MAJOR ARTICLE

Duration and Clearance of Anal Human Papillomavirus (HPV) Infection among Women: The Hawaii HPV Cohort Study

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(See the editorial commentary by Chiao on pages 547–9)

Background. The association of anal cancer with human papillomavirus (HPV) infection is well established; however, little is known about the epidemiology of anal HPV in healthy women. We investigated patterns of duration and clearance of anal HPV infection in a cohort of healthy women in Hawaii.

Methods. Viral and nonviral determinants of anal HPV clearance were examined in a longitudinal cohort study of 431 sexually active women. At baseline and at 4-month intervals, interviews were conducted and cervical and anal cell specimens were obtained for detection of HPV DNA.

Results. Of the 431 women, 50% experienced a total of 414 incident anal HPV infections, reported at $\geqslant$1 clinic visits from baseline through a follow-up period of average duration of 1.2 years. Of these infections, 58% cleared during follow-up. The clearance rate for a high-risk anal infection was 9.2 per 100 woman-months (95% confidence interval [CI], 6.9–11.9 per 100 woman-months), with a median duration of 150 days (95% CI, 132–243 days). The slowest clearing high-risk HPV types were HPV-59 (median clearance time, 350 days) and HPV-58 (median clearance time, 252 days). The median clearance times for HPV-16 and HPV-18, the predominant types associated with anal cancer, were 132 days and 212 days, respectively. Nonviral factors that delayed clearance of anal HPV included douching, long-term tobacco smoking, and anal sex.

Conclusions. The majority of anal HPV infections resolve in a relatively short time. Although anal HPV is commonly acquired in healthy women, its rapid clearance suggests limited efficacy of HPV testing as an anal cancer screening tool.

Anal cancer is an uncommon malignancy and similar to cervical cancer, a causal role for high-risk human papillomavirus (HPV) infection has been postulated. A key feature of the disease is higher incidence among women compared with among men. In the United States, there will be an estimated 5070 new cases of anal cancer in 2008, with 3050 cases occurring among women and 2020 cases among men [1]. The reason for this sex difference is uncertain, although women with a history of cervical dysplasia and cervical cancer [2, 3], a history of anal receptive intercourse [4, 5], and multiple sexual partners [4, 6] are at greater risk for this disease.

HPV infection of the anal canal has now been established as a risk factor for anal precursor lesions [2, 7, 8] and anal cancer [9]. Although estimates vary, at least 70% of squamous cell carcinomas of the anus are HPV related, most of these with oncogenic types HPV-16 and HPV-18. Only a few investigators have examined prevalence and incidence of anal HPV infection, and the studies have been limited to HIV-infected and immunocompromised populations [8, 10, 11]. Little is known regarding the natural history of anal HPV infection among non–HIV infected women, particularly the correlates of HPV clearance among women who are generally healthy and not at high risk of sexually transmitted infections. Such knowledge is important because anal cancer incidence has increased worldwide

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during the past several decades [12–14]. Invasive anal squamous cell carcinoma rates increased by 1.7% per year among females in the United States from 1973 through 2005 (figure 1). During the same period, a marked annual increase (2.9% per year) in the rate of in situ tumors was observed among females.

Although not generally recognized, the recent US Food and Drug Administration licensure of a prophylactic vaccine against oncogenic HPV types 16 and 18 may have a profound effect on the incidence of anal cancer, potentially reducing the incidence of anal malignancy among women by ⩾2000 cases. An urgent need exists to improve our understanding of anal HPV epidemiology, to facilitate screening and prevention methods to combat this malignancy. In a longitudinal cohort study of women in Hawaii, we examined the natural history of anal HPV infection to identify risk factors and patterns of occurrence [17]. The objective of the present report was to determine viral and nonviral factors associated with the duration and clearance patterns of anal HPV infection.

MATERIALS AND METHODS

Patient recruitment and follow-up. From 1998 through 2003, a cohort of sexually active women was established [17–20] for a longitudinal study of cervical and anal HPV infection. Cohort participants were recruited among women who attended 5 clinics in Oahu, Hawaii, who were able to read, understand, and sign an informed consent form and a medical release form approved by the University of Hawaii Institutional Review Board. Potentially eligible patients included those with appointments for new or annual gynecological examinations or for family-planning services who were not pregnant or postpartum within the past 6 months and had no plans to relocate within 1 year.

Collection of anal specimens after the gynecological examination was optional. At the first and subsequent visits, anal cell specimens were obtained among willing women with use of a Dacron swab moistened with sterile water. The swab was inserted 1.5–2.0 cm into the anus and was placed in 1.0 mL buffered medium (Digene). Women who entered the cohort were asked to return every 4 months for repeat examination and testing.

After completion of each clinical examination, the study coordinator administered a study questionnaire to the participant. The baseline interview included demographic and sexual activity data, history of tobacco and alcohol use. A second, more detailed questionnaire, conducted during the second visit after a four-month interval, included gynecological, menstrual, reproductive and sexual histories, hormone use, medical history, history of sexually transmitted infections, and income. Information covered in the baseline questionnaire (sexual activity, tobacco and alcohol use) was also updated. The questionnaire used at subsequent interviews was modified slightly for use during the follow-up period; questions included changes in sexual and reproductive information during the intervening period between clinic visits.

Laboratory analysis. HPV DNA was extracted from exfoliated cervical and anal cell specimens with use of commercial reagents (Qiagen). Specimens were analyzed for presence of HPV DNA by PCR using a modified version of the PGMY09/PGMY11 primer system [21], which showed good sensitivity and accuracy of detection of HPV DNA in recent validation studies [22, 23]. HPV DNA–positive specimens were genotyped using a reverse line blot detection method (Roche Molecular Systems) [24] for 36 different HPV types, including high-risk (HR) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, and 82; low-risk (LR) types 6, 11, 42, 54, 61, 72, 81, and 89; and undetermined-risk types 44, 62, 67, 71, 83,

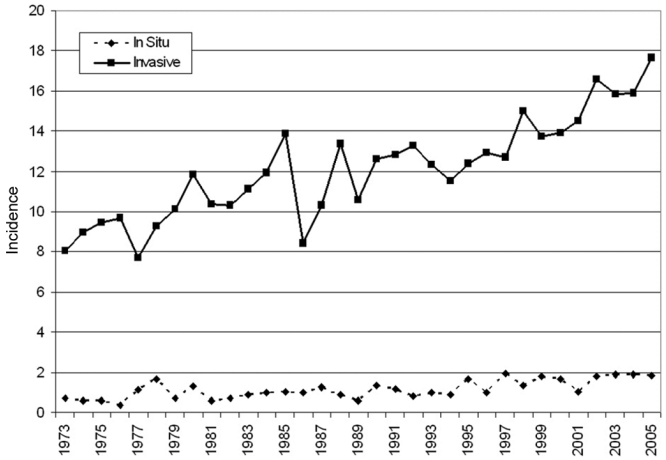

Figure 1. Age-adjusted incidence rates (per 1,000,000 persons) of in situ and invasive anal cancer among women, 1973–2005. Trends and incidence rates were calculated using SEER*Stat [15]. Source: Survey epidemiology and end results (SEER) program data file [16].

Table 1. Median duration and clearance rates of anal human papillomavirus (HPV) infection, by HPV genotype and the number of coinfections.

Genotype	No. of incident infections[a]	Duration of follow-up,[b] months	Median duration of infection,[c] days (95% CI)	Infections cleared within 1 year, %	All incident infections		Infection with no coinfection[e]		Infection with ⩾1 coinfection[e]	
					No. of cleared infections[d]	Clearance rate per 100 woman-months (95% CI)	No. of cleared infections[f]	Clearance rate per 100 woman-months (95% CI)	No. of cleared infections[g]	Clearance rate per 100 woman-months (95% CI)
Any HPV type[h]	119	780	238.0 (159–280)	70	58	7.44 (5.65–9.62)	36	4.62 (3.23–6.39)	22	2.82 (1.77–4.27)
HR HPV type[i]										
Any	107	622	150.0 (132–243)	74	57	9.16 (6.94–11.87)	24	3.86 (2.47–5.74)	33	5.30 (3.65–7.45)
16	17	102	132.0 (105–348)	82	12	11.77 (6.08–20.56)	2	1.96 (0.24–7.09)	10	9.81 (4.70–18.04)
18	13	55	211.5 (140–365)	83	6	10.83 (3.97–23.57)	0	(NA–6.66)	6	10.83 (3.97–23.57)
31	10	41	160.0 (125–250)	100	7	16.95 (6.81–34.92)	0	(NA–8.93)	7	16.95 (6.81–34.92)
33	2	4	119.0 (NA)	100	1	25.21 (0.64–140.46)	0	(NA–93.00)	1	25.21 (0.64–140.46)
35	3	15	161.0 (146–176)	100	2	13.19 (1.60–47.64)	0	(NA–24.32)	2	13.19 (1.60–47.64)
39	6	20	119.0 (106–135)	100	3	14.93 (3.08–43.62)	0	(NA–18.35)	3	14.93 (3.08–43.62)
45	6	61	210.0 (103–763)	60	5	8.15 (2.65–19.02)	3	4.89 (1.01–14.29)	2	3.26 (0.39–11.78)
51	14	46	131.0 (124–147)	100	7	15.14 (6.09–31.20)	3	6.49 (1.34–18.96)	4	8.65 (2.36–22.15)
52	18	114	135.0 (131–161)	83	11	9.64 (4.81–17.25)	2	1.75 (0.21–6.33)	9	7.89 (3.61–14.97)
53	25	116	174.0 (132–245)	100	11	9.46 (4.72–16.92)	4	3.44 (0.94–8.80)	7	6.02 (2.42–12.40)
56	15	100	160.0 (138–644)	71	8	8.02 (3.46–15.79)	2	2.00 (0.24–7.24)	6	6.01 (2.21–13.09)
58	9	25	252.0 (117–272)	100	3	12.18 (2.51–35.59)	0	(NA–14.98)	3	12.18 (2.51–35.59)
59	8	53	350.5 (146–434)	50	4	7.59 (2.07–19.42)	0	(NA–7.00)	4	7.59 (2.07–19.42)
66	7	42	131.0 (82–392)	80	5	11.77 (3.82–27.48)	2	4.71 (0.57–17.01)	3	7.06 (1.46–20.65)
68	8	35	136.0 (124–146)	83	6	17.39 (6.38–37.85)	0	(NA–10.69)	6	17.39 (6.38–37.85)
70	10	82	134.0 (127–182)	87	8	9.81 (4.24–19.33)	4	4.91 (1.34–12.56)	4	4.91 (1.34–12.56)
73	11	46	125.0 (120–134)	100	9	19.64 (8.98–37.28)	4	8.73 (2.38–22.35)	5	10.91 (3.54–25.46)
82	2	13	133.5 (132–135)	100	2	15.54 (1.88–56.15)	1	7.77 (0.20–43.30)	1	7.77 (0.20–43.30)
LR HPV type										
Any[j]	77	548	224.0 (163–267)	76	43	7.85 (5.68–10.57)	18	3.28 (1.95–5.19)	25	4.56 (2.95–6.73)
6	7	68	180.0 (118–NA)	81	5	7.40 (2.40–17.27)	0	(NA–5.46)	5	7.40 (2.40–17.27)
11	1	0	NA		0	NA		NA		NA
42	7	29	159.0 (98–NA)	100	4	13.97 (3.81–35.77)	1	3.49 (0.09–19.46)	3	10.48 (2.16–30.62)
54	10	49	170.0 (85–359)	100	7	14.40 (5.79–29.68)	1	2.06 (0.05–11.46)	6	12.35 (4.53–26.87)
61	17	97	186.0 (126–274)	78	10	10.33 (4.95–19.00)	5	5.17 (1.68–12.05)	5	5.17 (1.68–12.05)

81	10	89	156.5 (125–286)	87	8	8.96 (3.87–17.65)	3	3.36 (0.69–9.81)	5	5.60 (1.82–13.06)
89	9	50	187.0 (135–225)	100	5	10.08 (3.27–23.52)	0	(NA–7.44)	5	10.08 (3.27–23.52)
Undetermined-risk type										
44	6	60	141.0 (112–514)	60	4	6.67 (1.82–17.07)	2	3.33 (0.40–12.04)	2	3.33 (0.40–12.04)
62	13	108	170.0 (128–365)	80	9	8.34 (3.81–15.83)	0	(NA–3.42)	9	8.34 (3.81–15.83)
67	2	4	123.0 (NA)	100	1	24.39 (0.62–135.89)	0	(NA–89.97)	1	24.39 (0.62–135.89)
71	6	36	238.0 (163–NA)	67	2	5.55 (0.67–20.03)	1	2.77 (0.07–15.45)	1	2.77 (0.07–15.45)
83	11	67	239.0 (137–NA)	70	5	7.42 (2.41–17.32)	4	5.94 (1.62–15.20)	1	1.48 (0.04–8.27)
84	19	97	160.0 (108–280)	89	9	9.25 (4.23–17.55)	2	2.05 (0.25–7.42)	7	7.19 (2.89–14.82)
Species[k]										
1	16	74	176.0 (129–225)	100	8	10.76 (4.64–21.20)	1	1.34 (0.03–7.49)	7	9.41 (3.78–19.39)
3	70	383	181.0 (135–240)	82	31	8.09 (5.50–11.49)	14	3.66 (2.00–6.13)	17	4.44 (2.59–7.11)
5	16	59	132.0 (126–146)	100	9	15.23 (6.96–28.91)	4	6.77 (1.84–17.33)	5	8.46 (2.75–19.74)
6	47	240	160.0 (132–245)	85	21	8.75 (5.42–13.38)	8	3.34 (1.44–6.57)	13	5.42 (2.89–9.27)
7	51	267	145.5 (128–210)	78	24	8.99 (5.76–13.38)	6	2.25 (0.83–4.89)	18	6.75 (4.00–10.66)
9	61	278	145.0 (131–161)	91	29	10.42 (6.98–14.97)	4	1.44 (0.39–3.68)	25	8.98 (5.81–13.26)
10	14	104	160.5 (118–514)	70	8	7.71 (3.33–15.19)	2	1.93 (0.23–6.96)	6	5.78 (2.12–12.58)

NOTE. HR, high risk; LR, low risk; NA, not available (statistic could not be estimated from the available data).

[a] The overall number of genotype-specific incident infections was 414, including 184 HR HPV infections, 118 LR HPV infections, and 112 infections with unclassified types.

[b] Months of follow-up for patients at risk of clearing an infection, calculated by summing the durations across women for a specific HPV type or group.

[c] Estimated by the product-limit (Kaplan-Meier) method.

[d] The number of genotype-specific cleared infections was 179, including 110 HR HPV infections and 69 LR HPV infections

[e] Coinfection was defined as other HPV genotypes detected at the clinic visit preceding the clearance of the index infection.

[f] The number of genotype-specific cleared infections with no coinfection was 46, including 27 HR HPV infections and 19 LR HPV infections.

[g] The number of genotype-specific cleared infections with ⩾1 coinfection was 133, including 83 HR HPV infections and 50 LR HPV infections.

[h] Duration was measured from acquisition of the first HPV type until clearance of the last HPV type. An HPV-group specific infection was considered to have occurred at the visit (after visit 1) of the first detection of an anal HPV infection in the group of interest. The infection was considered resolved at the first subsequent visit where the anal specimen was negative for HPV infection in that group.

[i] Duration was measured from acquisition of the first HR HPV type until clearance of the last HR HPV type.

[j] Duration was measured from acquisition of the first LR HPV type until clearance of the last LR HPV type. Includes genotypes of undetermined oncogenic risk.

[k] 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; and species 10 comprises types 6, 11, and 44.

and 84 [25, 26]. We defined the risk (oncogenic potential) associated with various HPV types, using the International Agency for Research on Cancer definition [26]. HPV-positive specimens that subsequently had negative results of the genotyping assay were considered unclassified HPV-positive specimens. All specimens were also tested for the human β-globin gene as an internal control for sample sufficiency. The 163 specimens (20.2% of 805) that tested negative for β-globin were considered to be insufficient and were excluded from statistical analyses.

Statistical analysis. Analyses were conducted using SAS, version 9.1.3 (SAS Institute), and were limited to data for the 431 women who completed at least 2 clinic visits and the detailed questionnaire at visit 2. To prevent bias in estimates due to left censoring, we considered only incident infections—that is, infections first detected at the second visit or a subsequent visit. The duration of infection was the time from the first detection of anal HPV infection until the first negative result for that infection. The Kaplan-Meier method was used to calculate the median duration of anal and cervical HPV infections grouped by oncogenic risk and phylogenetic species. HPV type–specific clearance rates per 100 person-months were calculated for all detected anal HPV genotypes and were grouped by the number of other genotypes present at the clinic visit preceding clearance of the index infection. Poisson exact 95% CIs were calculated for all clearance rates [27]. Clearance rates for 5 age groups were calculated using the same techniques and were used to construct age-specific anal HPV clearance curves.

The association of anal HPV clearance with exposures of interest was modeled through Cox regression with days since acquisition of infection as the time metric, after adjustment for age at study entry. Infections with unclassified HPV types were excluded from the analysis. Because nearly 10% of study participants did not provide their lifetime number of 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 >10% change in the parameter estimates [28], nor in 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 time to HPV clearance [29]. Relative risks, as estimated by hazard ratios, and 95% CIs were used as measures of association. Because each patient was allowed to have >1 clearance event throughout the study, we used a robust sandwich variance estimate [30], aggregated over patients, to prevent artificially deflated SEs and CI estimates.

RESULTS

Among the 431 women included in this analysis, 215 (50%) experienced at least 1 incident anal HPV infection, and 177 (41%) were negative for HPV at all study visits. The remaining 9% had a prevalent infection at baseline but no incident infections. Baseline and follow-up included 1508 visits at which anal specimens were collected (median, 3.5 visits per patient). The cumulative follow-up experience for this cohort was 7004 woman-months (mean duration of follow-up, 487 days). The prevalence of anal HPV infection at enrollment was 42% (183 HPV-infected patients). The cohort had a multiethnic composition, with the majority of patients nonwhite women. The median age of cohort participants was 40 years (mean age, 39.4 years), 14% of women were current tobacco smokers, and 23% were current alcohol drinkers at baseline [17].

The rate of clearance of incident anal HPV infections was 8.57 per 100 woman-months (95% CI, 6.89–10.54 per 100 woman-months) (table 1). HR HPV infections cleared faster (9.16 per 100 woman-months; 95% CI, 6.94–11.87 per 100 woman-months) than did LR HPV infections (7.85 per 100 woman-months; 95% CI, 5.68–10.57 per 100 woman-months). Accordingly, the median duration of LR HPV infections (224 days) exceeded that of HR HPV infections (150 days). Two HR HPV types, HPV-59 and HPV-58, and 2 types of undetermined oncogenicity, HPV-83 and HPV-71, had the longest clearance times. Among the α-papillomavirus species, the fastest clearing infections were α-5 infections (15.23 per 100 woman-months; 95% CI, 6.96–28.91 per 100 woman-months), and the slowest clearing were α-10 infections (7.71 per 100 woman-months; 95% CI, 3.33–15.19 per 100 woman-months).

The presence of another HPV genotype increased the clearance rate of both HR and LR HPV infections, but the difference was not statistically significant. The rate of clearance of anal HR HPV infections was 3.86 per 100 woman-months (95% CI, 2.47–5.74 per 100 woman-months) among women without coinfection at the visit before clearance and was 5.30 per 100 woman-months (95% CI, 3.65–7.45 per 100 woman-months) among women with $\geqslant$1 HPV coinfection. This pattern was observed across most HPV groups. Compared with clearance rates among women infected with a single HPV genotype, the clearance rate among women with $\geqslant$1 coinfection was >4 times higher for infections with HPV-16, HPV-52, and HPV-54 and species α-1 and α-9 and was nearly 3 times higher for infections with HPV-56, HPV-42, HPV-84 and species α-7 and α-10, although the 95% CIs overlapped.

On the basis of Cox regression, the risk of clearance of LR HPV infection was higher in the presence of HPV-61 (relative risk, 3.95; 95% CI, 1.83–8.55) or any 2 other genotypes (relative risk, 2.54; 95% CI, 1.18–5.46) (table 2). Coinfections with other HPV types tended to increase the chances of clearance of LR HPV infection, although the differences were not significant. The presence of other genotypes did not substantially affect the clearance of HR HPV infection. A higher number of coexisting genotypes did not change anal HPV clearance rates.

No significant association was observed between the age of

Table 2. Clearance of anal human papillomavirus (HPV) infection by presence of coinfecting genotypes.

Variable	High-risk HPV infection			Low-risk HPV infection[f]			Any HPV infection		
	No. of patients[b]	No. of events[c]	Hazard ratio[d] (95% CI)[e]	No. of patients[b]	No. of events[c]	Hazard ratio[d] (95% CI)[e]	No. of patients[b]	No. of events[c]	Hazard ratio[d] (95% CI)[e]
High-risk HPV coinfection[a]									
Not present	…	…	…	21	19	…	…	…	…
Present	…	…	…	29	39	1.41 (0.83–2.39)	…	…	…
Low-risk HPV coinfection[a]									
Not present	26	27	…	…	…	…	…	…	…
Present	24	44	1.06 (0.70–1.61)	…	…	…	…	…	…
α-9 species coinfection[a]									
Not present	21	23	…	26	19	…	44	42	…
Present	15	24	1.16 (0.69–1.97)	14	17	1.36 (0.76–2.44)	20	41	1.29 (0.88–1.88)
α-7 species coinfection[a]									
Not present	21	20	…	22	19	…	41	39	…
Present	10	22	1.18 (0.71–1.97)	13	18	1.00 (0.52–1.91)	18	40	1.02 (0.69–1.49)
α-6 species coinfection[a]									
Not present	18	19	…	28	19	…	44	38	…
Present	10	16	1.18 (0.64–2.16)	10	14	1.41 (0.72–2.77)	13	30	1.37 (0.91–2.08)
α-3 species coinfection[a]									
Not present	26	27	…	10	5	…	34	32	…
Present	20	47	1.11 (0.72–1.71)	9	8	2.49 (0.89–6.97)	24	55	1.28 (0.86–1.90)
HPV-16 coinfection[a]									
Not present	25	25	…	28	19	…	50	44	…
Present	7	10	1.42 (0.81–2.49)	5	6	1.34 (0.43–4.24)	9	16	1.51 (0.88–2.58)
HPV-51 coinfection[a]									
Not present	24	24	…	27	19	…	47	43	…
Present	3	8	1.25 (0.66–2.36)	2	1	1.24 (0.14–11.44)	5	9	1.39 (0.74–2.61)
HPV-52 coinfection[a]									
Not present	23	25	…	27	19	…	47	44	…
Present	7	11	1.35 (0.68–2.70)	5	5	1.79 (0.60–5.31)	8	16	1.70 (0.98–2.94)
HPV-53 coinfection[a]									
Not present	23	23	…	28	19	…	49	42	…
Present	6	8	1.01 (0.50–2.07)	5	6	2.01 (0.82–4.96)	8	14	1.37 (0.79–2.40)
HPV-61 coinfection[a]									
Not present	27	27	…	23	14	…	48	41	…
Present	4	17	1.57 (0.83–2.98)	6	8	3.95 (1.83–8.55)*	6	25	2.04 (1.24–3.37)
HPV-62 coinfection[a]									
Not present	27	27	…	25	19	…	50	46	…
Present	7	17	1.05 (0.58–1.87)	6	5	0.67 (0.12–3.60)	8	22	0.97 (0.55–1.71)
HPV-84 coinfection[a]									
Not present	27	27	…	24	17	…	47	44	…
present	7	12	0.78 (0.46–1.33)	4	4	0.84 (0.29–2.42)	8	16	0.85 (0.54–1.36)
No. of coinfections									
0	25	27	…	20	19	…	43	46	…
1	24	36	1.12 (0.73–1.72)	24	30	1.59 (0.93–2.73)	30	66	1.29 (0.92–1.79)
2	8	11	1.30 (0.65–2.59)	8	9	2.54 (1.18–5.46)	9	20	1.76 (1.05–2.95)
⩾3	7	36	1.08 (0.71–1.66)	6	11	0.94 (0.45–1.95)	7	47	1.13 (0.79–1.62)
P for trend			.74			.76			.47

[a] Coinfection with the specified HPV type at the clinic visit preceding the clearance of the index infection.
[b] The number of patients who completed the questionnaire and at least 2 clinical visits.
[c] The number of cleared incident HPV infections during the study period.
[d] Hazard ratio was estimated using Cox regression, adjusted for the age of participants at study entry.
[e] 95% CI estimates indicated with an asterisk (*) are statistically significant after Bonferroni correction for multiple comparisons.
[f] Includes undetermined-risk HPV types.

Table 3. Baseline risk factors for clearance of anal human papillomavirus (HPV) infection.

Factor	High-risk HPV infection				Low-risk HPV infection[d]				Any HPV infection			
	No. of patients[a] (n = 64)	No. of events[b] (n = 110)	Hazard ratio[c] (95% CI)	P for trend	No. of patients[a] (n = 58)	No. of events[b] (n = 69)	Hazard ratio[c] (95% CI)	P for trend	No. of patients[a] (n = 89)	No. of events[b] (n = 179)	Hazard ratio[c] (95% CI)	P for trend
Age, years												
<25	16	22	…		15	19	…		22	41	…	
25–34	17	27	1.12 (0.71–1.74)		13	13	1.23 (0.63–2.40)		22	40	1.18 (0.81–1.71)	
35–44	16	28	1.07 (0.70–1.64)		9	11	0.94 (0.46–1.93)		20	39	1.06 (0.73–1.55)	
45–54	7	14	1.05 (0.52–2.12)		13	14	0.93 (0.54–1.62)		15	28	0.93 (0.61–1.43)	
⩾55	8	19	1.04 (0.64–1.67)	.98	8	12	0.86 (0.45–1.63)	.49	10	31	0.97 (0.66–1.42)	.57
Ethnicity												
Japanese	4	5	…		4	7	…		6	12	…	
White	33	62	1.65 (0.99–2.74)		34	42	0.90 (0.47–1.71)		48	104	1.24 (0.82–1.86)	
Hawaiian	8	21	1.81 (0.97–3.39)		4	5	0.55 (0.24–1.29)		9	26	1.22 (0.73–2.03)	
Filipino	4	4	1.60 (0.62–4.14)		3	4	0.76 (0.24–2.49)		6	8	1.04 (0.49–2.22)	
Other	15	18	1.42 (0.77–2.62)		13	11	0.86 (0.43–1.74)		20	29	1.10 (0.70–1.75)	
Education level												
High school or less	12	25	…		14	14	…		19	39	…	
Some college	17	25	1.14 (0.68–1.91)		14	17	3.37 (1.70–6.70)		23	42	1.85 (1.23–2.78)	
College graduate	24	35	1.26 (0.76–2.09)		23	27	2.74 (1.44–5.25)		36	62	1.82 (1.23–2.70)	
Graduate degree	11	25	0.99 (0.62–1.58)	.89	7	11	1.46 (0.70–3.03)	.04	11	36	1.24 (0.85–1.82)	.11
Annual income												
<$7500	17	27	…		15	16	…		23	43	…	
$7500–$19,999	11	22	0.72 (0.40–1.27)		14	19	0.98 (0.53–1.84)		18	41	0.85 (0.56–1.28)	
$20,000–$49,999	23	41	0.86 (0.57–1.30)		19	20	1.30 (0.70–2.44)		31	61	1.04 (0.74–1.48)	
⩾$50,000	10	16	1.25 (0.67–2.31)	.70	9	13	1.62 (0.86–3.06)	.11	14	29	1.38 (0.89–2.12)	.16
No. of pregnancies												
0	28	48	…		26	29	…		38	77	…	
1	8	13	1.26 (0.73–2.20)		12	11	1.01 (0.53–1.91)		15	24	1.09 (0.73–1.62)	
2	10	14	0.86 (0.55–1.34)		5	5	1.19 (0.62–2.30)		12	19	0.93 (0.65–1.34)	
⩾3	18	35	0.83 (0.54–1.26)	.36	15	24	0.85 (0.49–1.46)	.57	24	59	0.83 (0.60–1.16)	.3
Age at first sexual intercourse, years												
<16	13	29	…		14	17	…		19	46	…	
16–17	23	33	0.94 (0.65–1.36)		18	21	1.39 (0.79–2.44)		31	54	1.07 (0.79–1.46)	
18–19	15	31	0.95 (0.61–1.48)		15	18	1.51 (0.80–2.86)		21	49	1.14 (0.79–1.63)	
⩾20	12	15	1.46 (0.85–2.53)	.39	10	11	1.77 (0.79–3.93)	.12	17	26	1.54 (0.97–2.43)	.09
Lifetime no. of sexual partners												
<2	1	9	…		1	2	…		1	11	…	
2–5	20	23	0.89 (0.48–1.64)		20	22	0.84 (0.20–3.55)		32	45	0.79 (0.47–1.33)	
⩾6	40	72	0.79 (0.49–1.28)	.31	35	41	0.72 (0.17–3.04)	.47	53	113	0.71 (0.44–1.15)	.18
Oral contraceptive use at baseline												
Never	10	19	…		11	13	…		14	32	…	
Ever	54	91	0.99 (0.65–1.50)		47	56	1.09 (0.68–1.77)		75	147	1.08 (0.79–1.49)	
Past use	34	64	1.07 (0.69–1.66)		32	37	1.09 (0.65–1.84)		50	101	1.14 (0.81–1.60)	
Current use	20	27	0.82 (0.49–1.36)		15	19	1.10 (0.58–2.08)		25	46	0.95 (0.64–1.42)	

Regular oral contraceptive pill use, years										
None	19	33	…		17	21	…		24	54	…	
<2	7	19	1.03 (0.66–1.62)		4	6	0.99 (0.37–2.66)		9	25	1.15 (0.77–1.72)	
2–4	15	19	1.52 (0.93–2.49)		15	18	2.08 (1.19–3.62)		21	37	1.72 (1.21–2.46)	
5–9	12	11	0.79 (0.46–1.37)		9	10	0.88 (0.46–1.68)		17	21	0.82 (0.54–1.24)	
⩾10	11	28	0.84 (0.54–1.32)	.39	13	14	0.75 (0.41–1.38)	.40	18	42	0.83 (0.57–1.20)	.22
Noncontraceptive hormone use										
Never	57	94	…		50	60	…		78	154	…	
Past use	5	11	1.19 (0.59–2.38)		6	6	0.83 (0.45–1.53)		9	17	0.99 (0.62–1.58)	
Current use	2	5	0.84 (0.53–1.34)		2	3	0.62 (0.26–1.49)		2	8	0.72 (0.46–1.14)	
Tobacco smoking										
Never	38	61	…		31	37	…		52	98	…	
Ever	26	49	0.73 (0.52–1.01)		27	32	0.86 (0.55–1.36)		37	81	0.78 (0.60–1.02)	
Past	13	27	0.75 (0.50–1.15)		13	16	1.03 (0.60–1.77)		16	43	0.84 (0.60–1.17)	
Current	13	22	0.70 (0.47–1.04)		14	16	0.74 (0.43–1.29)		21	38	0.73 (0.53–1.01)	
Tobacco use, pack-years										
None	38	61	…		31	37	…		52	98	…	
<2	9	18	0.95 (0.59–1.51)		9	9	0.93 (0.47–1.84)		13	27	0.92 (0.63–1.35)	
2–10	11	22	0.65 (0.44–0.96)		9	12	0.88 (0.44–1.76)		13	34	0.76 (0.54–1.07)	
⩾10	6	9	0.60 (0.31–1.18)	.03	9	11	0.81 (0.46–1.42)	.45	11	20	0.67 (0.43–1.03)	.03
Alcohol use										
Never	30	50	…		24	28	…		39	78	…	
Ever	34	60	1.07 (0.78–1.46)		34	41	0.85 (0.55–1.32)		50	101	0.97 (0.76–1.25)	
Past	18	34	1.25 (0.85–1.85)		21	22	0.84 (0.51–1.40)		27	56	1.03 (0.76–1.40)	
Current	16	26	0.90 (0.62–1.30)		13	19	0.86 (0.49–1.49)		23	45	0.90 (0.66–1.23)	
Lifetime ethanol intake, no of drinks										
None	30	50	…		24	28	…		39	78	…	
<250	16	23	1.17 (0.76–1.82)		12	15	0.89 (0.47–1.69)		21	38	1.02 (0.71–1.48)	
250–1099	6	7	1.74 (0.97–3.12)		12	15	1.31 (0.72–2.36)		13	22	1.37 (0.87–2.14)	
⩾1100	12	30	0.92 (0.61–1.40)	.96	10	11	0.52 (0.28–0.98)	.21	16	41	0.80 (0.57–1.13)	.46
Condom use at baseline										
No	43	77	…		44	56	…		62	133	…	
Yes	21	33	1.37 (0.94–2.00)		14	13	0.67 (0.35–1.28)		27	46	1.03 (0.74–1.44)	
Use of douches at baseline										
No	53	96	…		48	59	…		74	155	…	
Yes	11	14	0.48 (0.33–0.71)		10	10	0.62 (0.36–1.07)		15	24	0.54 (0.39–0.74)	
Anal sex history										
Never	47	77	…		41	55	…		62	132	…	
Ever	17	33	1.05 (0.69–1.59)		17	14	0.44 (0.24–0.79)		27	47	0.73 (0.53–1.03)	
Past	11	23	1.42 (0.91–2.24)		9	7	0.44 (0.21–0.92)		17	30	0.89 (0.60–1.34)	
Current	6	10	0.66 (0.39–1.12)		8	7	0.43 (0.19–0.99)		10	17	0.54 (0.35–0.86)	

[a] The number of patients who completed at least 2 clinical visits and had an incident anal HPV infection.
[b] The number of cleared incident anal HPV infections during the study period.
[c] Estimated using Cox regression, adjusted for age of participants at study entry.
[d] Includes undetermined-risk HPV types.

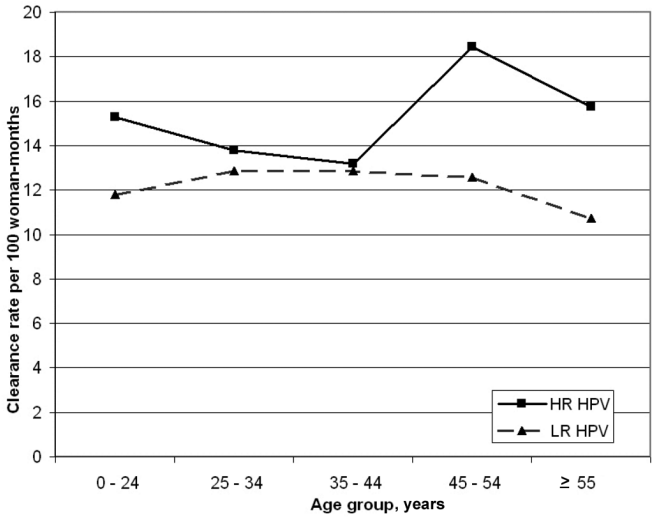

Figure 2. Clearance rates of anal human papillomavirus (HPV) infection, by age group and oncogenic risk of HPV genotype. Clearance rates were calculated among the 215 participants who experienced an incident anal HPV infection during the study period. HR, high risk; LR, low risk.

participants at baseline and anal HPV clearance (table 3). Clearance rates for HR HPV infection were slightly elevated for patients aged ⩾45 years, whereas clearance rates for LR HPV infection were nearly constant across age groups and were consistently lower than those for HR HPV infection (figure 2). Older age at first sexual intercourse was associated with higher clearance rates for any HPV, whereas a greater lifetime number of sexual partners was associated with reduced clearance rates, but the associations were not statistically significant. Women who took oral contraceptives for 2–4 years exhibited higher anal HPV clearance rates, but no particular trend was observed.

A history of tobacco smoking was associated with nonsignificantly reduced risk of anal HPV clearance, with a tendency toward increased HR HPV persistence with increased pack-years of tobacco smoking (table 3). A lower risk of HR HPV clearance was also observed among women who douched. Current practice of anal sex significantly reduced the chances of anal HPV clearance overall and among women with LR HPV infection. Inclusion of these factors in a multivariate Cox model yielded similar estimates (data not shown).

DISCUSSION

In this study of duration and clearance of anal HPV infection among healthy adult women, we found that anal HPV infections were moderately common [17] and had relatively short duration. Most anal HPV infections in our study were transient; 87% of cleared infections did so within 1 year. The median duration of anal HR HPV infection was 5 months, which is shorter than the median duration of 8 months for cervical HR HPV infection among the same group of women [20]. The latter figure is in agreement with the 8–20-month median duration of cervical HR HPV infection reported by most other studies [31]. It is unclear whether the much lower incidence of anal cancer, compared with cervical cancer, is a result of faster clearance of anal HPV or a different biology. Faster clearance of anal HR HPV infection, compared with cervical HR HPV infection, may result from a number of factors. A higher concentration of keratinized cells in the epithelial tissues of the anus may hinder HPV persistence and thus facilitate a more rapid clearance. Whether nonspecific immunity of the gastrointestinal tract could contribute to reduced duration of anal HR HPV infection is unclear and warrants further investigation. Association between cervical and anal HPV in our cohort will be the subject of a separate report.

The effect of multiple genotypes on clearance of anal HPV is largely unexplored. Hernandez et al. [18] speculated that women with multiple-type anal HPV infections are more susceptible to such infections because of impaired immune function or other factors. In the present study, clearance of both HR and LR HPV anal infections was enhanced in the presence of ⩾1 other HPV genotype. This could be explained by competition among the established HPV infections, generally not found in the cervix [32, 33]. An effect of multiple infections has also been found in our cohort for anal HPV acquisition. Goodman et al. [17] reported that the risk of acquisition of a new anal HPV infection was increased in the presence of another HPV genotype and that certain genotypes, such as HPV-16, had a greater effect on the acquisition of new HPV infection.

Overall, anal infections with LR HPV types in our cohort took longer to resolve than did infections with HR HPV types. This is in contrast to findings from most natural history studies of cervical HPV, in which LR HPV types generally clear faster

than do HR HPV types [31, 34]. HPV-16, the most common oncogenic genotype found in association with cervical malignancy, tends to persist longer in cervical tissue than do other types [35]. In contrast, anal HPV-16 infections generally cleared within ~4 months in our study, much faster than do many other genotypes. The ability to rapidly clear HPV-16 may protect anal cells from clonal progression of the persistently infected epithelium to anal precancer and invasion. Our observation supports the hypothesis that certain HPV types have different tropism to the anus than to the cervix [18]. Frisch et al. [6] found DNA of LR HPV in only 4% of anal cancers; therefore, the longer persistence of LR HPV types is unlikely to influence their oncogenic potential. Nonetheless, the presence of LR HPV genotypes may delay clearance of concurrent HR HPV infections or, through weakening of the host's immune system, increase susceptibility to subsequent acquisition of HR anal HPV infection.

Nonviral factors that delayed clearance of anal HPV in our study included long-term tobacco smoking. Tobacco smoking has been established as a risk factor for anal cancer [4, 36], but it was not associated with increased risk of anal HPV acquisition in our cohort [17] and in other studies [10]. The results of the present analysis suggest that the effect of smoking on the etiology of anal cancer is in part the result of a longer clearance time but not the higher acquisition rate of anal HPV. Behavioral factors, such as current practice of anal sex, also reduced the risk of anal HPV clearance in our cohort. One possible explanation is that increased exposure through anal intercourse contributes to continued repeat infection. Because we were unable to distinguish HPV infections that were resolved and then reacquired between clinic visits from those that persisted from one visit to the next, this repeat infection with the same HPV genotype may help explain the slower clearance we found in this study. An association of douching with reduced clearance time may also be a result of inadvertent repeat infection of the anus with HPV.

If rates of anal cancer continue to increase in the United States, more consideration should be given to the implementation of anal cancer screening programs. However, it is unclear whether anal HPV testing would be an effective cancer screening technique. The potential benefits of cervical HR HPV testing as a cancer screening tool have recently been addressed in the literature. In a study of 10,154 women, Mayrand et al. [37] reported the sensitivity of HPV testing for cervical intraepithelial neoplasia to be 94.6%, compared with 55.4% sensitivity of the Papanicolao smear. Given the highly transient nature of anal HPV infection and a relatively low incidence of anal cancer, a test for anal HPV is more likely to pick up short-term infections that resolve spontaneously, rather than persistent infections that have the potential to progress to precancerous lesions. Therefore, as a cancer screening tool, anal HPV testing would likely have lower sensitivity and a lower positive predictive value than would cervical HPV testing and thus may not be as cost-effective.

Furthermore, because we do not completely understand how specific HPV types affect anal cancer development, it is unclear which HPV genotypes should be targeted in a populationwide anal HPV testing program. Further research is necessary to address these issues. The risk factors identified in this report that hinder clearance of anal HPV may be helpful in designing a screening program on the basis of risk stratification, whereby individuals with higher perceived risk for anal cancer would be given priority screening [38].

The advantages of this study include a long mean follow-up period of ~16 months and relatively short intervals between visits. The unique ethnic composition of the population in Hawaii enabled us to compare anal HPV clearance rates among women from various racial and ethnic groups. The limitations of this study included its recruitment scheme. Study participants were recruited among college students and patients of health maintenance organizations, so our results may not be generalizable to the entire population. In addition, collection of anal specimens was optional; women who chose to provide specimens comprised 66% of cervical study participants and differed in age and ethnicity from the women who did not provide specimens [18]. Another limitation of this and other longitudinal studies of HPV infection is the assumption that the same genotype detected at consecutive visits represents the same persistent infection, rather than repeat infection after clearance. We defined clearance by a single visit with a negative finding after a positive finding, whereas some investigators have argued in favor of a definition that requires 2 visits with negative findings. In our study, the same genotype reappeared after a negative finding for 39 patients, indicating that these genotypes could have been missed during PCR hybridization-based genotyping.

In summary, the differences in duration between anal and cervical HPV infections found in this cohort suggest a different natural history of disease at these 2 sites. The shorter overall duration of anal HPV infection could reduce the sensitivity of anal HPV testing, rendering it less cost-effective than cervical HPV testing as a cancer screening tool. The potential of anal HPV testing for anal cancer prevention should be reevaluated when more-affordable, cost-effective HPV testing is developed and when the longer-term effects of HPV vaccination on the prevalence of HPV-16 are better understood.

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