sex partners.

The number of recent sexual partners has long been known as an important risk factor for HPV, which is sexually transmitted.

The strengths of this study include the longitudinal design with frequent follow up over 3 years as well as the multistate modeling approach to assessing incidence and clearance, which enables us to use a semi-mechanistic framework to estimate covariate effects. This approach is similar to one used to analyze recurring infections in the HIM study [40]. We also use a highly sensitive PCRbased technique for HPV detection [15]. The limitations of this study include the comparatively small sample size. We are also using self-reported vaccination and behavioral data, which are subject to misclassification.

Our work contributes an additional perspective on the longitudinal dynamics of oral and cervicogenital HPV and finds substantial differences between the sites, which may have implications for the design and measurement frequency for future studies to track HPV infection and clearance dynamics. Furthermore, our infection and clearance estimates have direct application into the development of HPV transmission dynamics simulation models and of models of the natural history of HPV-related cancers [37, 41–44]. Last, because HPV-associated cancer risk is related to persistent HPV infections, cancer screening by HPV testing requires a clear understanding of the implications of a positive HPV test. Our work emphasizes that more work is needed to understand the natural history of oral HPV.

Author contributions

AFB: Formal analysis, methodology, software, writing – original draft, writing – review & editing. LPC: Data curation, investigation, project administration, supervision, writing – review & editing. HMW: Investigation, supervision, writing – review & editing. BMM: Investigation, project administration. CMG: Investigation. TBT: Investigation. RLD: Investigation, project administration. YKL: Investigation, project administration. ECA: Investigation, project administration. TN: Investigation. TEC: Conceptualization, funding acquisition, supervision, writing – review & editing. RM: Conceptualization, funding acquisition, supervision, writing – review & editing. MCE: Conceptualization, funding acquisition, supervision, writing – review & editing

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available because of participant privacy concerns but are available from the corresponding author on reasonable request. IRB approval or a data use agreement may be required.

Competing interests

The authors declare that they have no competing interests.

Figure Legends

Figure 1: Participants transition between human papillomavirus (HPV) negative and positive states, and we observe these states at fixed time points. The multistate transition model estimates the underlying instantaneous infection and clearance rates that best explain the observed data when they are combined to estimate probabilities of being in each state at each visit.

Figure 2: Alluvial plots of the longitudinal a) oral and b) cervicogenital HPV status of participants in the Michigan HPV and Oropharyngeal Cancer (MHOC) Study (data collected in Ann Arbor, MI, 2015–17). Note that the cervicogenital testing was rolled out later than oral testing, so that the majority of "Invalid/not tested" participants in (b) represent individuals who participated in several study visits prior to the enrolling in the cervicogenital substudy.

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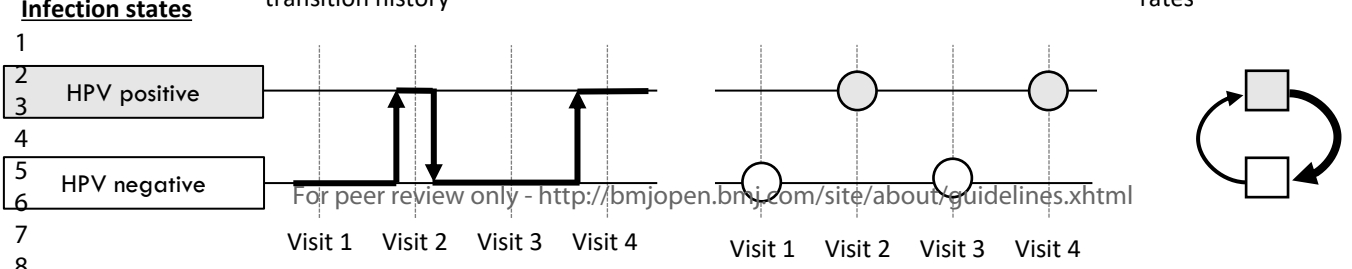

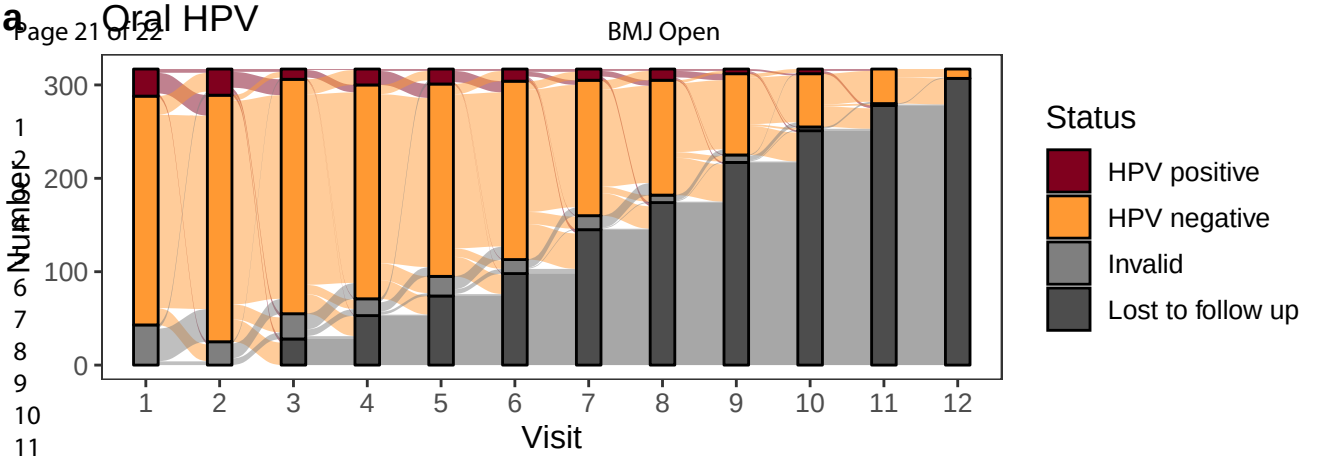

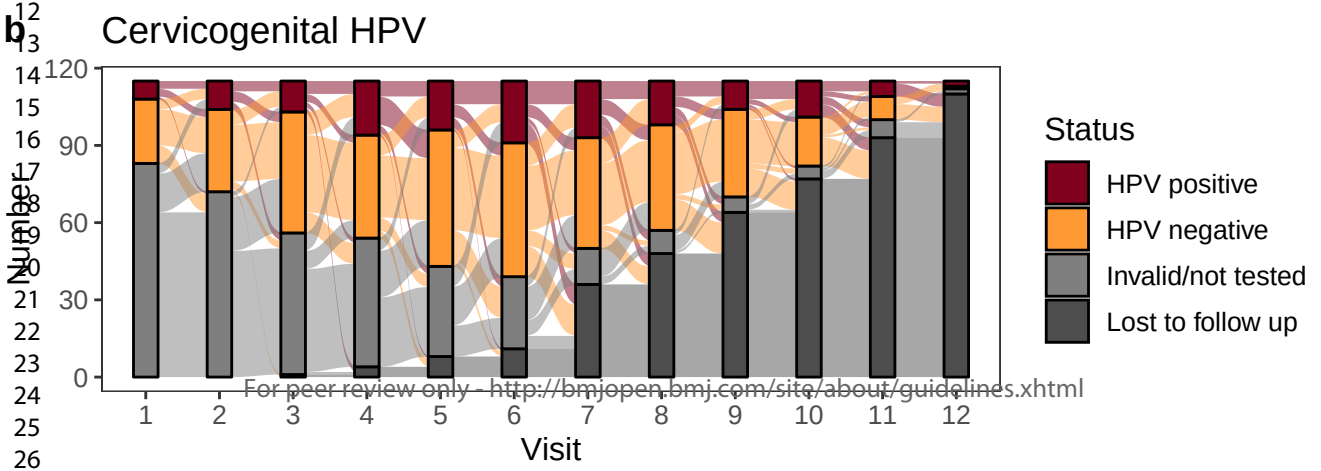

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4 (also given in [12])
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 (also given in [12])
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4 (also given in [12])
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	Given in [12]
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Given in [12]
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-8
		(b) Indicate number of participants with missing data for each variable of	Table 1

		interest	
		(c) Summarise follow-up time (eg, average and total amount)	4, 6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6, 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 1 & 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Incidence and clearance of oral and cervicogenital HPV infection: longitudinal analysis of the MHOC cohort study

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Abstract

Objectives: The Michigan HPV and Oropharyngeal Cancer (MHOC) Study aimed to evaluate patterns of oral and cervicogenital HPV infection prevalence, incidence, and clearance as well as their relationship to sexual behaviors.

Design: Cohort

Setting: General public in and around Ann Arbor, MI

Participants: 394 college-age and older-adult participants of both sexes provided oral samples, and 325 completed at least 2 visits. 130 who provided a cervicogenital samples, and 127 completed at least 2 visits.

Outcomes: Incidence and clearance rates as well as hazard ratios (HR) for oral and cervicogenital HPV.

Results: Oral HPV infections were transient, with only 16% of genotypes persisting to the next visit. The mean time to clearance of a genotype was 46 days (95% CI: 37–58). In contrast, cervicogenital infections were more persistent, with 56% of genotypes persisting to the next visit. The mean time to clearance of a genotype was 87 days (95% CI: 74–102). HPV vaccination was associated with reduced incidence of cervicogenital HPV infection (HR: 0.63; 95% CI: 0.47, 0.83) but not oral HPV infection. Incidence of oral HPV infection was associated with 2+ recent deep kissing partners (HR: 2.00; 95% CI: 1.13, 3.56). Incidence of both oral (HR: 1.70; 95% CI: 1.08, 2.68) and cervicogenital (HR: 2.46; 95% CI 1.69, 3.59) was associated with 2+ recent sexual partners.

Conclusions: Detection of oral HPV was highly transient, but incidence was associated with recent deep kissing and sexual partners. Detection of cervicogenital HPV was more persistent, and incidence was positively associated with recent sexual partners and negatively associated with HPV vaccination.

Article summary

Strengths and limitations of this study

- This study enrolled men and women and reports on both oral and cervicogenital HPV
- This study's longitudinal cohort design allowed for inference of HPV dynamics
- This study is limited by its comparatively small sample size and convenience sample design.

Introduction

The human papillomavirus (HPV) is the cause of virtually every cervical cancer and an increasing number and fraction of head and neck cancers [1–8]. Although vaccines are available that cover the most common cancer-causing genotypes, coverage is not complete among targeted age groups in the US [9], and there are oncogenic genotypes not covered by any of the available vaccines. In 2018, the US Preventive Services Task Force (USPSTF) updated its cervical cancer screening guidelines for women 21–65 to include an option of testing for high-risk HPV every five years, with or without cytology, in addition to the option of cervical cytology alone every three years [10]. While the USPSTF has concluded that the evidence for oral cancer screening in asymptomatic individuals is currently insufficient to recommend it, HPV testing could, in the future, be part of oral cancer screening either in the general population or in targeted, high-risk groups [2]. Because the most HPV infections clear without major consequences nor lead to cancer, it is essential that we understand the dynamics of cervicogenital and oral HPV infections, both to understand the implications of an oral HPV positive test and to understand the risk factors and transmission pathways associated with infection.

Cross-sectional studies, such as the National Health and Nutrition Examination Survey (NHANES) in the US, can identify risk factors associated with prevalence but are unable to assess those associated with infection dynamics—neither incidence nor clearance can be determined. Longitudinal studies of HPV, such as the HPV in Men (HIM) study [11], have provided estimates of site-specific incidence and clearance. However, most previous longitudinal studies have had a relatively long time period between follow-up, making it difficult to understand short-term infection and clearance dynamics.

The Michigan HPV and Oropharyngeal Cancer (MHOC) Study aims to evaluate patterns of oral HPV infection prevalence, incidence and clearance and their relationship to sexual history and sexual behaviors [12]. The epidemiological arm of the MHOC Study has tested a cohort of adults for oral and, in a substudy, cervicogenital HPV over 3 years, with follow-up visits every 3–4 months. Our analysis of baseline oral and cervicogenital HPV prevalence may be found elsewhere [13]. This shorter follow-up time allows us to determine incidence and clearance rates in our participants with greater precision. Using a multistate transition model, we estimate the underlying rates of incidence and clearance for oral and cervicogenital HPV and the associations (hazard ratios) of demographic and behavioral characteristics on incidence at each site.

Methods

We previously published the full MHOC study protocol [12]. We briefly describe the main aspects of the study here.

Study subjects

Study participants were recruited in Ann Arbor, Michigan and the immediate surrounding areas. Participants were recruited at University of Michigan campus dormitories, through community fliers, and through the UM Health Research website. Volunteers over the age of 18 without a history of head and neck cancer who were willing to return every 3–4 months for 3 years for follow-up visits were invited to enroll. We enrolled 394 participants between April 2015 and December 2017. Participants completed between 1 and 12 visits, with a median of 6 visits; 325 participants completed at least 2 visits. A substudy focusing on cervicogenital HPV enrolled 130 participants. Documented informed consent was obtained from all participants. The University of Michigan IRB approved consent documents and study protocol (HUM00090236). Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Michigan [14, 15].

Surveys

A baseline questionnaire was administered to each participant at their initial visit. Participant ID numbers were assigned to ensure participant confidentiality. Follow-up surveys were administered at each subsequent visit. The surveys were designed to individually assess a variety of topics including demographics, STI and preventive screening history, sexual health and behavior, alcohol and drug use, and vaccination status. Vaccination status was self-reported, and due to missingness in the number of vaccine doses variable, we classified any participant reporting at least one dose of an HPV vaccine as vaccinated. Given the time frame and geographic location of the study, most vaccinated participants would have received Gardasil (6, 11, 16, 18). Sexual behavior questions assessed current and past experiences of vaginal, oral, and anal sex. The baseline questionnaire collected a complete sexual behavior history, with the subsequent follow-up visits collecting more recent information and updates. Numbers of recent sexual partners were grouped into 0, 1, 2+ categories except for numbers of recent anal sex partners, which were grouped into 0 and 1+ because of smaller numbers.

HPV testing

All participants self-collected a saliva sample with Scope mouthwash (Proctor & Gamble; Cincinnati, OH) or an Oragene RE-100 kit (DNA Genotek; Kanata, Canada). Saliva samples were taken at each study visit. Participants who had a vagina, were not pregnant, and were not menstruating at the time of a study visit were invited to self-collect a cervicogenital sample with a HerSwab (Eve Medical; Toronto, Canada). The cervicogenital substudy was rolled out after the main study, so most substudy participants had their first cervicogenital test at a follow-up visit rather than at their baseline visit. DNA was extracted from samples and genotyped using PCR Mass Array; technical details of sample processing are given in our protocol paper [12], and technical details of the PCR Mass Array test are given in [16]. We tested for genotypes 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 90. Participants whose samples contained insufficient DNA or otherwise resulted in inconclusive test results were denoted as invalid.

Statistical analysis

We used Markov multistate transition modeling to estimate the incidence and clearance rate for oral HPV and cervicogenital HPV. Markov state transitions models are continuous-time, finite-state stochastic processes that assume that the transition hazard rate depends on one's current state but not on one's history (i.e., we assume that previous infection does not increase the likelihood of future infection) [17]. Infection and clearance occur at any time, but we only observe individuals states at certain points in time (Figure 1). For a given rate of infection and clearance, we can calculate the probability of each individual's observed trajectory. By maximizing this probability as a function of the infection and clearance rates, we estimate best-fit rates. Data were analyzed in R 4.0 (R Foundation for Statistical Computing; Vienna, Austria) using the msm package [18], 2018–20. Participants with missing data were excluded from analyses involving those missing data. Participants lost to follow up were included if they had at least two visits.

For this analysis, we assumed that incidence and clearance of each HPV genotype occurs independently of the others and that hazard ratios are the same for all genotypes. We estimated genotype-specific rates only if there were at least 25 detections and more than one observation of persistence. We estimated hazard ratios for incidence for selected covariates in univariable models. For these models, we assumed there is no impact of covariates on clearance—both due to the lack of biological justification for the impact of most behavioral and demographic covariates on clearance and also due to potential issues of practical

unidentifiability. That is, we want to avoid estimating increased incidence as reduced clearance if we are not observing at a sufficiently fine time scale. This will potentially neglect the impact of age on clearance, but we felt that the effect of age on incidence (e.g., via changes in risk, behavior, etc.) was more salient. We also separately tested the association of the detection of multiple HPV types with clearance in a model with fixed incidence.

Patient and Public Involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Among the 325 participants who had at least two study visits, 317 had two or more valid oral HPV tests across any of their visits. The characteristics of these 317 participants are given in Table 1. Oral HPV prevalence among first valid tests was 11% (34). An alluvial plot, which shows the number of participants in each state at each visit and the transition between statuses between subsequent visits, is shown in Figure 2a. Among the participants, we recorded 1,845 negative oral HPV tests and 148 positive oral HPV tests for at least one tested genotype. We observed 1,676 pairs of participant visits: 1,455 pairs of visits where the participant remained HPV negative, 94 pairs of visits where the participant transitioned from HPV negative to HPV positive, 107 pairs of visits where the participant transitioned from HPV positive to HPV negative, and 20 pairs of visits in which the participant remained positive for the same genotype. (Note: the numbers of transitions will not add up to the number of tests because each participant contributes one fewer transition than their number of tests, and so the correspondence between transitions and tests depends on the specific distribution of number of tests each participant has). Only 16% of detected genotypes persisted to the next study visit. Through the multistate transition model, we estimated the average time to clearance of a previously detected genotype was 46 days (95% CI: 37–58 days). No single genotype was detected as being persistent in an oral test more than once; accordingly, we did not estimate genotype-specific time-to-clearance for any genotypes. Time to clear one genotype was not significantly different if the participant had multiple genotypes detected (HR: 1.25, 95% CI: 0.65, 2.24). Only 8 individuals had multiple distinct detections of the same genotype, (i.e., two positive tests with at least one negative test in between).

Table 1: Baseline characteristics of participants in the MHOC Study with at least two study visits with valid HPV tests (data collected in Ann Arbor, MI, 2015-17, analyzed 2018-20). Note: percentages may not add up to 100% as participants could refuse to answer questions. *Other than HPV.

	Full cohort (N=317)		Cervicogenital substudy cohort (N= 115)	
	%	n	%	n
Age				
18	29%	91	25%	29
19-22	33%	104	32%	37
23-29	12%	38	11%	13
30-49	12%	37	16%	18
50+	15%	47	16%	18
Sex				
Female	68%	216	100%	115
Male	32%	101	0%	0
Race				
White	60%	189	64%	74
Asian	23%	73	18%	21
Black/Hispanic/multiracial/unknown	17%	55	17%	20
Marital/partner status				
Never married/partnered	77%	243	73%	84
Ever married/partnered	23%	72	27%	31
Circumcised (male only)				
Yes	68%	69	—	—
No	31%	31	—	—
Ever diagnosed with STI*				
No	93%	296	92%	106
Yes	7%	21	8%	9
HPV vaccination				
No	45%	142	45%	52
Yes	48%	152	50%	58
Alcohol use				
Never or non-current	31%	99	27%	31
Current	66%	210	71%	82
Ever cigarette use				
Never	77%	246	78%	90
Ever	21%	68	21%	24
Ever marijuana use				
Never	54%	171	53%	61

Ever	41%	130	44%	51
Sexual attraction				
Only to another gender	72%	229	73%	84
Mostly to another gender	15%	46	20%	23
Equal or mostly/only to same gender	10%	33	3%	4
Deep kissing partners (6 months)				
0	42%	132	79%	91
1	34%	109	14%	16
2+	24%	76	7%	8
Vaginal, oral, or anal sex partners (6 months)				
0	39%	124	35%	40
1	43%	137	44%	51
2+	17%	54	21%	24
Vaginal sex partners (6 months)				
0	49%	154	43%	50
1	38%	120	38%	44
2+	13%	41	18%	21
Received oral sex partners (6 months)				
0	48%	152	42%	48
1	36%	112	39%	45
2+	16%	51	19%	22
Performed oral sex partners (6 months)				
0	52%	165	44%	51
1	35%	110	43%	49
2+	13%	40	13%	15
Anal sex partners (6 months)				
0	89%	279	89%	101
1+	11%	34	11%	12

Among the 127 participants who provided cervicogenital samples for at least two study visits, 115 had two or more valid cervicogenital HPV tests; the characteristics of this subcohort mirror those of the full cohort, with the exception that the subcohort is entirely female. Cervicogenital HPV prevalence among first valid tests was 20% (23). The characteristics of these 115 participants are given in Table 1, and alluvial plots of participant statuses are shown in Figure 2b. Among these participants, we recorded 396 negative cervicogenital HPV tests and 166 positive cervicogenital HPV tests for at least one tested genotype. We observed 447 pairs of participant visits: 250 pairs of visits where the participant remained HPV negative, 74 pairs of visits where the participant transitioned from HPV negative to HPV positive, 54 pairs of visits

where the participant transitioned from HPV positive to HPV negative, and 69 pairs of visits in which the participant remained positive for the same genotype. Unlike oral infections, cervicogenital infections were persistent, with 56% of detected genotypes persisting to the next study visit. Using the multistate transition model, we estimated the average time to clearance of a previously detected genotype was 87 days (95% CI: 74–102 days). We estimated genotype-specific time-to-clearance for HPV59 (85 days, 95% CI: 54–135), HPV66 (76 days; 95% CI: 56–102), and HPV90 (70 days; 95% CI: 47–104), which were all comparable. Time to clear one genotype was not significantly different if the participant had multiple genotypes detected (HR: 0.79, 95% CI: 0.33, 1.91). Twenty-one individuals had multiple distinct detections of the same genotype.

Hazard ratios for HPV incidence are given in Table 2. In this population, participants ages 23–29 and 50+ were less likely to acquire an oral HPV infection. There were no significant differences in incidence of cervicogenital HPV by age. Sex, race, marital status, circumcision status, previous sexually transmitted infection (STI) diagnosis, current alcohol use, and ever cigarette use were not associated with incidence of either oral or cervicogenital HPV. Ever marijuana use was associated with greater incidence of cervicogenital HPV. Being vaccinated for HPV was significantly associated with lower incidence of cervicogenital HPV but not associated with incidence of oral HPV.

A greater number of deep kissing partners was associated with increased incidence of oral HPV but not significantly associated with cervicogenital HPV incidence. The number of recent (6 month) sexual partners (oral, vaginal, anal) and number of recent vaginal sex partners were each associated with greater incidence of both oral and cervicogenital HPV, with stronger associations for cervicogenital HPV. The number of recent sexual partners that one has received oral sex from or performed oral sex on were each associated with greater incidence of cervicogenital HPV but not associated with oral HPV incidence. Having at least one recent anal sex partner was not associated with either oral or cervicogenital HPV incidence.

Table 2: Hazard ratios for the incidence rate of oral and cervicogenital HPV in the MHOC Study (data collected in Ann Arbor, MI, 2015-17, analyzed 2018-20). *Other than HPV. †Cells with fewer than 5 participants are censored.

	Oral HPV incidence			Cervicogenital HPV incidence		
	n	Hazard ratio	95% CI	n	Hazard ratio	95% CI
Age						
18	91	1 (ref)	—	29	1 (ref)	—
19-22	104	0.73	(0.49, 1.1)	37	1.18	(0.82, 1.69)
23-29	38	**0.32**	(0.15, 0.68)	13	1.03	(0.63, 1.67)
30-49	37	0.77	(0.45, 1.29)	18	1.23	(0.78, 1.94)
50+	47	**0.46**	(0.27, 0.79)	18	0.92	(0.59, 1.41)
Sex						
Female	216	1 (ref)	—	115	1 (ref)	—
Male	101	0.85	(0.59, 1.23)	0	—	—
Race						
White	189	1 (ref)	—	74	1 (ref)	—
Asian	73	0.61	(0.37, 1.02)	21	0.91	(0.63, 1.32)
Black/Hispanic/multiracial/unknown	55	1.24	(0.83, 1.85)	20	1.33	(0.95, 1.87)
Marital/partner status						
Never married/partnered	243	1 (ref)	—	84	1 (ref)	—
Ever married/partnered	72	0.80	(0.54, 1.19)	31	0.82	(0.59, 1.14)
Circumcised (male only)						
Yes		1 (ref)	—	—	—	—
No		0.70	(0.33,1.47)	—	—	—
Ever diagnosed with STI*						
No	296	1 (ref)	—	106	1 (ref)	—
Yes	21	0.81	(0.41, 1.59)	9	1.20	(0.74, 1.92)
HPV vaccination						
No	142	1 (ref)	—	52	1 (ref)	—
Yes	152	1.22	(0.87, 1.71)	58	**0.63**	(0.47, 0.83)
Alcohol use						
Never or non-current	99	1 (ref)	—	31	1 (ref)	—
Current	210	1.32	(0.91, 1.94)	82	1.11	(0.82, 1.51)

Ever cigarette use						
Never	246	1 (ref)	—	90	1 (ref)	—
Ever	68	1.37	(0.71, 2.62)	24	0.92	(0.65, 1.29)
Ever marijuana use						
Never	171	1 (ref)	—	61	1 (ref)	—
Ever	130	1.05	(0.74, 1.47)	51	**1.48**	(1.12, 1.96)
Sexual attraction						
Only to another gender	229	1 (ref)		84	1 (ref)	
Mostly to another gender	46	**1.57**	(1.02, 2.43)	23	**1.53**	(1.09, 2.17)
Equal or mostly/only to same gender	33	0.92	(0.50, 1.68)	4	†	†
Deep kissing partners (6 months)						
0	132	1 (ref)	—		1 (ref)	—
1	109	1.65	(0.96, 2.83)		0.87	(0.49, 1.52)
2+	76	**2.00**	(1.13, 3.56)		0.57	(0.25, 1.28)
Vaginal, oral, or anal sex partners (6 months)						
0	124	1 (ref)	—		1 (ref)	—
1	137	1.26	(0.87, 1.84)		**1.62**	(1.17, 2.26)
2+	54	**1.70**	(1.08, 2.68)		**2.46**	(1.69, 3.59)
Vaginal sex partners (6 months)						
0	154	1 (ref)	—		1 (ref)	—
1	120	1.24	(0.86, 1.78)		**1.44**	(1.05, 1.98)
2+	41	**1.96**	(1.23, 3.11)		**3.35**	(2.34, 4.78)
Received oral sex partners (6 months)						
0	152	1 (ref)	—		1 (ref)	—
1	112	1.22	(0.85, 1.74)		**1.60**	(1.18, 2.17)
2+	51	1.07	(0.65, 1.76)		**1.81**	(1.24, 2.65)
Performed oral sex partners (6 months)						
0	165	1 (ref)	—		1 (ref)	—
1	110	1.41	(1.00, 2.00)		**1.88**	(1.39, 2.53)
2+	40	0.93	(0.52, 1.69)		**1.97**	(1.31, 2.97)
Anal sex partners (6 months)						
0	279	1 (ref)	—		1 (ref)	—
1+	34	0.88	(0.50, 1.56)		1.33	(0.89, 1.99)

Discussion

In this study, we assessed the longitudinal dynamics of oral and cervicogenital HPV using frequent (every 3-4 months) testing over 3 years. We found that oral HPV was highly transient, with only 16% of detected genotypes persisting to the next study visit and an estimated mean of 46 days (about 1.5 months) to clearance. In contrast, cervicogenital HPV was more persistent, with 56% of detected genotypes persisting to the next study visit and an estimated mean of 87 days (about 3 months) to clearance. Incidence of oral and cervicogenital HPV were also associated with different behavioral patterns.

Previous studies estimating oral HPV clearance, including the HPV in Men (HIM) Study [19], the Finnish Family Study [20–22], and the Persistent Oral Human Papillomavirus Study [23], among others [24, 25], have varied substantially in their populations of interest, their sample collection and testing methodology, and their frequency of follow up [26, 27]. Estimates of time to clearance were substantially greater in the previous literature, on the order of 6 months or more, compared to the 1.5 months estimated here. Many previous studies of cervicogenital clearance, including the Hawaii Cohort Study [28] and others [29–34] have estimated mean or median clearance times of about 6–12 months, with some evidence of low-risk types clearing more quickly. In our study, we did not have the statistical power to differentiate between low- and high-risk genotypes, but we estimated a mean clearance time of about 3 months.

Most previous studies had comparatively long periods between follow-up, potentially obscuring underlying dynamics, particularly if clearance is fast but reinfection from a reservoir (either self or partner) is common. Other work has suggested that there may be substantial variation in short-term detectability of HPV DNA that may impact results of our and previous studies [35]. If detectability varies, then more frequent sampling is more likely to record an apparent break in infection persistence. This phenomenon could contribute to the overall shorter times to oral or cervicogenital HPV clearance in this study compared to previous studies with longer times between follow up. We are also specifically tracking genotypes individually and not whether an individual has an infection of any HPV type, which would increase estimates of persistence. Further study of the optimal sampling frequency and methodology for oral HPV measurements is needed—if oral infection dynamics are more rapid and variable, more frequent measurements may be needed to fully assess clearance and reinfection patterns. Finally, regarding the very low persistence of oral HPV in particular, it may be that the HPV DNA we are detecting in our participants' oral cavities do not reflect true basal layer infections but rather more superficial infections. Given that PCR testing is highly sensitive and detects DNA rather than viable virions, it may also be that

some of these transient detections are from non-viable virus. However, the same detection methods were used for the oral and cervicogenital samples, and we do not see the same transience in the cervicogential samples, which points to the results being driven by differences in the tissues or perhaps the collection methods.

In this analysis, HPV vaccination was associated with reduced incidence of cervicogenital HPV but not oral HPV. Previous, cross-sectional work has indicated the HPV vaccination does reduce prevalence of oral HPV [36–38]. Our longitudinal results, then, may give further credence to the hypothesis that we are detecting superficial oral infections. However, because oral HPV infections were relatively rare, we may have not had the power to detect an impact of vaccination. Cohort and age differences between our study sample and others might also explain the lack of detected association. Also, if most of the observed genotypes were not covered by the participants' vaccines (and cross-protection is likely minimal), then this result might be expected. However, of the 193 distinct detections of genotypes in oral tests, more than half (109) were type 6, 11, 16, or 18 (Table S1). In comparison, about one-fifth (36) of the 166 distinct cervicogenital detections were type 6, 11, 16, or 18. These results may suggest that vaccination had a greater impact on cervicogenital infection than on oral infection in this cohort.

Greater oral HPV incidence was associated with 2 or more recent deep kissing partners, vaginal sex partners, and any sex partners but was not associated with oral sex specifically. Previous literature has shown that oral HPV infection is most likely related to oral sex behaviors [23, 39, 40], so our lack of association may be due to confounding. Indeed, the association between oral sex behavior and oral HPV infection was shown to be confounded by age-cohort and race in a previous study [40]. Greater cervicogenital HPV incidence was not associated with recent deep kissing partners but was associated with 1 or 2 or more recent vaginal or oral sex partners. The number of recent sexual partners has long been known as an important risk factor for HPV, which is sexually transmitted. Ever marijuana use, which was associated with increased incidence of cervicogenital HPV infection, may not be a direct risk factor but instead be associated with true underlying risk factors that are difficult to measure directly. Although there is some laboratory evidence of immune modulation by cannabinoids [41], epidemiological evidence for an association between marijuana use and cervicogential HPV has been mixed [42-45], suggesting that it is indeed likely confounded with other behaviors. Incidence of both oral and cervicogenital HPV was greater in participants who indicated sexual attraction mostly but not only to another gender; this type of "heteroflexible" orientation has been previously associated with higher-risk sexual behavior and STIs [46].

There was no indication of increased incidence for participants expressing sexual attraction to multiple genders equally or mostly or only to the same gender.

The strengths of this study include the longitudinal design with frequent follow up over 3 years as well as the multistate modeling approach to assessing incidence and clearance, which enables us to use a semi-mechanistic framework to estimate covariate effects. This approach is similar to one used to analyze recurring infections in the HIM study [47]. We also use a highly sensitive PCR-based technique for HPV detection [16]. The limitations of this study include the comparatively small sample size. We are also using self-reported vaccination and behavioral data, which are subject to misclassification.

Our work contributes an additional perspective on the longitudinal dynamics of oral and cervicogenital HPV and finds substantial differences between the sites, which may have implications for the design and measurement frequency for future studies to track HPV infection and clearance dynamics. Furthermore, our infection and clearance estimates have direct application into the development of HPV transmission dynamics simulation models and of models of the natural history of HPV-related cancers [38, 48–51]. Lastly, because HPV-associated cancer risk is related to persistent HPV infections, cancer screening by HPV testing requires a clear understanding of the implications of a positive HPV test. Our work emphasizes that more work is needed to understand the natural history of oral HPV.

Author contributions

AFB: Formal analysis, methodology, software, writing – original draft, writing – review & editing. LPC: Data curation, investigation, project administration, supervision, writing – review & editing. HMW: Investigation, supervision, writing – review & editing. BMM: Investigation, project administration. CMG: Investigation. TBT: Investigation. RLD: Investigation, project administration. YKL: Investigation, project administration. ECA: Investigation, project administration. TN: Investigation. TEC: Conceptualization, funding acquisition, supervision, writing – review & editing. RM: Conceptualization, funding acquisition, supervision, writing – review & editing. MCE: Conceptualization, funding acquisition, supervision, writing – review & editing

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available because of participant privacy concerns but are available from the corresponding author on reasonable request. IRB approval or a data use agreement may be required.

Competing interests

The authors declare that they have no competing interests.

Figure Legends

Figure 1: Participants transition between human papillomavirus (HPV) negative and positive states, and we observe these states at fixed time points. The multistate transition model estimates the underlying instantaneous infection and clearance rates that best explain the observed data when they are combined to estimate probabilities of being in each state at each visit.

Figure 2: Alluvial plots of the longitudinal a) oral and b) cervicogenital HPV status of participants in the Michigan HPV and Oropharyngeal Cancer (MHOC) Study (data collected in Ann Arbor, MI, 2015–17). Note that the cervicogenital testing was rolled out later than oral testing, so that the majority of "Invalid/not tested" participants in (b) represent individuals who participated in several study visits prior to the enrolling in the cervicogenital substudy.

Ethical Approval Statement

This study was approved by the University of Michigan IRB (HUM00090236).

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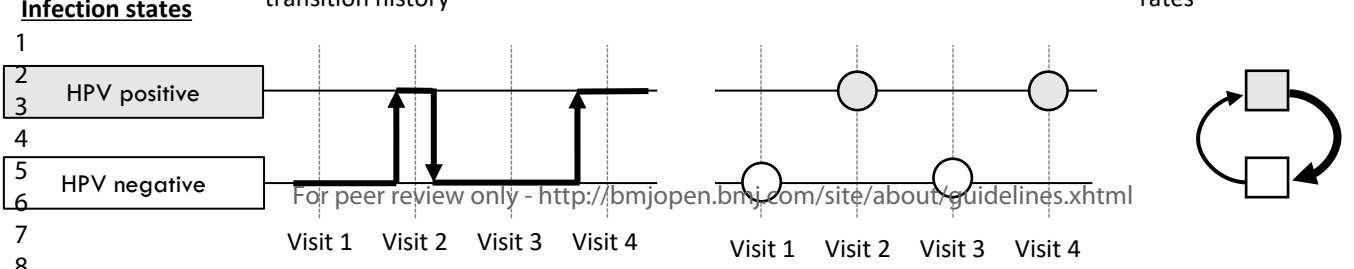

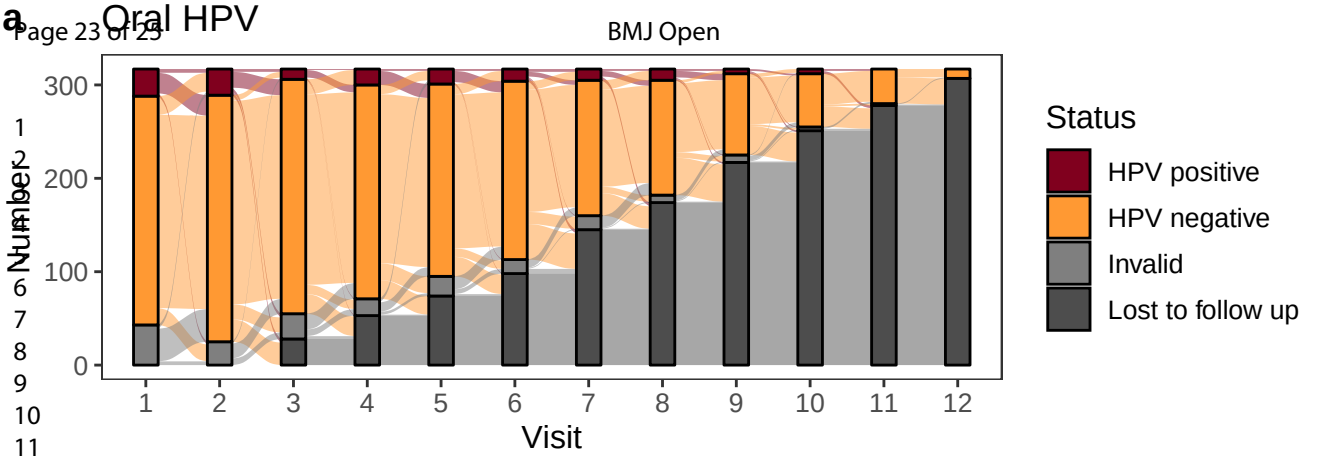

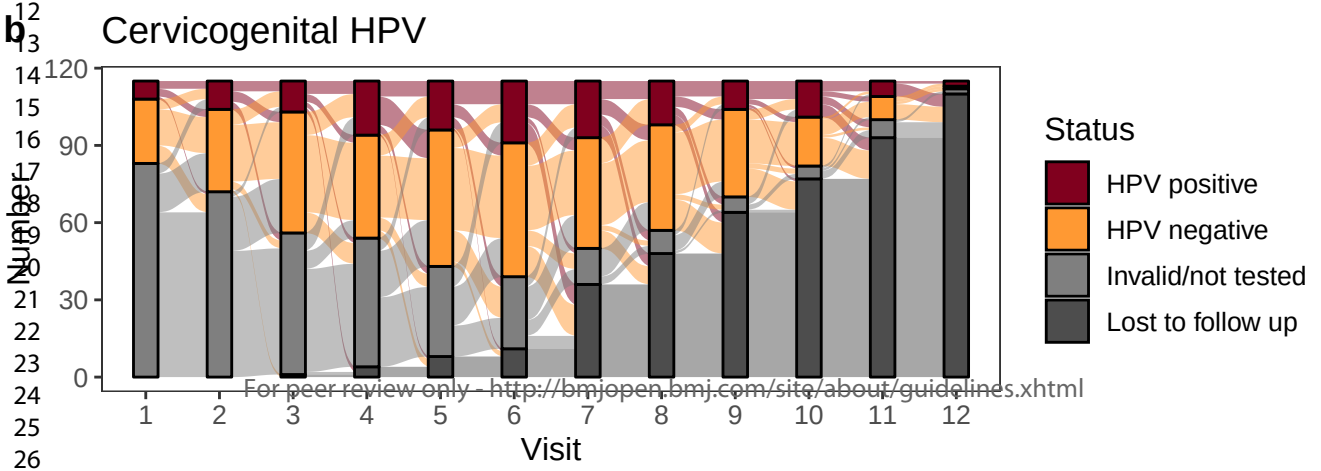

Table S1: Number of ever HPV positive participants and total number of positive tests overall and for each HPV genotype tested, for both the oral and cervicogenital tests.

HPV Type	Oral		Cervicogenital	
	Number ever positive	Number of total positive tests	Number ever positive	Number of total positive tests
Any	110	148	81	166
6	25	27	13	14
11	2	2	0	0
16	38	40	7	13
18	37	40	9	9
31	4	4	1	1
33	2	2	0	0
35	1	1	2	3
39	6	6	12	24
45	2	2	3	4
51	3	3	7	13
52	4	4	11	17
56	10	16	13	20
58	7	7	3	4
59	3	5	30	40
66	10	16	59	86
68	0	0	0	0
73	5	5	10	13
90	11	13	39	54

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4 (also given in [12])
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 (also given in [12])
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4 (also given in [12])
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	Given in [12]
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Given in [12]
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-8
		(b) Indicate number of participants with missing data for each variable of	Table 1

		interest	
		(c) Summarise follow-up time (eg, average and total amount)	4, 6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6, 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 1 & 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.