The Influence of Multiple Human Papillomavirus Types on the Risk of Genotype-Concordant Incident Infections of the Anus and Cervix: The Hawaii HPV Cohort Study

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The influence of multiple human papillomavirus (HPV) types on detection of concordant incident HPV infections of the cervix or anus following infection at the other anatomic site was examined in a cohort of 897 women. Multiple HPV infections at the anus were not significantly associated with subsequent acquisition of a concordant cervical infection, whereas prior coinfections in the cervix increased risk of a new cervical HPV infection. Incident anal HPV infections following concordant cervical HPV infections increased significantly among women with preexisting cervical or anal coinfections. Potential synergy in acquisition of cervical and anal HPV infections has implications for prophylactic vaccine effectiveness.

We recently reported that the acquisition of an anal human papillomavirus (HPV) infection is a relatively common event among women [1, 2]. Seventy percent of women participating in our cervical HPV natural history cohort tested positive for anal HPV infection at 1 or more clinic visits from baseline through a follow-up period that averaged 1.3 years [2]. We observed a high degree of genotypic concordance in the sequential acquisition of cervical and anal HPV infections [3]: Women with the same genotype observed previously in the adjacent anatomic site (ie, cervix or anus) were significantly more likely to have an incident anal or cervical HPV infection than were women with a discordant HPV type or no previous HPV infection. The risk of acquisition of a concordant anal HPV infection following a cervical infection with the same HPV type was especially high, suggesting that the cervix (vagina) may serve as a reservoir for anal HPV infection.

The potential biological interaction between various HPV types in the acquisition or clearance of HPV infection is germane to prophylactic vaccine effectiveness. Cervical and anal coinfection with multiple HPV types was relatively common among Hawaii cohort participants [3], and the risk of acquiring anal high-risk HPV types was enhanced among women with coexisting cervical infection of any HPV type. In the present analysis, we explored the dynamics of sequential cervical and anal HPV infections in the presence of other HPV types. In particular, we were interested in determining whether consecutive detection of a concordant HPV type in the secondary anatomic site (anus or cervix) occurred more frequently than would be expected if additional HPV types were present in the primary anatomic site (cervix or anus) or at the secondary site on the visit preceding initial infection.

MATERIALS AND METHODS

Between 1998 and 2008, sexually active women, 18–85 years of age, were recruited from 5 clinics on Oahu, Hawaii, to participate in a longitudinal cohort study of cervical and anal HPV infection [4, 5]. Informed consent was obtained from all study participants using a protocol and forms were approved by the University of Hawaii Institutional Review Board. At each visit, trained clinicians obtained exfoliated cervical and anal cell samples for cytology and HPV DNA detection. Upon completion of the examination, a study questionnaire was interviewer-administered covering demographics, reproductive history, sexual activity, history of sexually transmitted infections, hormone use, medical history, and tobacco and alcohol use. Women who were enrolled in the study were asked to return to the clinic every 4 months for examination and testing.

A total of 897 women who were recruited and completed at least 2 visits were tested for the presence or absence of HPV DNA by polymerase chain reaction using a modified version of the PGMY09/PGMY11 primer system [6]. β-globin–positive

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and HPV DNA–positive specimens were genotyped using a reverse line blot detection method for 36 different HPV types [7]. We defined the risk (oncogenic potential) associated with various HPV types using the definition of Castle [8].

Cox regression was used to estimate the risk of anal or cervical HPV acquisition when it was preceded by a same-type infection at the other anatomic site at the prior visit, and to compare the risk in the presence of single (referent) or multiple (exposure group) HPV genotypes [3]. Days since infection acquisition at the primary site were used as the time metric, and an Anderson-Gill model was created based on visit pairs. Analyses were adjusted for participant age and for existing HPV infection at the secondary site at the prior visit. We only considered incident infections at the secondary site, that is, infections initially detected at the second or subsequent clinic visit. Prevalent infections detected at the first clinic visit, as well as incident infections, were both considered in determining HPV status at the primary site. We assigned a separate infection path to every HPV genotype, since a woman could become infected with various HPV types following the primary infection. Because each subject was allowed to experience more than 1 event throughout the course of the study, we used a robust sandwich variance estimate [9], aggregated over subjects, to prevent artificially deflated standard errors and confidence interval estimates. Infections acquired concurrently in the cervix and the anus were not included in the analyses.

For a number of participant visits we only had a valid cervical sample, but not an anal sample, because anal sample collection was optional and the proportion of β-globin–negative samples was higher among anal samples (9.2%) than among cervical samples (.6%). All such visits were excluded from the analyses.

We also analyzed the association of HPV infection at the prior visit with acquisition of a new HPV type at the same anatomic site. A similar Cox regression was used for this analysis with time since study entry as the time metric, including adjustment for participants' age at study entry and HPV infection status at the other anatomic site at the prior visit. If a study participant tested positive for the same HPV genotype after clearance, only the first acquisition of that genotype was considered.

Because nearly 10% of study participants did not provide the number of their lifetime sexual partners, this factor was not included as an adjustment variable. Other adjustment factors were considered, but their inclusion in the models did not result in at least a 10% change in the parameter estimates [10], nor in a significantly better fit according to the likelihood ratio test. The proportional hazards assumption for Cox models was verified by Schoenfeld residuals [11]. Hazard ratios (RRs) and 95% confidence intervals (CIs) were used as measures of association. All analyses were conducted using SAS software version 9.2 (SAS Institute, Inc). All P values were 2-sided, and $P < 0.05$ was defined as significant.

RESULTS

During the follow-up period, cohort participants experienced 909 incident cervical and anal infections, defined as HPV genotypes not identified on a previous visit. The analyses included 2955 visits in which paired cervical-anal specimens were collected (mean, 3.3 visits/woman) (data not shown). The mean age of the multiethnic cohort was 32 years. The majority of women were Caucasian, followed by mixed race, Asian, and Native Hawaiian.

The risk of acquiring an anal HPV infection increased significantly (P for trend $<.001$) among women with a cervical HPV infection with a concordant genotype and cervical coinfection with 1 or more additional HPV types compared to women without a preceding cervical HPV infection (Table 1). For example, the risk of an incident anal HPV infection among women following a concordant single-type cervical HPV infection was 17.3 (95% CI: 10.2–29.4). The risk of a consecutive cervical infection followed by an anal infection was increased significantly among women with 2 or more HPV types compared to a single type in the cervix. Similar differences were observed for the association of cervical high-risk (HR) and low-risk (LR) HPV infections, as well as phylogenetic species, with the subsequent risk of a concordant anal HPV infection. However, the only significant difference in the influence of multiple compared to single HPV types in the cervix on the risk of subsequent anal infections was observed for the α9/α11 species with an RR of 3.13 (95% CI: 1.13–8.62).

The risk of an incident cervical HPV infection increased significantly (P for trend <0.001) among women with an anal HPV infection with a concordant genotype and anal coinfection with 1 or more additional HPV types compared to women without a preceding anal HPV infection (Table 1). The difference in the influence of multiple-type and single-type HPV infections at the anus on the acquisition of HPV at the cervix was similarly not significant for LR types or HR types or for comparisons by phylogenetic species and specific HPV types.

We also examined the influence of multiple infections in the cervix or anus at the prior visit on the subsequent acquisition of an additional HPV genotype at the same site. The risk of acquiring a new anal HPV infection increased 29% (95% CI: 0%–65%) among women with an anal coinfection with any other HPV type at the previous visit (Table 2). The risk of acquiring a new cervical HPV infection was also increased significantly among women with other preexisting cervical HPV infections compared to women who were uninfected by HPV at the previous visit (RR: 1.66; 95% CI: 1.35–2.04).

DISCUSSION

In our earlier analysis of Hawaii HPV Cohort Study data we found that it was common for anal and cervical HPV infections

Table 1. The Risk of Subsequent Acquisition of Cervical and Anal HPV Infection After a Single or Multiple HPV Type at the Other Anatomic Site

HPV Infection[a] at the Secondary Site	No. of Prior HPV Infections[b] at the Primary Site	Cervical (Primary) HPV Followed by Anal (Secondary) HPV				Anal (Primary) HPV Followed by Cervical (Secondary) HPV			
		Events[c]	Follow-up[d]	Hazard Ratio[e] (95% CI)	Hazard Ratio[f] (95% CI)	Events[c]	Follow-up[d]	Hazard Ratio[e] (95% CI)	Hazard Ratio[f] (95% CI)
Any HPV type	None	184	835.9	1		354	1678.2	1	
	1 genotype	22	108.0	17.33 (10.22–29.39)	1	9	37.1	9.39 (4.76–18.52)	1
	2 genotypes	48	229.3	45.52 (32.65–63.46)	2.56 (1.44–4.56)	8	30.9	7.39 (3.60–15.14)	0.80 (0.30–2.09)
	⩾3 genotypes	107	468.1	44.72 (33.68–59.38)	2.31 (1.32–4.04)	28	110.0	14.20 (9.75–20.67)	1.36 (0.62–2.96)
	P for trend			<.0001	.005			<.0001	.18
HR-HPV	None	67	300.9	1		140	644.8	1	
	1 genotype	13	69.2	17.95 (9.34–34.52)	1	4	16.2	10.62 (3.84–29.36)	1
	2 genotypes	14	66.4	26.18 (14.06–48.75)	1.74 (0.77–3.91)	2	7.5	3.97 (0.97–16.24)	0.33 (0.06–1.88)
	⩾3 genotypes	53	234.6	41.77 (26.52–65.81)	2.46 (1.25–4.84)	8	26.9	12.77 (6.08–26.80)	1.79 (0.52–6.14)
	P for trend			<.0001	.002			<.0001	.38
LR-HPV[g]	None	117	535.0	1		214	1033.4	1	
	1 genotype	9	38.9	16.24 (6.57–40.16)	1	5	20.9	8.50 (3.41–21.15)	1
	2 genotypes	34	163.0	64.14 (43.08–95.47)	3.19 (1.40–7.29)	6	23.4	10.07 (4.33–23.44)	1.32 (0.33–5.23)
	⩾3 genotypes	54	233.6	47.46 (32.94–68.37)	2.17 (0.90–5.27)	20	83.2	14.87 (9.64–22.93)	1.03 (0.37–2.87)
	P for trend			<.0001	.56			<.0001	.38
HR-HPV other than HPV-16, 18	None	47	211.8	1		114	521.2	1	
	1 genotype	10	44.7	22.00 (10.29–47.00)	1	3	12.4	11.52 (3.61–36.78)	1
	2 genotypes	11	54.2	31.58 (15.74–63.35)	1.59 (0.66–3.85)	2	7.5	5.33 (1.28–22.18)	0.54 (0.10–2.89)
	⩾3 genotypes	36	165.5	37.39 (21.35–65.49)	1.80 (0.83–3.90)	5	17.1	9.41 (3.70–23.95)	1.27 (0.32–5.07)
	P for trend			<.0001	.09			<.0001	.78
HPV-16, 18	None	20	89.1	1		26	123.6	1	
	1 genotype	3	24.5	13.25 (3.43–51.22)	1	1	3.8	6.60 (0.74–58.66)	1
	⩾2 genotypes	20	81.2	26.91 (13.76–52.63)	6.44 (0.96–43.03)	3	9.8	13.94 (3.87–50.23)	1.46 (0.10–21.03)
α9/α11	None	36	167.4	1		70	323.7	1	
	1 genotype	8	46.0	18.19 (7.59–43.57)	1	0	.0	N/A	1
	⩾2 genotypes	40	192.7	51.03 (29.81–87.34)	3.13 (1.13–8.62)	7	23.3	20.47 (9.27–45.20)	N/A
α3/α15	None	57	254.3	1		94	467.0	1	
	1 genotype	2	8.7	3.82 (0.49–30.01)	1	4	16.9	12.94 (4.64–36.08)	1
	⩾2 genotypes	37	171.5	45.36 (28.35–72.58)	6.17 (0.92–41.20)	12	44.6	19.62 (10.89–35.35)	1.24 (0.40–3.88)
α5/α6	None	28	138.1	1		68	349.0	1	
	1 genotype	4	18.6	34.48 (11.09–107.24)	1	0	.0	N/A	1
	⩾2 genotypes	32	142.5	47.35 (27.02–82.99)	1.09 (0.39–3.03)	5	20.5	6.73 (2.65–17.08)	N/A
α7	None	36	161.3	1		64	290.1	1	
	1 genotype	4	17.3	27.63 (8.36–91.34)	1	4	16.2	27.46 (9.88–76.31)	1
	⩾2 genotypes	24	96.1	39.52 (21.15–73.86)	1.66 (0.54–5.12)	1	3.3	2.07 (0.28–15.34)	0.16 (0.03–0.95)

Table 1. (*Continued*)

HPV Infection[a] at the Secondary Site	No. of Prior HPV Infections[b] at the Primary Site	Cervical (Primary) HPV Followed by Anal (Secondary) HPV				Anal (Primary) HPV Followed by Cervical (Secondary) HPV			
		Events[c]	Follow-up[d]	Hazard Ratio[e] (95% CI)	Hazard Ratio[f] (95% CI)	Events[c]	Follow-up[d]	Hazard Ratio[e] (95% CI)	Hazard Ratio[f] (95% CI)
α1/α8/α10/α13	None	27	114.8	1		58	248.4	1	
	1 genotype	4	17.4	25.30 (5.81–110.19)	1	1	4.0	4.79 (0.65–35.58)	1
	⩾2 genotypes	22	94.6	40.96 (21.18–79.24)	3.38 (0.42–27.11)	11	49.1	12.52 (6.38–24.60)	2.78 (0.26–29.96)

NOTE. High-risk (oncogenic) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; possibly oncogenic types 26, 34, 53, 66, 69, 70, 73, and 82; nononcogenic types 6, 11, 40, 42, 44, 54, 61, 72, 81, and 89; undetermined-risk types 62, 67, 71, 83, and 84. α-Papillomavirus species: species 1 comprises types 42 and 89; species 3 comprises types 61, 62, 81, 83, and 84; species 5 comprises types 51 and 82; species 6 comprises types 53, 56, and 66; species 7 comprises types 18, 39, 45, 59, 68, and 70; species 9 comprises types 16, 31, 33, 35, 52, 58, and 67; species 10 comprises types 6, 11, and 44; species 11 comprises types 34 and 73; and species 13 comprises type 54.

CI, confidence interval; HPV, human papillomavirus; HR-HPV, high-risk HPV; LR-HPV, low-risk HPV; N/A, not available.

[a] Incident (detected at a visit other than the first) HPV infection at the secondary site.

[b] At least 1 of the genotypes at the primary site is concordant with the HPV infection at the secondary site.

[c] The number of incident HPV infections at the secondary site after same-type HPV infections at the primary site during the study period.

[d] Cumulative follow-up (months) across all participants/visits for the indicated exposure group.

[e] Reference: no HPV infection at the primary site. Adjusted for age of participants at study entry and prior HPV coinfection at the secondary site.

[f] Reference: single-type HPV infection at the primary site. Participants with no prior HPV infection at the primary site are excluded. Adjusted for age of participants at study entry and prior HPV coinfection at the secondary site.

[g] Includes possibly oncogenic, nononcogenic, and undetermined-risk HPV types.

to occur consecutively with concordant genotypes [3]. The present findings argue that the genotypic concordance in the sequential incidence of cervical and anal HPV infections may also be influenced by HPV coinfection at the primary anatomic site or by an HPV infection at the secondary (target) site detected at the preceding visit. This was especially true for incident anal infections in which the presence of multiple HPV types in the cervix significantly enhanced the risk of subsequent infection to the anus by more than 2.5-fold. Clustering of HR-HPV types in the cervix placed a woman at particularly high risk of acquiring 1 or more of those types in the anus at a subsequent visit.

The competition between viral types to colonize the cervical epithelium has been studied extensively [5, 12–15]. Investigators who have examined the dynamics of cervical HPV infection in the presence of other types reported that the concurrent acquisition of multiple HPV types exceeded that expected by chance [5, 12, 13], and that type-specific HPV acquisition was dependent on a cervical infection with another type [5, 12]. Although these associations may be biological, including interaction between HPV types or the effect of host susceptibility to viral infection (ie, prior infection with multiple HPV types may be a marker of poor immune response), behavioral factors must also be considered. For example, common risk factors and modes of transmission, including number of sexual partners and frequency of anal sex [1, 4, 5], would increase the risk of both anal and cervical HPV infection, as well as the acquisition of multiple HPV types.

Potential limitations of the study included (1) our inability to determine whether HPVs of the same genotype present in the cervix and anus were part of a transmission event; (2) the potential that some incident infections may have represented reactivations from latency or previously missed infections due to sampling error or viral levels below the limit of detection; (3) the possibility that exfoliated cells from the perianal region may have contaminated our anal specimens; and (4) the exclusion of 24% of potential visits from the analysis because women refused anal sampling or because the levels of β-globin were insufficient for HPV genotyping.

The question of whether different HPV types are acquired independent of one another has implications for the natural history of HPV-related disease and HPV prophylactic vaccine effectiveness. Antagonism between viral types in the infection of target tissues would enhance replacement of vaccine types by competitive species, whereas synergy would reduce HPV types that are afforded a survival benefit through coinfection. Our results suggest that the reduction of covered viral types in the cervix and anus among women receiving the prophylactic vaccine may have an impact on the incidence of cervical and anal HPV infections of other HPV types.

Table 2. The Risk of Acquisition of Cervical and Anal HPV Infection After a Coinfection With Other HPV Types at the Same Anatomic Site

		Anal HPV			Cervical HPV		
Incident HPV Infection[a]	Prior HPV Coinfection[b]	Events[c]	Follow-up[d]	Hazard Ratio[e] (95% CI)	Events[c]	Follow-up[d]	Hazard Ratio[e] (95% CI)
Any HPV	None	208	944.2		231	1071.2	
	Any HPV	91	421.5	1.29 (1.00–1.65)	168	785.0	1.66 (1.35–2.04)
Any HPV	None	247	1125.0		268	1225.6	
	HR-HPV	52	240.8	1.33 (0.98–1.81)	131	630.5	1.82 (1.47–2.24)
Any HPV	None	230	1054.4		252	1170.0	
	LR-HPV[f]	69	311.4	1.23 (0.93–1.63)	147	686.2	2.39 (1.93–2.96)
HR-HPV	None	81	369.7		96	433.8	
	Any HPV	40	187.4	1.28 (0.87–1.90)	58	261.5	1.48 (1.05–2.08)
HR-HPV	None	103	477.3		108	479.7	
	HR-HPV	18	79.8	1.00 (0.60–1.67)	46	215.7	1.75 (1.23–2.48)
HR-HPV	None	88	399.9		102	464.9	
	LR-HPV[f]	33	157.2	1.27 (0.83–1.95)	52	230.5	2.20 (1.55–3.12)
LR-HPV[f]	None	127	574.5		135	637.3	
	Any HPV	51	234.1	1.31 (0.95–1.80)	110	523.5	1.78 (1.38–2.31)
LR-HPV[f]	None	144	647.6		160	746.0	
	HR-HPV	34	161.0	1.60 (1.09–2.34)	85	414.8	1.85 (1.42–2.42)
LR-HPV[f]	None	142	654.5		150	705.1	
	LR-HPV[f]	36	154.1	1.24 (0.86–1.80)	95	455.7	2.51 (1.91–3.29)

NOTE. High-risk (oncogenic) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; possibly oncogenic types 26, 34, 53, 66, 69, 70, 73, and 82; non-oncogenic types 6, 11, 40, 42, 44, 54, 61, 72, 81, and 89; undetermined-risk types 62, 67, 71, 83, and 84.

CI, confidence interval; HPV, human papillomavirus; HR-HPV, high-risk HPV; LR-HPV, low-risk HPV.

[a] Incident (detected at a visit other than the first) HPV infection at the indicated anatomic site.

[b] Infection with the other HPV genotypes at the clinic visit preceding the index HPV type acquisition.

[c] The number of incident HPV infections at the indicated anatomic site during the study period.

[d] Cumulative follow-up (months) across all participants/visits for the indicated exposure group.

[e] Reference: no prior HPV coinfection at the indicated anatomic site. Adjusted for age of participants at study entry and prior concordant HPV infection at the other anatomic site.

[f] Includes possibly oncogenic, non-oncogenic, and undetermined-risk HPV types.

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