MAJOR ARTICLE

Sequential Acquisition of Human Papillomavirus (HPV) Infection of the Anus and Cervix: The Hawaii HPV Cohort Study

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Background. Relatively little is known about the epidemiology of anal human papillomavirus (HPV) infection in healthy women and its association with cervical HPV infection.

Methods. The association of an incident cervical (or anal) HPV infection with the subsequent risk of a genotype-concordant incident anal (or cervical) HPV infection was examined in a longitudinal cohort study of 751 sexually active women. Age-adjusted hazard ratios, obtained using Cox regression, served as measurements of relative risk (RR).

Results. Among women, the RR of acquiring an anal HPV infection after a cervical infection with HPV of the same genotype was 20.5 (95% confidence interval, 16.3–25.7), and the RR of acquiring a cervical HPV infection after an anal infection with HPV of the same genotype was 8.8 (95% confidence interval, 6.4–12.2), compared with women without a previous anal/cervical infection with HPV of a concordant genotype. RRs varied by phylogenetic species, with HPV $\alpha 3/\alpha 15$ and $\alpha 1/\alpha 8/\alpha 10$ types having a greater likelihood than other types of HPV infecting the anus among women with a previous infection at the cervix with HPV of the same genotype.

Conclusions. It appears common for anal and cervical HPV infections to occur consecutively. The high degree of genotype-specific concordance suggests that the cervix (vagina) and anus may serve as reservoirs for HPV infection at the other anatomical site.

Anal cancer is an uncommon malignancy with an incidence of ~1 case per 100,000 individuals, but rates have been increasing among women and men in the United States for >3 decades. Although the cause of this increase is uncertain, it is notable that the incidence of anal cancer among women in the United States is higher than that among men [1]. Human papillomavirus (HPV), predominantly oncogenic types 16 (HPV-16) and 18 (HPV-18), has been detected in ~80% of squamous cell anal cancers, which account for the majority of anal cancers in the United States and Europe [2].

The histology of the anus shares important parallels with that of the cervix, including a transition zone from the squamous epithelium of the anus to the columnar epithelium of the rectum, where most malignancies are identified [3]. The natural histories of HPV-associated malignancies of the anus and cervix begin with viral infection and progress to a dysplastic precursor lesion, "intraepithelial neoplasia," followed by cancer [4]. Women with cervical dysplasia and cervical cancer have an increased risk for anal cancer [5–8], presumably because of a shared exposure to oncogenic HPV types. The prevalence of anal HPV infection is reported to be higher than the prevalence of cervical HPV infection among human immunodeficiency virus (HIV)–infected women [4]. Indeed, the positive association between the lifetime number of sexual partners and the incidence of high-risk (HR) anal HPV infection supports the notion that sexual intercourse is the primary route of anal infection [9]. However, we [9] and other in-

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vestigators [4, 10, 11] have found that a history of anal intercourse is not a significant risk factor for incident anal HR-HPV infection or anal cancer, suggesting alternative routes of transmission. Aside from potential underreporting of anal sex, other sexual and nonsexual routes of transmission are possible, including nonpenetrative sex or inoculation through fomites, fingers, or vaginal discharge [12, 13].

In a previous analysis of the Hawaii HPV Cohort Study, we observed a high degree of genotype-specific concordance among concurrent anal and cervical HPV infections, indicating a common source of infection [14]. The objective of the present analysis was to extend this observation through a longitudinal evaluation of anal and cervical HPV infection concordance. Specifically, we wished to determine whether cervical HPV infection was a risk factor for anal HPV infection with the same viral genotype and, conversely, whether anal HPV infection predicted future genotype-specific cervical HPV infection.

MATERIALS AND METHODS

Subject recruitment and data collection. Between 1998 and 2008, sexually active women who were 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 [14, 15]. Women scheduled for gynecologic appointments who were not pregnant or postpartum within the past 6 months, who had received no treatment for cervical disease or abnormal cytologic findings within the past 18 months, and who had no plans to relocate in the next year were approached to participate in the cohort. Written informed consent was obtained from all study participants by use of a protocol and forms approved by the institutional review board of the University of Hawaii.

At each visit, trained clinicians obtained exfoliated cervical cell samples for cytologic analysis and HPV DNA detection. A Dacron swab and cytology brush were used consecutively to sample the entire ectocervix and endocervix, including the entire transformation zone. The swab and brush were then each placed in separate vials of 1.0 mL of buffered medium (Digene). The 2 cervical samples were later combined in the laboratory for HPV DNA testing. Collection of anal specimens was optional for study subjects. After cervical specimen collection, an exfoliated anal cell specimen was obtained using a Dacron swab moistened with sterile water. The swab was inserted ~1.5–2.0 cm into the anus and rotated 360 degrees clockwise (5 times) and counterclockwise (5 times). The swab was placed in 1.0 mL of medium. After completion of the examination, a study questionnaire covering demographic characteristics, reproductive history, sexual activity, history of sexually transmitted infections, hormone use, medical history, and tobacco and alcohol use was administered by an interviewer.

Selection and follow-up of cohort. The results of cervical smear screening and HPV DNA testing performed at baseline were necessary to establish the final eligibility of the women for participation in the study. Women whose specimens were inadequate (ie, were negative for the human β-globin gene) at baseline were excluded, and women who were enrolled in the study were asked to return to the clinic every 4 months for examination and testing. Women who were treated for an abnormal cervical finding were excluded from the study. A more detailed interview was conducted during the second and subsequent follow-up visits. A total of 751 women were recruited, were tested for anal and cervical HPV DNA by polymerase chain reaction (PCR) analysis of β-globin–positive specimens, and completed $\geqslant$2 visits.

Detection and genotyping of HPV. HPV DNA was extracted from exfoliated cervical cell and anal cell specimens by use of commercial reagents (Qiagen). Specimens were analyzed for the presence or absence of HPV DNA by PCR performed using a modified version of the PGMY09/PGMY11 primer system [16]. HPV DNA–positive specimens were genotyped using a reverse line-blot detection method for 36 different HPV types [17], including HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; possible HR types 26, 34, 53, 66, 70, 73, and 82; low-risk (LR) types 6, 11, 40, 42, 44, 54, 61, 72, 81, and 89; and undetermined-risk types 62, 67, 71, 83, and 84 [18, 19]. We defined the risk (oncogenic potential) associated with various HPV types by using the definition of Castle [19]. HPV-positive specimens that subsequently had negative results in the genotyping assay were considered to be unclassified HPV-positive specimens. All specimens were also tested for the human β-globin gene as an internal control for sample adequacy.

Statistical analysis. We analyzed the sequential concordance of cervical and anal HPV infections, when an infection at 1 site (cervix or anus) was followed at a subsequent visit by an HPV infection of the same type at the other anatomical site (anus or cervix). Anal and cervical HPV infections were classified by oncogenic risk (all infections; infections due to HR genotypes; and infections due to possible HR genotypes, LR genotypes, or genotypes of undetermined risk) and by phylogenetic species (for α1/α8/α10: HPV 6, 11, 32, 40, 42, 44, and 74; for α3/α15: types 61, 62, 71, 72, 81, 83, and 84; for α5/α6: types 26, 51, 53, 56, 66, 69, and 82; for α7: types 18, 39, 45, 59, 68, and 70; and for α9/α11: types 16, 31, 33–35, 52, 58, 67, and 73). Because we were interested in sequential acquisition, we considered only incident, not prevalent, infections at the subsequent (ie, second, or target) anatomical 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 the determination of HPV status at the initial (presumptive source) site. Infections acquired concurrently in the cervix and the anus were not included in the analyses. Our approach was conser-

vative, because including such infections would likely result in stronger associations.

For a number of participant clinic visits, we had only a valid cervical sample, not an anal sample, because anal sample collection was optional and because the proportion of β-globin–negative samples was higher among anal samples (27%) than among cervical samples (0.6%). All such visits were excluded from the analyses. Because inadequate anal samples were not significantly associated with the cervical HPV status or important baseline characteristics of the participants, this exclusion is unlikely to have biased the analysis results.

The risk of HPV acquisition at the second site (cervix or anus) after infection with HPV of the same genotype at the first site (anus or cervix) was modeled through Cox regression using the number of days since acquisition of infection at the first site as the time metric, after adjustment for age at study entry. Infections with unclassified HPV types were excluded from the analysis. If a study participant tested positive for the same HPV genotype after clearance, only the first acquisition of that genotype was considered. A woman could experience a subsequent incident infection with the same HPV type during follow-up and could be infected with >1 HPV type at one time. We assigned a separate infection path to every HPV genotype detected. For every HPV group or genotype, the risk of a subsequent infection at the second site among "exposed" participants with an infection due to HPV of the same type at the first site was compared with that among "unexposed" participants with no previous infection with HPV of the same type at the first site, as well as with the risk among the participants exposed to other HPV groups or genotypes. Because each subject was allowed to experience >1 event throughout the course of the study, we used a robust sandwich variance estimate [20], aggregated over subjects, to prevent artificially deflated standard errors and confidence interval estimates.

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 either a change of $\geqslant$10% in the parameter estimates [21] or a significantly better fit according to the likelihood ratio test. The proportional hazards assumption for Cox models was verified by plotting scaled Schoenfeld residuals against the time to HPV acquisition at the second site [22]. Relative risks (RRs) and 95% confidence intervals (CIs) were used as measurements of association. All analyses were conducted using SAS software (version 9.2; SAS Institute). All P values were 2-sided, and $P < .05$ was considered to denote statistical significance.

RESULTS

Characteristics of the cohort. During follow-up, the 751 cohort participants experienced 382 incident cervical infections and 383 incident anal infections, which were defined as HPV genotypes not identified during a previous visit. Baseline and follow-up analyses included 3990 visits (mean, 5.3 visits/woman) at which cervical specimens were collected and 2348 visits (mean, 3.1 visits/woman) at which anal specimens were collected (Table 1). The mean age of the multiethnic cohort was 34 years. At baseline, only 14% of the women were current tobacco smokers, and 55% were current alcohol drinkers. Anal sex was practiced by 8% of the women at enrollment.

Sequential acquisition of an anal HPV infection after a cervical HPV infection with a concordant genotype. The risk of an incident anal HPV infection was increased significantly (RR, 20.5; 95% CI, 16.3–25.7) among women with a preceding concordant cervical HPV infection, compared with women without a preceding cervical HPV infection with a concordant genotype (Table 2). In general, the risk of acquiring an HR-

Table 1. Characteristics of the 751 Study Participants with $\geqslant$2 Clinic Visits

Characteristic	Value
Visits, no.	
Total	2348
Mean (range)	3.1 (2–12)
Duration of follow-up, mean (range), days	372 (68–1667)
Age, years	
At first sexual intercourse, mean	17.5
At first visit, mean (range)	34 (18–73)
Lifetime sexual partners, median (IQR), no.	6 (3–12)
Race/ethnicity	
White	42.2
Japanese	9.3
Chinese	3.7
Hawaiian or part Hawaiian	14.1
Filipino	5.3
Other or mixed	25.3
Smoking status	
Current smoker	14.0
Current nonsmoker	86.0
Drinking status	
Current drinker	55.5
Current nondrinker	44.5
Anal sex practice history at baseline	
Never practiced	70.6
Practiced in the past	21.4
Currently practicing	8.0
Condom use at baseline	
Current user	33.9
Current nonuser	66.1
Oral contraceptive use at baseline	
Ever used	79.8
Never used	20.2

NOTE. Data are the percentage of subjects, unless otherwise indicated. IQR, interquartile range.

Table 2. Risk of Sequential Acquisition of Cervical and Anal Human Papillomavirus (HPV) Infection

Comparison, HPV infection[a] at index site (prior HPV infection[b] at reference site)	Cervical (reference) HPV infection followed by anal (index) HPV infection			Anal (reference) HPV infection followed by cervical (index) HPV infection			Risk of anal HPV infection followed by cervical HPV,[f] RR[e] (95% CI)
	Subjects,[c] no. (n = 751)	Events,[d] no.	RR[e] (95% CI)	Subjects,[c] no. (n = 751)	Events,[d] no.	RR[e] (95% CI)	
Between discordant and concordant HPV infections							
Any HPV type (none)	124	284	1.00	156	342	1.00	
Any HPV type (any HPV type)	75	99	20.5 (16.3–25.7)	29	40	8.83 (6.36–12.2)	0.55 (0.38–0.81)
HR-HPV (none)	83	114	1.00	95	145	1.00	
HR-HPV (HR-HPV)	34	40	14.2 (9.86–20.5)	12	13	7.08 (3.94–12.7)	0.53 (0.28–1.00)
LR-HPV[g] (none)	103	170	1.00	122	197	1.00	
LR-HPV[g] (LR-HPV)[g]	52	59	27.3 (20.4–36.7)	22	27	10.1 (6.79–14.9)	0.53 (0.33–0.85)
α1/α8/α10 (none)	29	31	1.00	33	36	1.00	
α1/α8/α10 (α1/α8/α10)	15	15	39.7 (21.0–75.1)	4	5	8.62 (3.83–19.4)	0.31 (0.13–0.78)
α3/α15 (none)	64	78	1.00	76	93	1.00	
α3/α15 (α3/α15)	23	24	25.6 (16.2–40.4)	12	13	9.09 (5.05–16.4)	0.43 (0.22–0.86)
α5/α6 (none)	50	55	1.00	48	62	1.00	
α5/α6 (α5/α6)	21	21	17.3 (10.5–28.6)	5	5	4.89 (1.97–12.2)	0.34 (0.14–0.85)
α7 (none)	44	53	1.00	50	58	1.00	
α7 (α7)	14	15	22.7 (12.7–40.6)	5	5	6.84 (2.67–17.5)	0.38 (0.14–1.09)
α9/α11 (none)	44	56	1.00	62	77	1.00	
α9/α11 (α9/α11)	22	23	17.2 (10.5–28.0)	5	7	12.9 (5.88–28.2)	0.99 (0.38–2.56)
HPV-16 (none)	15	15	1.00	16	16	1.00	
HPV-16 (HPV-16)	9	9	9.03 (3.89–21.0)	2	2	5.02 (1.08–23.2)	0.58 (0.08–4.47)
HPV-18 (none)	14	14	1.00	9	9	1.00	
HPV-18 (HPV-18)	4	4	34.8 (9.69–124)	1	1	9.25 (0.81–106.0)	4.51 (0.25–80.6)
HPV-52 (none)	10	10	1.00	21	21	…	…

HPV-52 (HPV-52)	7	7	9.17 (3.67–23.0)	0	0	…	…
HPV-53 (none)	19	19	1.00	18	18	1.00	
HPV-53 (HPV-53)	10	10	16.8 (8.29–34.0)	1	1	2.60 (0.39–17.5)	0.13 (0.04–0.43)
HPV-84 (none)	23	23	1.00	19	19	1.00	
HPV-84 (HPV-84)	7	7	10.6 (4.62–24.1)	2	2	4.17 (0.94–18.5)	0.53 (0.09–3.16)
Between concordant HPV infections from different genotype groups							
LR-HPV[g] (LR-HPV)[g]	41	59	1.00	17	27	1.00	
HR-HPV (HR-HPV)	34	40	0.58 (0.39–0.86)	12	13	0.88 (0.46–1.69)	…
α9/α11 (α9/α11)	21	23	1.00	5	7	1.00	
α1/α8/α10 (α1/α8/α10)	15	15	2.91 (1.57–5.41)	4	5	0.51 (0.19–1.42)	…
α3/α15 (α3/α15)	23	24	2.37 (1.34–4.19)	12	13	0.93 (0.39–2.27)	…
α5/α6 (α5/α6)	21	21	1.61 (0.91–2.85)	5	5	0.52 (0.16–1.76)	…
α7 (α7)	14	15	1.77 (0.93–3.34)	5	5	0.56 (0.18–1.74)	…
HPV-16 (HPV-16)	9	9	1.00	2	2	1.00	
HPV-18 (HPV-18)	4	4	2.30 (0.71–7.40)	1	1	7.19 (0.17–312.0)	…
HPV-52 (HPV-52)	7	7	0.89 (0.36–2.21)	0	0	…	
HPV-53 (HPV-53)	10	10	2.94 (1.16–7.47)	1	1	0.17 (0.04–0.75)	…
HPV-84 (HPV-84)	7	7	1.75 (0.66–4.67)	2	2	1.26 (0.20–7.98)	…

NOTE. The α-papillomavirus species are as follows: species α1 comprises types 42 and 89; species α3 comprises types 61, 62, 81, 83, and 84; species α5 comprises types 51 and 82; species α6 comprises types 53, 56, and 66; species α7 comprises types 18, 39, 45, 59, 68, and 70; species α9 comprises types 16, 31, 33, 35, 52, 58, and 67; species α10 comprises types 6, 11, and 44; and species α11 comprises types 34 and 73. CI, confidence interval; HR-HPV, high-risk HPV; LR-HPV, low-risk HPV; RR, hazard ratio (relative risk).

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

[b] Infection with HPV of the same genotype as that which caused the index infection. For example, for index HR-HPV and reference HR-HPV infection, only subjects who had HPV-16 in the cervix and HPV-16 in the anus, HPV-18 in the cervix and HPV-18 in the anus, etc, are included.

[c] The no. of subjects who completed the questionnaire and ⩾2 clinic visits.

[d] The no. of incident HPV infections at the index site after previous HPV infections with HPV of the same type that caused infection at the reference site during the study period.

[e] Adjusted for the age of the participants at study entry.

[f] Compared with the risk of cervical HPV infection followed by anal HPV infection.

[g] Includes HPV types of undetermined risk.

HPV anal infection was lower (RR, 0.58; 95% CI, 0.39–0.86) than that of acquiring an LR-HPV anal infection, among women infected with a concordant cervical HPV genotype, compared with women who were not previously infected with a concordant cervical HPV genotype. Risk varied by phylogenetic species, with HPV types $\alpha 3/\alpha 15$ and $\alpha 1/\alpha 8/\alpha 10$ having a greater likelihood than other HPV types of infecting the anus among women with a preceding cervical infection with the same type. When single types were considered, the risk of acquiring an anal HPV-18 infection was 34.8 (95% CI, 9.7–124.0) in women with a previous cervical HPV-18 infection, compared with women without a previous cervical HPV-18 infection.

Sequential acquisition of a cervical HPV infection after an anal HPV infection with a concordant genotype. The risk of a cervical HPV infection after an anal HPV infection with a concordant genotype was 8.8 (95% CI, 6.4–12.2), which is somewhat lower than the risk of an anal HPV infection after a cervical HPV infection with a concordant genotype. Unlike the results for cervical HPV infection followed by anal HPV infection, the risk of acquiring an LR-HPV infection or an HR-HPV infection in the cervix was similar after an anal HPV infection with a concordant genotype. Although the number of events was small, compared with that associated with other HPV types, the HPV $\alpha 9/\alpha 11$ types had a slightly higher probability of infecting the cervix after a concordant anal HPV infection.

Factors at baseline associated with an incident anal/cervical HPV infection after a concordant cervical/anal HPV infection. The risk of an incident anal/cervical HPV infection after a concordant incident cervical/anal HPV infection decreased significantly with age (Table 3). The risk of an incident cervical HPV infection after a concordant incident anal HPV infection increased significantly with a history of anal sex. None of the other baseline factors were significantly associated with the sequential acquisition of an incident cervical or anal HPV after a concordant HPV infection at the other anatomical site.

DISCUSSION

A high degree of genotypic concordance was observed in the sequential incidence of cervical and anal HPV infections. Women were significantly more likely to have an incident anal or cervical HPV infection with the same genotype previously observed in the adjacent anatomical site (ie, cervix or anus) than infection with a discordant HPV type or no previous HPV infection. Although this result might be expected, considering the sexual nature of genital HPV transmission, the degree of HPV concordance in the sequential acquisition of HPV was high, especially for the risk of an anal HPV infection after a cervical infection with the same HPV type.

In previous analyses of the Hawaii HPV Cohort Study [9], we found that acquisition of anal HPV infections was a relatively common event: 70% of women in the cohort had ≥ 1 anal HPV infection during follow-up (average duration of follow-up, 1.3 years). We also observed that 87% of anal HPV infections were cleared within 1 year; this finding may explain why the incidence of anal cancer is much lower than that of cervical cancer, in spite of the finding that the rate of HR-HPV infection is similar at both anatomical sites. The present analysis extends these findings, suggesting that women with a cervical HPV infection are at greater risk of an anal HPV infection. These results are consistent with the observation that women with cervical intraepithelial neoplasia or cervical cancer are at increased risk of anal intraepithelial neoplasia or cancer [5–8].

Several studies suggest that HPV types associated with a low or undetermined oncogenic risk demonstrate tropism for the squamous epithelium of the vagina, compared with the squamocolumnar epithelium of the cervix [23–26]. Although we were unable to examine this possibility in our data, both the HPV $\alpha 3/\alpha 15$ and HPV $\alpha 1/\alpha 8/\alpha 10$ phylogenetic species appear to preferentially infect or persist in vaginal epithelium rather than in cervical epithelium [24–26]. It is plausible that vaginal/vulvar infections may later migrate to both the anus and cervix via intercourse or sexual foreplay, shedding of vaginal cells, or autoinoculation through fingers and other means. This migration is particularly important when considering HPV-16 and HPV-18, which are implicated in anal cancer [2]. Our data suggest that the risk of acquiring an anal HPV-18 infection given a previous cervical HPV-18 infection was quite high. Alternatively, vaginal squamous epithelium and anal epithelium may be more similar than cervical and anal epithelium, thereby explaining the tropism of low-risk HPV types for these tissues.

The risk of incident cervical HPV infection after a concordant anal HPV infection increased significantly with a history of anal sex. However, in the present analysis, we found that 48% of cases of incident cervical HPV infection occurring after anal HPV infection and 63% of cases of incident anal HPV infection occurring after cervical HPV infections developed in the absence of a self-reported history of anal sex. Although it is possible that cohort participants were embarrassed by our questions regarding anal sex and provided false-negative responses, in our population the 29% prevalence of ever having practiced anal sex was similar to the 23% prevalence of anal intercourse reported in another study of sexually active university students [27] and the 22% prevalence of anal intercourse reported among sexually active women in a population-based study in northern California [28]. Furthermore, a population-based Danish case-control study found that the majority of men and women with anal cancer did not engage in anal sex [29]. Piketty et al [11] reported that anal HPV infection was acquired in the absence of anal intercourse in HIV-infected men. Other modes of transmission should be considered.

In considering the generalizability of the results of the present

Table 3. Risk Factors at Baseline for Sequential Acquisition of Cervical and Anal Human Papillomavirus (HPV) Infection

Risk factor	Cervical (reference) HPV infection followed by anal (index) HPV infection				Anal (reference) HPV infection followed by cervical (index) HPV infection			
	Subjects,[a] no. (N = 250)	Events,[b] no.	RR[c] (95% CI)	P, for trend[d]	Subjects,[a] no. (N = 200)	Events,[b] no.	RR[c] (95% CI)	P, for trend[d]
Age, years								
<25	106	48	1.00		70	24	1.00	
25–34	72	32	0.90 (0.58–1.40)		55	7	0.29 (0.13–0.68)	
35–44	38	11	0.60 (0.31–1.14)		30	7	0.36 (0.16–0.81)	
⩾45	34	8	0.42 (0.21–0.88)	.007	45	2	0.07 (0.02–0.33)	<.001
Race/ethnicity								
White	110	46	1.00		98	13	1.00	
Japanese	25	10	1.38 (0.73–2.61)		10	2	1.72 (0.41–7.20)	
Hawaiian	23	9	0.82 (0.35–1.90)		26	6	1.22 (0.26–5.72)	
Filipino	13	5	0.69 (0.24–2.03)		11	5	1.44 (0.28–7.49)	
Other	79	29	0.47 (0.24–0.92)		55	14	1.07 (0.25–4.57)	
Income, US$/year								
<7500	50	17	1.00		44	14	1.00	
7500–19,999	69	37	1.69 (0.96–2.98)		43	5	0.42 (0.15–1.18)	
20,000–49,999	67	22	1.38 (0.76–2.52)		60	6	0.53 (0.17–1.70)	
⩾50,000	57	21	1.26 (0.67–2.36)	.75	49	14	1.04 (0.49–2.20)	.82
Age at menarche, years								
<12	54	22	1.00		56	12	1.00	
12	71	28	1.03 (0.60–1.77)		46	12	1.41 (0.64–3.11)	
13	63	23	0.79 (0.44–1.41)		52	6	0.49 (0.18–1.30)	
⩾14	62	26	0.99 (0.57–1.73)	.75	45	9	0.88 (0.37–2.10)	.35
OC use at baseline								
Never	47	26	1.00		33	6	1.00	
Ever	203	73	0.86 (0.56–1.32)		167	34	1.35 (0.59–3.06)	
Past user	115	45	0.91 (0.57–1.46)		106	23	2.03 (0.86–4.80)	
Current user	88	28	0.78 (0.47–1.30)	.33	61	11	0.85 (0.33–2.20)	.31
Hormone cream use at baseline								
Never	239	93	1.00		183	40	…	
Ever	11	6	1.75 (0.75–4.08)		17	0	…	
Past user	7	4	1.54 (0.57–4.16)		12	0	…	
Current user	4	2	2.41 (0.48–12.2)	.18	5	0	…	
Tobacco smoking history								
Never	157	67	1.00		127	25	1.00	
Ever	93	32	0.77 (0.50–1.18)		73	15	1.02 (0.56–1.86)	
Past	44	13	0.73 (0.41–1.30)		39	9	1.18 (0.55–2.52)	
Current	49	19	0.80 (0.48–1.34)	.32	34	6	0.86 (0.36–2.01)	.84
Condom use at baseline								
No	155	57	1.00		126	20	1.00	
Yes	95	42	1.05 (0.70–1.59)		74	20	1.33 (0.70–2.50)	
Spermicide use at baseline								
No	226	89	1.00		173	35	1.00	
Yes	24	10	0.78 (0.40–1.51)		27	5	0.74 (0.31–1.77)	
Sanitary pad use at baseline								
No	108	34	1.00		76	20	1.00	
Yes	142	65	1.43 (0.95–2.14)		124	20	0.59 (0.33–1.08)	
History of anal sex								
Never	170	62	1.00		131	19	1.00	
Ever	80	37	1.06 (0.71–1.58)		69	21	1.84 (1.01–3.36)	
Past	60	25	0.97 (0.61–1.53)		48	14	1.68 (0.86–3.26)	
Current	19	12	1.40 (0.76–2.56)	.45	20	7	2.42 (1.02–5.71)	.03

NOTE. CI, confidence interval; OC, oral contraceptive; RR, hazard ratio (relative risk).

[a] The no. of subjects who completed the questionnaire and ⩾2 clinic visits and who had an HPV infection at the reference site.

[b] The no. of incident HPV infections at the index site after a previous infection with the same HPV type at the reference site during the study period.

[c] Adjusted for the age of the participants at study entry.

[d] For never/ever/past/current variables, the test for trend compares individuals who were never users, past users, and current users.

study, the collection of anal specimens was optional, so only 66% of women agreed to participate in both cervical and anal specimen collection. Although there is no reason to think that this may have biased our findings, it is possible that women who participated in anal specimen collection considered themselves to be at greater risk for sexually transmitted infection. A further weakness of our methodology was the inability to determine whether the presence of HPV of the same genotype in the cervix and anus was part of a transmission event. Analysis of sequence variants would permit distinction between the same or different infection with the same genotype and may be included in future investigations. Similarly, some incident infections may have represented reactivations from the latent state or infections previously missed because of a sampling error or viral levels below the limit of detection. Exfoliation of cells from the perianal region may have contaminated our anal specimens, although we had no means of examining this possibility. Swab specimens obtained from the back of the participant as well as from the examination table were routinely collected as clinical and environmental control specimens, to monitor possible HPV contamination during the collection process. HPV DNA was not detected in any clinical or environmental control specimens. Some potential visits (25%) were excluded from the analysis because women refused anal sampling or because the levels of β-globin were insufficient for HPV genotyping. Women excluded from the analysis did not significantly differ from women included in the analysis, in terms of the demographic characteristics or sexual behaviors, such as anal receptive intercourse, that may have influenced the results. Finally, we note that few incident HR-HPV events were observed, particularly for cervical HPV infection occurring after anal HR-HPV infection. It is possible that anal HPV infections are cleared too quickly for transmission to the cervix to occur.

The results of this study suggest that it is common for anal and cervical HPV infections to occur consecutively. The high degree of genotype-specific concordance indicates a common source of infection, such as vaginal and anal intercourse with the same infected partner(s), although alternate routes of transmission, including nonpenetrative sexual contact and autoinoculation, need to be explored. The clinical consequences of our observations include higher rates of genital warts and anal and cervical cancers among HPV-infected women, through the spread of infection within the anogenital area, although cytologic information was not included in this analysis. These results provide at least a partial basis for the finding that women with cervical intraepithelial neoplasia or cancer are at higher risk of anal cancer. Although anal cytologic screening is cost-effective in HIV-infected men who have sex with men [30], studies of the efficacy of this approach in other HR groups have not been conducted.

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References

1. Joseph DA, Miller JW, Wu X, et al. Understanding the burden of human papillomavirus-associated anal cancers in the US. Cancer **2008**; 113: 2892–900.
2. Hoots BE, Palefsky JM, Pimenta JM, Smith JS. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. Int J Cancer **2009**; 124:2375–83.
3. Palefsky JM. Human papillomavirus infection and anogenital neoplasia in human immunodeficiency virus-positive men and women. J Natl Cancer Inst Monogr **1998**; 23:15–20.
4. Palefsky JM, Holly EA, Ralston ML, Da Costa M, Greenblatt RM. Prevalence and risk factors for anal human papillomavirus infection in human immunodeficiency virus (HIV)-positive and high-risk HIV-negative women. J Infect Dis **2001**; 183:383–91.
5. Scholefield JH, Sonnex C, Talbot IC, et al. Anal and cervical intraepithelial neoplasia: possible parallel. Lancet **1989**; 2:765–9.
6. Rabkin CS, Biggar RJ, Melbye M, Curtis RE. Second primary cancers following anal and cervical carcinoma: evidence of shared etiologic factors. Am J Epidemiol **1992**; 136:54–8.
7. Frisch M, Olsen JH, Melbye M. Malignancies that occur before and after anal cancer: clues to their etiology. Am J Epidemiol **1994**; 140:12–9.
8. Edgren G, Sparén P. Risk of anogenital cancer after diagnosis of cervical intraepithelial neoplasia: a prospective population-based study. Lancet Oncol **2007**; 8:311–6.
9. Goodman MT, Shvetsov YB, McDuffie K, et al. Acquisition of anal human papillomavirus (HPV) infection in women: the Hawaii HPV Cohort Study. J Infect Dis **2008**; 197:957–66.
10. Williams AB, Darragh TM, Vranizan K, Ochia C, Moss AR, Palefsky JM. Anal and cervical human papillomavirus infection and risk of anal and cervical epithelial abnormalities in human immunodeficiency virus-infected women. Obstet Gynecol **1994**; 83:205–11.
11. Piketty C, Darragh TM, Da Costa M, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. Ann Intern Med **2003**; 138:453–9.
12. Palefsky J. Biology of HPV in HIV infection. Adv Dent Res **2006**; 19: 99–105.
13. Moscicki AB, Hills NK, Shiboski S, et al. Risk factors for abnormal anal cytology in young heterosexual women. Cancer Epidemiol Biomarkers Prev **1999**; 8:173–8.
14. Hernandez BY, McDuffie K, Zhu X, et al. Anal human papillomavirus infection in women and its relationship with cervical infection. Cancer Epidemiol Biomarkers Prev **2005**; 14:2550–6.
15. Goodman MT, Shvetsov YB, McDuffie K, et al. Prevalence, acquisition, and clearance of cervical human papillomavirus infection among women with normal cytology: Hawaii Human Papillomavirus Cohort Study. Cancer Res **2008**; 68:8813–24.

16. Gravitt PE, Peyton CL, Alessi TQ, et al. Improved amplification of genital human papillomaviruses. J Clin Microbiol **2000**; 38:357–61.
17. Gravitt PE, Peyton CL, Apple RJ, Wheeler CM. Genotyping of 27 human papillomavirus types by using L1 consensus PCR products by a single-hybridization, reverse line blot detection method. J Clin Microbiol **1998**; 36:3020–7.
18. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology **2004**; 324:17–27.
19. Castle PE. The evolving definition of carcinogenic human papillomavirus. Infect Agent Cancer **2009**; 4:7
20. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. J Am Stat Assoc **1989**; 84:1074–8.
21. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol **1989**; 129:125–37.
22. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika **1994**; 81:515–26.
23. Castle PE, Schiffman M, Bratti MC, et al. A population-based study of vaginal human papillomavirus infection in hysterectomized women. J Infect Dis **2004**; 190:458–67.
24. Castle PE, Rodriguez AC, Porras C, et al. A comparison of cervical and vaginal human papillomavirus. Sex Transm Dis **2007**; 34:849–55.
25. Castle PE, Jeronimo J, Schiffman M, et al. Age-related changes of the cervix influence human papillomavirus type distribution. Cancer Res **2006**; 66:1218–24.
26. Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Koutsky LA. Comparison of incident cervical and vulvar/vaginal human papillomavirus infections in newly sexually active young women. J Infect Dis **2009**; 199:815–8.
27. Baldwin JI, Baldwin JD. Heterosexual anal intercourse: an understudied, high-risk sexual behavior. Arch Sex Behav **2000**; 29:357–73.
28. Misegades L, Page-Shafer K, Halperin D, McFarland W, YWS Study Investigators Group. Young Women's Survey. Anal intercourse among young low-income women in California: an overlooked risk factor for HIV? AIDS **2001**; 15:534–5.
29. Frisch M, Glimelius B, van den Brule AJ, et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med **1997**; 337:1350–8.
30. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. JAMA **1999**; 281:1822–9.