Prevalence, Acquisition, and Clearance of Cervical Human Papillomavirus Infection among Women with Normal Cytology: Hawaii Human Papillomavirus Cohort Study

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Abstract

Few natural history studies of cervical human papillomavirus (HPV) incidence and duration have been conducted among older women, especially from multiethnic populations. Viral and nonviral determinants of HPV acquisition and clearance were examined among 972 sexually active women, ages 18 to 85 years, recruited from clinics on Oahu, Hawaii, and followed for a mean duration of 15 months (range, 2–56 months). Interviews and cervical cell specimens for cytology and HPV DNA detection by PCR, using the PGMY09/PGMY11 primer system, were obtained at baseline and at 4-month intervals. The prevalence of cervical HPV infection was 25.6% at study entry. A total of 476 incident genotype-specific infections were observed during the follow-up period. The incidence of high-risk (HR) HPV types (9.26 per 1,000 woman-months) was similar to low-risk (LR) HPV types (8.24 per 1,000 woman-months). The most commonly acquired HR-HPV types were HPV-52, HPV-16, and HPV-31; and their incidence was increased significantly with a coexisting cervical HPV infection. Cervical HPV acquisition decreased with age, income, and long-term use of oral contraceptives and increased with number of sexual partners, use of hormonal creams, alcohol drinking, and condom use by a sexual partner. Cohort participants cleared 265 of the 476 incident infections during follow-up. LR-HPV infections cleared more rapidly than did HR-HPV infections (median, 180 days versus 224 days). Clearance times were enhanced among older women and women with multiple infections. Our data suggest several viral and nonviral determinants of cervical HPV acquisition and clearance that might be used in cervical cancer prevention programs. [Cancer Res 2008;68(21):8813–24]

Introduction

The contribution of human papillomavirus (HPV) infection to the pathogenesis of cervical cancer is well established (1). The identification of viral and nonviral factors that influence the acquisition and persistence of cervical HPV is necessary to further our understanding of HPV-related carcinogenesis. Understanding the determinants of persistent infections, in which the same viral type is detected on consecutive examinations, has been the subject of intensive study (2–21). Longitudinal investigations of viral and nonviral cofactors in the natural history of cervical HPV infection have identified several key determinants of incident and persistent infection. The prevalence of cervical HPV infection peaks among younger women in many populations, but it is unclear whether younger women are more vulnerable to incident HPV infection than older women or whether clearance is delayed (22–24). Behaviors, such as oral contraceptive pill use, barrier methods of contraception, and tobacco smoking, and viral factors, such as preexisting infection with other HPV genotypes, may influence the risk of initial viral infection and subsequent clearance, but results have been inconsistent across populations (25–27). Natural history studies have shown that sequential or concurrent detection of multiple cervical HPV types is a common event, yet there is little consensus regarding the independence of these infections (8, 18, 20, 21, 28–31). The effectiveness of HPV-based screening strategies might be enhanced through improved knowledge of viral competition to colonize the cervical epithelium.

We initiated a Hawaii cohort study of women for long-term follow-up to identify determinants of infection and persistence of type-specific HPV infection of the cervix (32). A unique aspect of the study design was the inclusion of both younger and older women to facilitate the analysis of age-related risk factors. This is the first prospective study of HPV infection conducted among a multiethnic population of women of Pacific Island, Asian, and European ancestry. In this analysis, we examine determinants of HPV infection and duration among women with normal cervical cytology.

Materials and Methods

Subject recruitment and data collection. Between 1998 and 2003, sexually active women, 18 to 85 years of age, were recruited from five clinics on Oahu, Hawaii, to participate in a longitudinal cohort study of cervical HPV infection. Women scheduled for gynecology appointments, who were not pregnant or postpartum within the past 6 mo, had no treatment for cervical disease or abnormal cytology within the past 18 mo and had no plans to relocate in the next year were approached for participation in the cohort. Informed consent was obtained from all study participants using a protocol and forms approved by the University of Hawaii Institutional Review Board.

At the first and subsequent visits, a gynecologic examination was performed, an exfoliated cervical specimen for a Pap smear and HPV DNA analysis was collected, and a blood sample was drawn. Upon completion of the examination, a study questionnaire was interviewer-given covering demographics, reproductive history, sexual activity and history of sexually transmitted infections, hormone use, medical history, and tobacco and alcohol use. Follow-up visits were scheduled every 4 mo including repeat examination and testing and administration of a follow-up questionnaire.

At baseline, 2,389 women were recruited and tested for HPV DNA by PCR. Women with inadequate specimens, i.e., negative for the human

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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Table 1. Prevalence at enrollment and incidence rates of cervical HPV infection by genotype and number of coinfections

Genotype	Prevalence at entry, *n* (%)*	Woman-months of follow-up †	All incident infections		No coinfection ‡		One or more coinfection ‡	
			No. incident infections§	Incidence rate per 1,000 woman-months (95% CI)	No. incident infections‖	Incidence rate per 1,000 woman-months (95% CI)	No. incident infections¶	Incidence rate per 1,000 woman-months (95% CI)
Any HPV**	603 (25.6)	9075	118	13.00 (10.76–15.57)				
HR-HPV ††	493 (20.9)	10150	94	9.26 (7.48–11.33)	45	4.43 (3.23–5.93)	49	4.83 (3.57–6.38)
16	110 (4.7)	13596	24	1.77 (1.13–2.63)	3	0.22 (0.05–0.64)	21	1.54 (0.96–2.36)
18	40 (1.7)	14068	7	0.50 (0.20–1.03)	2	0.14 (0.02–0.51)	5	0.36 (0.12–0.83)
26	2 (0.1)	14330	2	0.14 (0.02–0.50)	0	0.00 (0.00–0.26)	2	0.14 (0.02–0.50)
31	43 (1.8)	13955	24	1.72 (1.10–2.56)	7	0.50 (0.20–1.03)	17	1.22 (0.71–1.95)
33	13 (0.6)	14257	5	0.35 (0.11–0.82)	1	0.07 (0.00–0.39)	4	0.28 (0.08–0.72)
35	19 (0.8)	14225	6	0.42 (0.15–0.92)	1	0.07 (0.00–0.39)	5	0.35 (0.11–0.82)
39	50 (2.1)	13999	17	1.21 (0.71–1.94)	3	0.21 (0.04–0.63)	14	1.00 (0.55–1.68)
45	25 (1.1)	14217	12	0.84 (0.44–1.47)	3	0.21 (0.04–0.62)	9	0.63 (0.29–1.20)
51	55 (2.3)	13943	17	1.22 (0.71–1.95)	2	0.14 (0.02–0.52)	15	1.08 (0.60–1.77)
52	83 (3.5)	13388	27	2.02 (1.33–2.93)	5	0.37 (0.12–0.87)	22	1.64 (1.03–2.49)
53	57 (2.4)	13903	22	1.58 (0.99–2.40)	2	0.14 (0.02–0.52)	20	1.44 (0.88–2.22)
56	36 (1.5)	14043	15	1.07 (0.60–1.76)	4	0.28 (0.08–0.73)	11	0.78 (0.39–1.40)
58	44 (1.9)	13910	9	0.65 (0.30–1.23)	4	0.29 (0.08–0.74)	5	0.36 (0.12–0.84)
59	36 (1.5)	14069	15	1.07 (0.60–1.76)	3	0.21 (0.04–0.62)	12	0.85 (0.44–1.49)
66	44 (1.9)	14062	14	1.00 (0.54–1.67)	4	0.28 (0.08–0.73)	10	0.71 (0.34–1.31)
68	23 (1.0)	14168	10	0.71 (0.34–1.30)	5	0.35 (0.11–0.82)	5	0.35 (0.11–0.82)
70	14 (0.6)	14217	3	0.21 (0.04–0.62)	0	0.00 (0.00–0.26)	3	0.21 (0.04–0.62)
73	16 (0.7)	14245	9	0.63 (0.29–1.20)	1	0.07 (0.00–0.39)	8	0.56 (0.24–1.11)
82	14 (0.6)	14233	5	0.35 (0.11–0.82)	1	0.07 (0.00–0.39)	4	0.28 (0.08–0.72)

(*Continued on the following page*)

β-globin gene or inadequate cytology were not eligible (n = 20). We also excluded women with high-grade squamous intraepithelial lesions (n = 13). Because of the costs of HPV testing and follow-up, we randomly retained every third woman by ID order, who was cervical HPV-negative at baseline. A total of 1,156 participants were randomly excluded, yielding a total of 1,200 eligible women among whom 972 (80.5%) completed at least one follow-up visit. In women with a minimum of one follow-up visit, 247 experienced a prevalent HPV infection only and 237 experienced at least one incident HPV infection (oncogenic and nononcogenic) defined as an HPV genotype not identified on a previous visit.

Detection and genotyping of HPV. DNA was extracted from exfoliated cervical cell specimens using commercial reagents (Qiagen, Inc.). Specimens were analyzed for the presence or absence of HPV DNA by PCR using a modified version of the PGMY09/PGMY11 primer system (33). HPV DNA-positive specimens were genotyped using a reverse line blot detection method for 37 different HPV types, including 6, 11,16,18, 26, 31, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, and 89 (refs. 34, 35; Roche Molecular Systems). PCR products were denatured and hybridized to a nylon membrane containing the immobilized HPV probes. This genotyping assay included probes for high and low levels of human β-globin gene. Amplicons hybridized to probes were detected using streptavidin-horseradish peroxidase–mediated color precipitation.

Statistical analysis. Prevalence of HPV at entry into the study was calculated among the 2,356 participants who satisfied the inclusion criteria and completed at least one clinical visit. All other analyses were limited to the 972 women who completed the interview questionnaire and at least two clinical visits. To prevent bias in clearance and duration estimates due to left censoring of prevalent infections, we only considered incident infections, i.e., infections first detected at the second or subsequent clinical visit.

Acquisition of an HPV infection was defined as the first positive result for a specific HPV type or group following a negative result. For example, if a woman tested positive for HPV-16 at her second clinical visit and for HPV-18 at her third visit, it would count as an acquisition event for HPV-18 type-specific analysis, but not for high-risk (HR) HPV analysis. Time to acquisition was defined as the time of the positive test result. The Kaplan-Meier method was used to construct cumulative acquisition curves, grouped by oncogenic risk and phylogenetic species (species 1, types 42 and 89; species 3, types 61, 62, 72, 81, 83, and 84; species 5, types 26, 51, and 82; species 6, types 53, 56, and 66; species 7, types 18, 39, 45, 59, 68, and 70; species 9, types 16, 31, 33, 35, 52, 58, and 67; species 10, types 6, 11, and 55), and to calculate median infection duration for each HPV genotype. The time to clearance was defined as the time from the first detection of a cervical HPV genotype until the first negative visit for that genotype. After the definition of Winer and colleagues (9), if a woman tested positive, negative, and then positive for the same HPV type over three consecutive visits, the infection was considered to be persistent with an intercurrent false negative result. HPV type–specific incidence and clearance rates per 1,000 person-months were calculated for all detected HPV genotypes, as well as grouped by the number of other genotypes present. The number of other genotypes was measured at the time of acquisition of the index infection, for incidence rates, or at the visit preceding clearance of the index infection, for clearance rates. In the acquisition analysis, coinfecting genotypes were already present or were acquired together with the index genotype. Because coinfection for the "any-HPV" group would be limited to simultaneous acquisition or clearance of multiple HPV types, no coinfection-specific rates were computed. Woman-months of follow-up were calculated by adding all time intervals during which a subject was positive for a specific HPV type or group. Poisson exact confidence intervals were constructed for all

Table 1. Prevalence at enrollment and incidence rates of cervical HPV infection by genotype and number of coinfections (Cont'd)

Genotype	Prevalence at entry, *n* (%)*	Woman-months of follow-up †	All incident infections		No coinfection ‡		One or more coinfection ‡	
			No. incident infections§	Incidence rate per 1,000 woman-months (95% CI)	No. incident infections‖	Incidence rate per 1,000 woman-months (95% CI)	No. incident infections¶	Incidence rate per 1,000 woman-months (95% CI)
LR HPV ‡ ‡	175 (7.4)	11893	98	8.24 (6.69–10.04)	45	3.78 (2.76–5.06)	84	7.06 (5.63–8.74)
Low risk								
6	42 (1.8)	14195	14	0.99 (0.54–1.65)	2	0.14 (0.02–0.51)	12	0.85 (0.44–1.48)
11	5 (0.2)	14293	5	0.35 (0.11–0.82)	1	0.07 (0.00–0.39)	4	0.28 (0.08–0.72)
40	4 (0.2)	14363	1	0.07 (0.00–0.39)	0	0.00 (0.00–0.26)	1	0.07 (0.00–0.39)
42	25 (1.1)	14104	15	1.06 (0.60–1.75)	3	0.21 (0.04–0.62)	12	0.85 (0.44–1.49)
54	35 (1.5)	14098	28	1.99 (1.32–2.87)	7	0.50 (0.20–1.02)	21	1.49 (0.92–2.28)
61	38 (1.6)	13944	25	1.79 (1.16–2.65)	7	0.50 (0.20–1.03)	18	1.29 (0.77–2.04)
72	8 (0.3)	14301	3	0.21 (0.04–0.61)	2	0.14 (0.02–0.51)	1	0.07 (0.00–0.39)
81	15 (0.6)	14183	11	0.78 (0.39–1.39)	2	0.14 (0.02–0.51)	9	0.63 (0.29–1.20)
89	40 (1.7)	13907	29	2.09 (1.40–2.99)	4	0.29 (0.08–0.74)	25	1.80 (1.16–2.65)
Undetermined risk								
34	1 (0.0)	14358	2	0.14 (0.02–0.50)	1	0.07 (0.00–0.39)	1	0.07 (0.00–0.39)
44	17 (0.7)	14184	17	1.20 (0.70–1.92)	3	0.21 (0.04–0.62)	14	0.99 (0.54–1.66)
62	55 (2.3)	13862	25	1.80 (1.17–2.66)	8	0.58 (0.25–1.14)	17	1.23 (0.71–1.96)
67	22 (0.9)	14224	11	0.77 (0.39–1.38)	1	0.07 (0.00–0.39)	10	0.70 (0.34–1.29)
71	6 (0.3)	14312	2	0.14 (0.02–0.50)	1	0.07 (0.00–0.39)	1	0.07 (0.00–0.39)
83	23 (1.0)	14191	12	0.85 (0.44–1.48)	3	0.21 (0.04–0.62)	9	0.63 (0.29–1.20)
84	33 (1.4)	14063	33	2.35 (1.62–3.30)	5	0.36 (0.12–0.83)	28	1.99 (1.32–2.88)
Species§§								
1	64 (2.7)	13672	39	2.85 (2.03–3.90)	7	0.51 (0.21–1.05)	32	2.34 (1.60–3.30)
3	152 (6.5)	12925	89	6.89 (5.53–8.47)	27	2.09 (1.38–3.04)	62	4.80 (3.68–6.15)
5	71 (3.0)	13798	23	1.67 (1.06–2.50)	3	0.22 (0.04–0.64)	20	1.45 (0.89–2.24)
6	127 (5.4)	13376	40	2.99 (2.14–4.07)	10	0.75 (0.36–1.37)	30	2.24 (1.51–3.20)
7	168 (7.1)	13058	52	3.98 (2.97–5.22)	14	1.07 (0.59–1.80)	38	2.91 (2.06–3.99)
9	290 (12.3)	11758	63	5.36 (4.12–6.86)	20	1.70 (1.04–2.63)	43	3.66 (2.65–4.93)
10	64 (2.7)	13947	32	2.29 (1.57–3.24)	6	0.43 (0.16–0.94)	26	1.86 (1.22–2.73)

*Prevalence among the 2,356 women who completed at least one clinical visit.

† Months of follow-up for subjects at risk of acquiring an infection.

‡ Other HPV genotypes detected at time of acquisition of the index infection.

§Overall number of genotype-specific incident infections: 476, including HR-HPV: 243; LR-HPV: 233.

‖Number of genotype-specific incident infections with no coinfection: 101, including HR-HPV: 51; LR-HPV: 50.

¶Number of genotype-specific incident infections with 1+ coinfection: 375, including HR-HPV: 192; LR-HPV: 183.

**Acquisition of any HPV type after an HPV-negative result. For example, if a woman tested positive for HPV-16 at her second clinical visit and for HPV-81 at her third visit, this would not count as an acquisition event for any HPV analysis.

† † Acquisition of an HR-HPV type after an HR-HPV–negative result. For example, if a woman tested positive for HPV-16 at her second clinical visit and for HPV-18 at her third visit, this would not count as an acquisition event for HR-HPV analysis.

‡ ‡ Acquisition of a LR-HPV type after an LR-HPV–negative result. Includes genotypes of undetermined oncogenic risk.

§§α-Papillomavirus species: species 1 comprises types 42 and 89; species 3 comprises types 61, 62, 72, 81, 83, and 84; species 5 comprises types 26, 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.

incidence and clearance rates (36). Incidence and clearance rates for five age groups were calculated using the same techniques and were used to construct age-specific HPV acquisition and clearance curves.

Cox regression was used to model the association of HPV acquisition and clearance with factors of interest. Hazard ratios (RR) and 95% confidence intervals (95% CI) were calculated. Incident HPV infections were classified by oncogenic risk: all infections, HR, and low or undetermined risk (LR) genotypes. All models were adjusted for age of the participants at study entry. Other adjustment factors were considered, but their inclusion in the models did not result in a significantly better fit according to the likelihood ratio test. Baseline risk factors for acquisition of a cervical HPV infection included a variety of sociodemographic, lifestyle, and reproductive variables. *P* values for trend, based on the Wald χ^2 statistic, were calculated for all variables with three or more levels. Because no stratification on factors of interest was performed, our modeling approach followed that of Andersen and Gill (37). The proportional hazards assumption for Cox models was verified by plotting scaled Schoenfeld residuals against time to HPV acquisition (38). Because each subject was allowed to experience more than one clearance event throughout the course of the study, we used a robust sandwich variance estimate (39), aggregated over subjects, to prevent artificially deflated SEs and confidence interval estimates. All analyses were conducted using SAS version 9.1.3 (SAS Institute, Inc.). All *P* values were two-sided, and $P < 0.05$ was defined as significant.

Results

Characteristics of the cohort. The 1,156 randomly excluded subjects were similar to the 972 retained subjects with respect to age (P = 0.47) and tobacco smoking (P = 0.98) but differed by alcohol drinking (P = 0.007) and education (P = 0.002). A total of 3,878 visits were completed among the 972 women included in this study. The follow-up experience accumulated for this cohort was 14,367 woman-months (mean, 14.8 months/participant; range, 2.1–55.7 months), the mean number of visits per woman was 4.0 (±2.6), and the median time between visits was 4.3 months (Supplementary Table S1). The follow-up rate on the cohort was 93% for those women remaining in the cohort with two or more visits. The cohort composition was multiethnic with the majority of subjects non-White women (61%). The median age of the participants was 33 years (mean, 35 years). Only 15% of women were current tobacco smokers and 24% were current alcohol drinkers at baseline. The mean number of lifetime sexual partners was 10.4 (±12.1) and the mean age at first sexual intercourse was 17.6 years (±3.4).

Prevalence at enrollment and incidence of cervical HPV infection. The prevalence of cervical HPV infection was 25.6% at study entry, including 20.9% with an HR-HPV infection (Table 1).

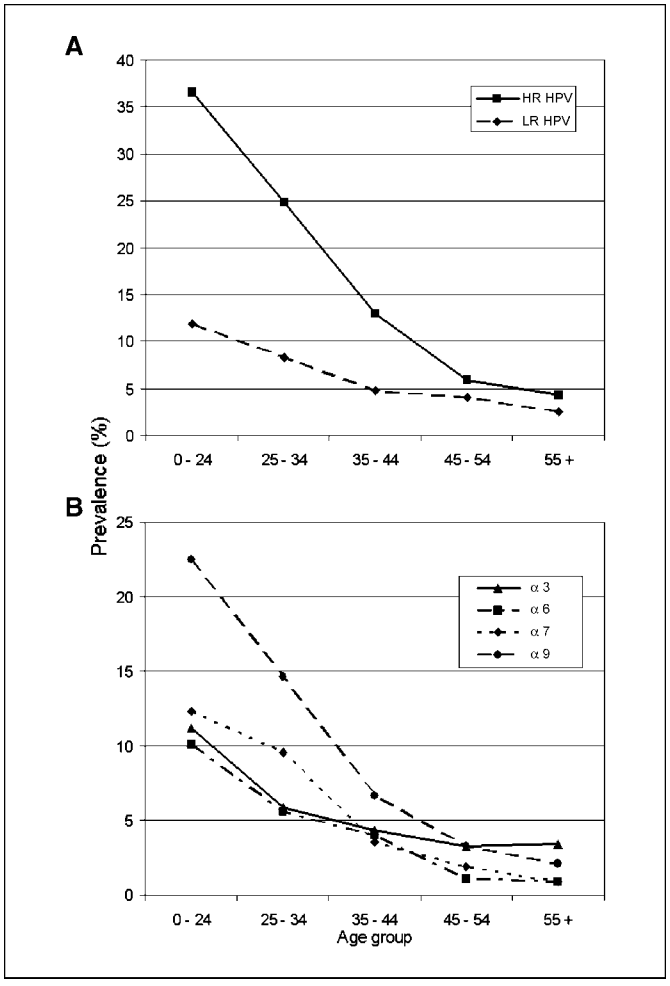

Figure 1. Prevalence of cervical HPV infection by oncogenic risk and phylogenetic species. Prevalence among the 2,356 study participants who completed at least one clinical visit. *A,* prevalence by oncogenic risk. *B,* prevalence by phylogenetic species.

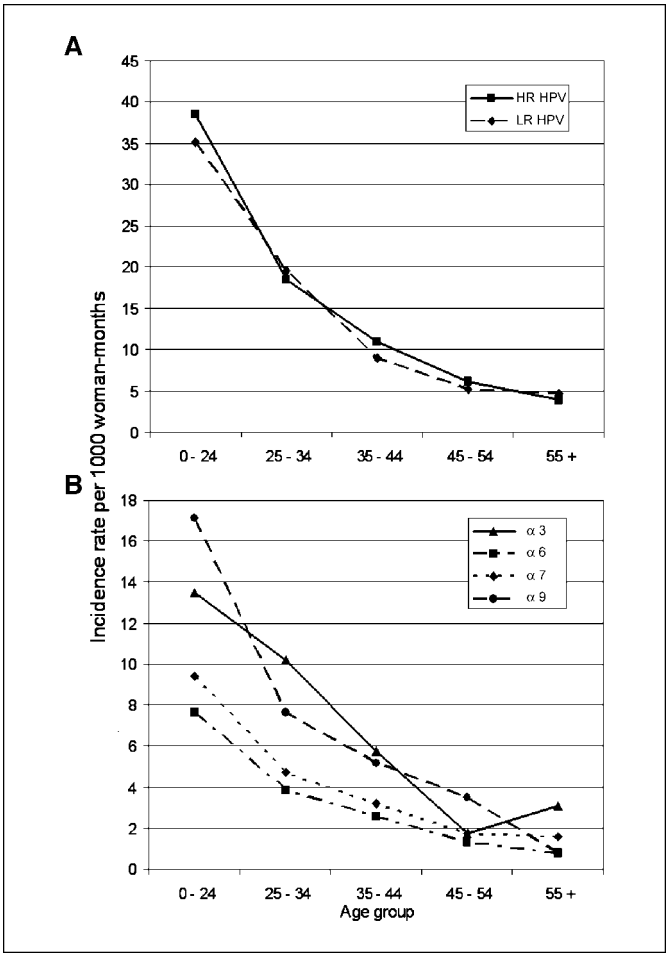

Figure 2. Incidence rates of cervical HPV infection by oncogenic risk and phylogenetic species. Incidence rates among the 941 participants who provided the information on the number of lifetime sexual partners. *A,* incidence rates by oncogenic risk. *B,* incidence rates by phylogenetic species.

A total of 237 women (24.4%) experienced at least one incident cervical HPV infection. HPV-16 was the most common prevalent type, followed by HPV-52, HPV-53, HPV-51, and HPV-62. At baseline, α-papillomavirus species 9 was the most common type of cervical infection (12.3%), followed by species 7, 3, and 6. Baseline HPV prevalence was inversely associated with age, with the highest prevalence among women who were <25 years (Fig. 1).

Acquisition of an incident cervical HPV infection: viral factors. Cohort participants experienced a total of 476 incident cervical HPV infections, defined as an HPV genotype that was first identified in a woman during follow-up, including 101 infections in the absence of other types and 375 infections in the presence of other types (Table 1). The risk of acquiring any cervical HPV infection was 13.0 (95% CI, 10.76–15.57) per 1,000 woman-months. The incidence of HR-HPV types (9.26 per 1,000 woman-months) was similar to the incidence of LR-HPV types (8.24 per 1,000 woman-months; see Fig. 2).

The most commonly acquired HR viral type was HPV-52 (2.0 per 1,000 woman-months), followed by HPV-16 (1.8 per 1,000 woman-months) and HPV-31 (1.7 per 1000 woman-months). The risk of an incident HPV infection varied by species, with the greatest risk among α-papillomavirus 3 types (6.9 per 1,000 woman-months) and 9 types (5.4 per 1,000 woman-months).

Table 2. Baseline risk factors for acquisition of cervical HPV infection

	Subjects* *n* (=972)	High-risk HPV			Low-risk HPV †			Any HPV		
		Events ‡ *n* (=284)	Hazard ratio§ (95% CI)	P_{trend}	Events ‡ *n* (=286)	Hazard ratio§ (95% CI)	P_{trend}	Events ‡ *n* (=570)	Hazard ratio§ (95% CI)	P_{trend}
Age (y)										
<25	267	123			114			237		
25–34	250	66	0.48 (0.36–0.65)		71	0.56 (0.42–0.76)		137	0.52 (0.42–0.64)	
35–44	198	35	0.30 (0.20–0.44)		29	0.27 (0.18–0.41)		64	0.29 (0.22–0.38)	
45–54	180	14	0.15 (0.09–0.26)		12	0.14 (0.08–0.26)		26	0.15 (0.10–0.22)	
≥55	77	5	0.12 (0.05–0.30)	<.0001	7	0.19 (0.09–0.40)	<.0001	12	0.15 (0.09–0.27)	<.0001
Ethnicity										
Japanese	112	22			20			42		
Caucasian	383	93	1.01 (0.64–1.60)		88	1.07 (0.66–1.75)		181	1.04 (0.74–1.45)	
Hawaiian	130	22	0.74 (0.41–1.33)		24	0.91 (0.50–1.65)		46	0.82 (0.54–1.24)	
Filipino	55	9	0.55 (0.25–1.19)		12	0.82 (0.40–1.71)		21	0.68 (0.40–1.15)	
Other	292	97	1.05 (0.66–1.66)		89	1.10 (0.67–1.80)		186	1.07 (0.77–1.50)	
Income										
<7,500	223	102			72			174		
7,500–19,999	222	49	0.62 (0.44–0.87)		48	0.86 (0.60–1.24)		97	0.72 (0.56–0.92)	
20,000–49,999	246	45	0.56 (0.39–0.80)		61	1.12 (0.78–1.61)		106	0.78 (0.61–1.01)	
≥50,000	248	32	0.48 (0.32–0.71)	<.0001	35	0.77 (0.51–1.17)	0.51	67	0.60 (0.45–0.80)	0.001
Age at menarche										
<12	212	52			67			119		
12	258	59	0.94 (0.65–1.37)		57	0.70 (0.50–1.00)		116	0.81 (0.63–1.04)	
13	251	58	0.88 (0.61–1.28)		52	0.61 (0.43–0.88)		110	0.73 (0.56–0.95)	
≥14	249	72	1.30 (0.91–1.85)	0.20	57	0.79 (0.55–1.12)	0.15	129	1.01 (0.79–1.29)	0.91
No. pregnancies										
None	403	117			133			250		
1	186	64	1.38 (1.02–1.86)		41	0.75 (0.53–1.06)		105	1.04 (0.83–1.31)	
2	123	24	1.20 (0.75–1.90)		21	0.84 (0.52–1.36)		45	1.01 (0.72–1.40)	
≥3	259	38	1.13 (0.78–1.64)	0.34	38	0.88 (0.61–1.28)	0.37	76	1.00 (0.77–1.30)	0.99
Age at first sexual intercourse										
<16	219	59			41			100		
16–17	287	83	1.18 (0.85–1.65)		73	1.49 (1.02–2.19)		156	1.31 (1.02–1.68)	
18–19	246	60	1.25 (0.87–1.79)		72	2.16 (1.47–3.18)		132	1.62 (1.25–2.10)	
≥20	204	38	1.06 (0.71–1.61)	0.57	46	1.83 (1.19–2.82)	0.0003	84	1.38 (1.03–1.85)	0.003
No. lifetime sexual partners										
<2	111	7			15			22		
2–5	314	94	3.62 (1.68–7.80)		82	1.45 (0.83–2.51)		176	2.14 (1.37–3.33)	
≥6	520	138	3.33 (1.56–7.11)	0.03	132	1.46 (0.86–2.49)	0.28	270	2.05 (1.33–3.17)	0.02
Oral contraceptive use at baseline										
Never	175	51			44			95		
Ever	797	192	0.75 (0.55–1.03)		189	0.87 (0.63–1.21)		381	0.81 (0.65–1.01)	
Past user	465	76	0.69 (0.48–0.99)		77	0.81 (0.56–1.18)		153	0.74 (0.57–0.97)	
Current user‖	332	116	0.80 (0.58–1.11)		112	0.92 (0.65–1.30)		228	0.86 (0.68–1.09)	
Years of oral contraceptive pill use										
Never used	312	91			98			189		
<2 y	91	26	0.85 (0.55–1.31)		23	0.71 (0.45–1.12)		49	0.78 (0.57–1.06)	
2–4 y	214	54	0.73 (0.53–1.02)		52	0.67 (0.48–0.94)		106	0.70 (0.55–0.89)	
5–9 y	191	45	0.70 (0.49–0.99)		37	0.53 (0.37–0.78)		82	0.61 (0.47–0.79)	
≥10 y	163	27	0.74 (0.47–1.18)	0.04	23	0.56 (0.35–0.90)	0.0003	50	0.65 (0.46–0.90)	<.0001
Hormonal cream use at baseline										
Never	880	228			217			445		
Past user	63	8	0.56 (0.28–1.15)		8	0.60 (0.29–1.22)		16	0.58 (0.35–0.96)	
Current user‖	29	7	1.83 (0.86–3.89)		8	2.14 (1.07–4.31)		15	1.98 (1.19–3.31)	
Tobacco smoking history										
Never	611	160			162			322		
Ever	361	83	0.96 (0.74–1.26)		71	0.80 (0.61–1.06)		154	0.88 (0.73–1.07)	
Past	216	42	0.88 (0.63–1.24)		33	0.67 (0.46–0.98)		75	0.78 (0.60–1.00)	

(*Continued on the following page*)

Table 2. Baseline risk factors for acquisition of cervical HPV infection (Cont'd)

	Subjects* *n* (=972)	High-risk HPV			Low-risk HPV †			Any HPV		
		Events ‡ *n* (=284)	Hazard ratio§ (95% CI)	P_{trend}	Events ‡ *n* (=286)	Hazard ratio§ (95% CI)	P_{trend}	Events ‡ *n* (=570)	Hazard ratio§ (95% CI)	P_{trend}
Current‖	145	41	1.07 (0.76–1.50)		38	0.97 (0.68–1.38)		79	1.02 (0.80–1.30)	
Alcohol history										
Never	529	138			122			260		
Ever	443	105	1.02 (0.79–1.32)		111	1.22 (0.94–1.58)		216	1.12 (0.93–1.34)	
Past	205	30	0.65 (0.44–0.96)		41	1.00 (0.70–1.42)		71	0.81 (0.62–1.06)	
Current‖	238	75	1.33 (1.00–1.76)		70	1.40 (1.04–1.87)		145	1.36 (1.11–1.67)	
History of tubal ligation										
No	841	223			218			441		
Yes	131	20	1.66 (0.96–2.86)		15	1.07 (0.60–1.91)		35	1.34 (0.90–2.00)	
Condom use by a sexual partner at baseline										
No	698	135			133			268		
Yes‖	274	108	1.37 (1.05–1.80)		100	1.33 (1.02–1.75)		208	1.35 (1.12–1.64)	
Spermicide use at baseline										
No	840	201			192			393		
Yes‖	132	42	1.05 (0.75–1.47)		41	1.12 (0.79–1.58)		83	1.08 (0.85–1.38)	
History of anal sex										
Never	794	185			182			367		
Ever	178	58	1.14 (0.85–1.53)		51	1.03 (0.75–1.41)		109	1.08 (0.87–1.34)	
Past	113	33	1.10 (0.76–1.59)		31	1.06 (0.73–1.55)		64	1.08 (0.83–1.41)	
Current‖	63	25	1.22 (0.81–1.86)		19	0.96 (0.59–1.54)		44	1.09 (0.80–1.49)	

*The number of subjects who completed the questionnaire and at least two clinical visits.
† Includes undetermined-risk HPV types.
‡ The number of incident HPV infections during the study period.
§Adjusted for age of participants at study entry.
‖Use within the last 4 mo before the first clinical visit.

The risk of an incident HR-HPV-16, HR-HPV-31, HR-HPV-39, HR-HPV-51, HR-HPV-52, HR-HPV-53, HR-HPV-59, and HR-HPV-73 was increased significantly among women with one or more coexisting cervical HPV infections (Table 1). The risk of acquiring a new HPV-53 infection was 10.0 (95% CI, 2.34–42.8), and the risk of a new HPV-16 infection was 7.00 (95% CI, 2.09–23.5) among women with one or more coinfections compared with women with a single infection.

The incidence of HR-HPV and LR-HPV infections decreased significantly with increasing age at baseline up to the age of 55 years or more when the rate of decline flattened (Fig. 2). This increased incidence among older women was pronounced for α-papillomavirus species 3 and modified by adjustment for the number of lifetime sexual partners (data not shown).

Acquisition of an incident cervical HPV infection: nonviral factors. Strong inverse associations of baseline age and family income with the acquisition of HPV were observed (Table 2). Number of lifetime sexual partners at baseline, but not age at first sexual intercourse, was positively associated with the risk of HR-HPV incidence. Users of oral contraceptive pills (OCP) were not at increased risk of incident HR-HPV, although past users of OCPs seemed protected. Compared with never users of OCPs, the incidence of HPV decreased with years of OCP use. Women who were current users of hormone creams were at increased risk of acquiring cervical HPV compared with never users, although the difference was not significant for HR types. Tobacco smoking was generally unrelated to the acquisition of HPV, but current alcohol drinkers at baseline were at increased risk of HPV acquisition. Condom use by a male partner at baseline was associated with a significantly increased risk of HPV acquisition, including HR and LR types, even after adjustment for lifetime number of sexual partners.

Clearance of an incident cervical HPV infection: viral factors. Cohort participants cleared 265 of the 476 incident infections during follow-up, including 134 of 243 HR-HPV infections (median infection duration, 224 days; 95% CI, 169–248) and 131 of 233 LR-HPV infections (median infection duration, 180 days; 95% CI, 154–236; Table 3). A total of 69% of HR infections and 81% of LR infections cleared within 1 year. Among HR types, infection with HPV-70 had the lowest rate of clearance (31.9 per 1,000 woman-months), followed by infection with HPV-33 and HPV-18. The clearance rate for α-papillomavirus species 9 was slower than for other species types, with a median duration of 246 days (95% CI, 181–358).

Clearance of cervical HR-HPV infection overall was nonsignificantly reduced among women with a coinfection compared with women infected with a single HPV type (RR, 0.85; 95% CI, 0.48–1.48). The clearance rate for LR-HPV and α-papillomavirus species 3, 5, 9, and 10 was higher among women with a concurrent infection compared with women infected with a single HPV type.

Clearance of an incident cervical HPV infection: nonviral factors. A modest positive trend in any-HPV clearance was

observed with age: women 45 years and older cleared their infections significantly faster than women <25 years at baseline. HR-HPV clearance was significantly enhanced among women with a late age at menarche and significantly reduced among women with three or more pregnancies compared with nulliparous women (Table 4).

Discussion

The prevalence of cervical HPV infection at study entry was 25.6% in the Hawaii cohort, similar to the prevalence found in two population-based surveys conducted in the United States (40, 41). Although there is wide international variation in the estimates of cervical HPV infection (42), the prevalence and distribution of cervical HPV genotypes in the present study was similar to other clinic-based and most population-based cohorts: HPV-16 was the most frequent type, followed by HPV-52, HPV-53, HPV-51, and HPV-62. This result is consistent with a meta-analysis showing that HPV-16 is the most common cervical infection worldwide (42). It is notable that HPV-18, HPV-31, and HPV-58 were not found as commonly in our study participants as in other cohorts in North America or Asia (42).

The age distribution of cervical HPV prevalence has been observed to vary between populations (24). Similar to other studies in North America and Europe (9, 40, 43, 44), we found that the prevalence of cervical HPV decreased significantly with age: there was more than an 8-fold variation in the prevalence of HR-HPV between women <25 years and those ≥55 years at study entry. Our investigation contrasts with Latin American studies that report a U-shaped age distribution for cervical HPV prevalence (4, 22, 45); and IARC HPV prevalence surveys showing flat age curves in low income areas of Asia and Nigeria (24).

The incidence of LR-HPV types was similar to the incidence of HR-HPV types in our cohort with the most common type, HPV-84, belonging to phylogenetic species 3. We also observed a high incidence of anal HPV-84 among these women, suggesting a common source of infection (46). Species 9 types, including HPV-52 and HPV-16, were also commonly acquired, closely paralleling their prevalence at study entry and reflecting their biological advantage to infect the cervix.

Castle and colleagues (22) observed that cervical HPV persistence, but not acquisition, increased significantly with age for both HR-HPV and LR-HPV types in a cohort of women in Guanacaste, Costa Rica, implying that viral persistence accounted for the increased prevalence of infections among older women. Women in the Hawaii cohort generally experienced a monotonic decline in the rate of HPV acquisition with age, although α-species 3 acquisition increased slightly among older women. In contrast to Costa Rican women, older Hawaii women may have had a lower cervical HPV prevalence compared with younger women because of more rapid clearance, rather than decreased acquisition, of new HPV infections.

An interaction between distinct HPV types in the acquisition or clearance of cervical infection may influence the effectiveness of prophylactic HPV vaccines in preventing cervical cancer (47). Cervical coinfection with multiple HPV types was relatively common among Hawaii cohort participants, and the risk of acquiring some HR types (e.g., HPV-16 and HPV-53) was enhanced among women with a coexisting infection. Other 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 (19, 47), although only Mendez and colleagues (47) found that type-specific HPV acquisition was dependent on a cervical infection with another type. Rousseau and colleagues (20, 29) note that HPV acquisition was more likely among women with another HPV type at study entry and that certain coinfections (e.g., HPV-16 and HPV-52) occurred with a significant frequency. These observations suggest common exposures or common routes of transmission, although alternative explanations, such as a biological interaction between various HPV types, cannot be excluded (47).

Cervical infection with multiple HPV types, which may increase the risk of dysplasia (29) and cancer (30), reduced the time to clearance of cervical HR-HPV in the present study, but the association was not significant. Results from other investigations are mixed in this regard, in part because the time between cervical HPV sampling and the definitions of persistence and clearance vary between studies. Ho and colleagues (18) and Perrons and colleagues (48) reported that viral clearance was significantly delayed by multiple HPV types detected in a previous visit, although this finding was not confirmed in other studies (20, 21, 31). Woodman and colleagues (8) observed that the clearance of an HPV-16 infection was delayed by coinfection with another type. Whether the simultaneous presence of multiple oncogenic types in the cervix is an important disease marker is an open question.

Consistent with other natural history studies of cervical HPV infection (13, 26, 27), the majority of incident HPV infections in our cohort were transient, lasting <6 months, and the rate of clearance was more rapid than the rate of acquisition for all HPV types. Clearance rates vary between studies, but Trottier and Franco (27) estimate the median duration of HPV detection at ~4 to 20 months. The relatively rapid clearance times in our study may be attributed to a shorter interval between visits (~4 months) compared with most other prospective investigations (~6–12 months). The clearance of HR-HPV infections was slower than LR-HPV infections, taking 24% longer to reach undetectable levels. Most other investigators (5, 7, 11, 12, 14, 18) have also reported a longer duration of oncogenic HPV infections than nononcogenic types.

Young age and greater lifetime number of sexual partners were important determinants of incident HPV infection in the Hawaii cohort, as reported by other investigators (9, 12, 17, 18, 28, 29). An association of alcohol drinking with the acquisition of cervical HPV is likely explained by high-risk behaviors. We found that tobacco smoking was unrelated to the risk of acquiring an HPV infection. Tobacco smoking has been implicated as a cofactor with HPV in CIN-3 and cervical cancer, but findings are inconsistent regarding a role of tobacco smoking and the risk of initial HPV infection (25, 26, 28). Although it is difficult to separate the effects of oral contraceptive pill use and sexual activity on the risk of HPV infection, most investigations have found no association (25, 26). Although the association of OCP use in our study was restricted to past and long-term users, it may be worthy of further exploration. The finding that current use of hormonal creams increased the risk of acquiring cervical HPV in the present study is novel. It is possible that hormonal creams may be prescribed for women with vaginal dryness, increasing their risk of microtrauma and viral entry during heterosexual intercourse. This may also be an explanation for an increased risk of HPV infection among postmenopausal women reviewed above. An increased incidence of cervical HPV with a partner's

Table 3. Median duration and clearance rates of cervical HPV infection by genotype and number of coinfections

Genotype	No. incident infections*	Woman-months of follow-up†	Median duration (d)‡ (95% CI)	Patients not cleared after 1 y	All incident infections		No coinfection§		One or more coinfections§	
					No. cleared infections‖	Clearance rate per 1,000 woman-months (95% CI)	No. cleared infections¶	Clearance rate per 1,000 woman-months (95% CI)	No. cleared infections**	Clearance rate per 1,000 woman-months (95% CI)
Any HPV††	118	790	259 (176–385)	39	56	70.9 (53.5–92.0)				
HR-HPV‡‡	94	626	245 (169–360)	36	48	76.7 (56.5–101.7)	26	41.5 (27.1–60.9)	22	35.1 (22.0–53.2)
16	24	139	291 (135–725)	42	10	72.0 (34.5–132.4)	0	0.0 (0.0–26.6)	10	72.0 (34.5–132.4)
18	7	52	428 (146–)	53	3	58.1 (12.0–169.7)	2	38.7 (4.7–139.8)	1	19.4 (0.5–107.8)
26	2	27	398 (180–616)	50	2	75.4 (9.1–272.3)	0	0.0 (0.0–139.0)	2	75.4 (9.1–272.3)
31	24	174	245 (126–373)	29	16	91.7 (52.4–148.9)	3	17.2 (3.5–50.3)	13	74.5 (39.7–127.4)
33	5	26	N/A‖‖	50	1	38.7 (1.0–215.4)	0	0.0 (0.0–142.6)	1	38.7 (1.0–215.4)
35	6	27	127 (119–434)	25	4	148.7 (40.5–380.7)	1	37.2 (0.9–207.1)	3	111.5 (23.0–325.9)
39	17	84	176 (118–370)	34	9	107.5 (49.1–204.0)	2	23.9 (2.9–86.3)	7	83.6 (33.6–172.2)
45	12	37	123 (104–144)	0	7	188.0 (75.6–387.4)	1	26.9 (0.7–149.6)	6	161.1 (59.1–350.7)
51	17	105	248 (132–486)	33	9	85.3 (39.0–162.0)	1	9.5 (0.2–52.8)	8	75.9 (32.7–149.5)
52	27	231	342 (224–524)	45	15	64.9 (36.3–107.0)	5	21.6 (7.0–50.5)	10	43.2 (20.7–79.5)
53	22	80	181 (114–259)	0	11	137.4 (68.6–245.9)	3	37.5 (7.7–109.5)	8	100.0 (43.2–197.0)
56	15	72	142 (101–167)	11	10	138.9 (66.6–255.4)	3	41.7 (8.6–121.8)	7	97.2 (39.1–200.3)
58	9	59	268 (132–453)	36	5	85.4 (27.7–199.3)	1	17.1 (0.4–95.2)	4	68.3 (18.6–175.0)
59	15	93	149 (122–311)	23	10	107.6 (51.6–197.9)	2	21.5 (2.6–77.7)	8	86.1 (37.2–169.6)
66	14	75	203 (126–)	36	5	66.8 (21.7–155.9)	3	40.1 (8.3–117.2)	2	26.7 (3.2–96.5)
68	10	52	210 (149–403)	33	5	97.1 (31.5–226.6)	2	38.8 (4.7–140.3)	3	58.3 (12.0–170.2)
70	3	63	666 (594–737)	100	2	31.9 (3.9–115.2)	2	31.9 (3.9–115.2)	0	0.0 (0.0–58.8)
73	9	58	246 (126–616)	21	6	103.9 (38.1–226.2)	0	0.0 (0.0–63.9)	6	103.9 (38.1–226.2)
82	5	18	137 (98–166)	0	4	223.5 (60.9–572.2)	1	55.9 (1.4–311.3)	3	167.6 (34.6–489.8)

(*Continued on the following page*)

condom use was unanticipated, but may have resulted from its association with increased sexual activity. Although of potential scientific and public health interest, we urge caution in the interpretation of these results until they are replicated by other investigators.

There are several limitations to the present study that must be considered in evaluating our findings. The study sample was selected from sexually active college students, health maintenance organization members, and members of family planning clinics. The lack of a population basis limits our ability to extrapolate our results to other communities. Based on cost constraints, we randomly excluded some women who were HPV-negative at baseline. The exclusion of these women may have biased the sample with regard to incidence or clearance of HPV infection. Persistence was defined as the detection of the same HPV type on two or more successive cervical specimens taken ~4 months apart. We cannot exclude the possibility that the sequential detection of the same type was, in fact, a reinfection rather than a sustained infection. Clearance in our study was defined as a single negative visit, whereas some investigators have defined clearance as two or more consecutive negative visits with the index HPV type. As in other longitudinal studies of cervical HPV infection, the duration of infection was underestimated because some infections did not clear or some women were lost before the end of the follow-up period.

This natural history study adds to the sparse data on cervical HPV infection in older women. The more rapid clearance of HPV infection among older than younger women may be a chance finding, but may also explain the inverse association of HPV prevalence with age reported by several investigators. The possibility of a biological interaction between HPV types on the acquisition and clearance of viral infection may influence the effectiveness of HPV vaccines and suggest the need for more research among women with multiple HR-HPV cervical infections.

Disclosure of Potential Conflicts of Interest

L. Kamemoto: advisory board, GlaxoSmithKline; speaker's bureau, Merck & Co., Inc. B.Y. Hernandez: commercial research grant, Merck & Co., Inc. The other authors disclosed no potential conflicts of interest.

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Table 3. Median duration and clearance rates of cervical HPV infection by genotype and number of coinfections (Cont'd)

Genotype	No. incident infections*	Woman-months of follow-up †	Median duration (d) ‡ (95% CI)	Patients not cleared after 1 y	All incident infections		No coinfection§		One or more coinfections§	
					No. cleared infections‖	Clearance rate per 1,000 woman-months (95% CI)	No. cleared infections¶	Clearance rate per 1,000 woman-months (95% CI)	No. cleared infections**	Clearance rate per 1,000 woman-months (95% CI)
LR HPV§§	98	761	193 (168–247)	26	72	94.6 (74.1–119.2)	28	36.8 (24.5–53.2)	44	57.8 (42.0–77.6)
Low risk										
6	14	62	154 (113–249)	12	9	145.3 (66.4–275.9)	0	0.0 (0.0–59.6)	9	145.3 (66.4–275.9)
11	5	43	N/A‖‖	75	1	23.3 (0.6–129.9)	0	0.0 (0.0–86.0)	1	23.3 (0.6–129.9)
40	1	0	N/A‖‖	N/A‖‖	0	N/A‖‖	0	N/A‖‖	0	N/A‖‖
42	15	106	185 (174–274)	19	11	103.5 (51.7–185.2)	5	47.1 (15.3–109.8)	6	56.5 (20.7–122.9)
54	28	95	170 (117–248)	0	14	146.6 (80.2–246.1)	3	31.4 (6.5–91.8)	11	115.2 (57.5–206.2)
61	25	162	248 (188–359)	25	13	80.2 (42.7–137.2)	4	24.7 (6.7–63.2)	9	55.5 (25.4–105.4)
72	3	9	136 (130–142)	0	2	220.6 (26.7–796.8)	1	110.3 (2.8–614.5)	1	110.3 (2.8–614.5)
81	11	92	329 (114–563)	25	8	86.8 (37.5–171.1)	3	32.6 (6.7–95.2)	5	54.3 (17.6–126.6)
89	29	166	153 (133–326)	21	20	120.7 (73.7–186.4)	5	30.2 (9.8–70.4)	15	90.5 (50.7–149.3)
Undetermined risk										
34	2	4	133 (N/A‖‖)	0	1	225.6 (5.7–1256.8)	0	0.0 (0.0–832.1)	1	225.6 (5.7–1256.8)
44	17	103	137 (114–632)	49	8	77.6 (33.5–153.0)	3	29.1 (6.0–85.1)	5	48.5 (15.8–113.2)
62	25	164	140 (119–290)	20	16	97.8 (55.9–158.9)	6	36.7 (13.5–79.9)	10	61.1 (29.3–112.5)
67	11	29	127 (98–133)	0	6	206.2 (75.7–448.8)	0	0.0 (0.0–126.8)	6	206.2 (75.7–448.8)
71	2	16	244 (N/A‖‖)	0	1	61.6 (1.6–343.2)	0	0.0 (0.0–227.2)	1	61.6 (1.6–343.2)
83	12	52	N/A‖‖	53	2	38.4 (4.6–138.7)	0	0.0 (0.0–70.8)	2	38.4 (4.6–138.7)
84	33	142	188 (145–236)	0	19	133.8 (80.6–209.0)	2	14.1 (1.7–50.9)	17	119.7 (69.8–191.7)
Species¶¶										
1	39	238	175 (139–274)	20	31	130.2 (88.5–184.8)	10	42.0 (20.1–77.2)	17	71.4 (41.6–114.3)
3	89	482	198 (160–248)	19	60	124.4 (95.0–160.2)	16	33.2 (19.0–53.9)	31	64.3 (43.7–91.3)
5	23	129	167 (135–336)	27	15	115.9 (64.9–191.2)	2	15.5 (1.9–55.8)	12	92.8 (47.9–162.0)
6	40	203	153 (126–226)	15	26	128.0 (83.6–187.5)	9	44.3 (20.3–84.1)	11	54.1 (27.0–96.9)
7	52	325	183 (138–312)	33	36	110.7 (77.6–153.3)	10	30.8 (14.8–56.6)	20	61.5 (37.6–95.0)
9	63	399	246 (181–358)	34	57	143.0 (108.3–185.2)	10	25.1 (12.0–46.1)	21	52.7 (32.6–80.5)
10	32	199	174 (117–563)	37	18	90.6 (53.7–143.1)	3	15.1 (3.1–44.1)	13	65.4 (34.8–111.9)

*Overall number of genotype-specific incident infections: 476, including HR-HPV: 243; LR-HPV: 233.

† Months of follow-up for subjects at risk of clearing an infection.

‡ Estimated by product-limit (Kaplan-Meier) method.

§Other HPV genotypes detected at the clinical visit preceding clearance of the index infection.

‖Number of genotype-specific cleared infections: 265, including HR-HPV: 134; LR-HPV: 131.

¶Number of genotype-specific cleared infections with no coinfection: 64, including HR-HPV: 32; LR-HPV: 32.

**Number of genotype-specific cleared infections with 1+ coinfection: 201, including HR-HPV: 102; LR-HPV: 99.

† † From acquisition of the first HPV type until clearance of the last HPV type. For example, if a woman tested positive for HPV-16 at her second clinical visit and for HPV-81 at her third visit, the absence of HPV-16 at the third visit would not count as a clearance event for any HPV analysis.

‡ ‡ From acquisition of the first HR-HPV type until clearance of the last HR-HPV type. For example, if a woman tested positive for HPV-16 at her second clinical visit and for HPV-18 at her third visit, the absence of HPV-16 at the third visit would not count as a clearance event for HR-HPV analysis.

§§From acquisition of the first LR-HPV type until clearance of the last LR-HPV type. Includes genotypes of undetermined oncogenic risk.

‖‖The indicated statistic could not be estimated from the available data.

¶¶α-Papillomavirus species: species 1 comprises types 42 and 89; species 3 comprises types 61, 62, 72, 81, 83, and 84; species 5 comprises types 26, 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.

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Table 4. Baseline risk factors for clearance of cervical HPV infection

	High-risk HPV				Low-risk HPV*				Any HPV			
	Subjects[†] *n* (=128)	Events[‡] *n* (=162)	Hazard ratio[§] (95% CI)	P_{trend}	Subjects[†] *n* (=126)	Events[‡] *n* (=170)	Hazard ratio[§] (95% CI)	P_{trend}	Subjects[†] *n* (=185)	Events[‡] *n* (=332)	Hazard ratio[§] (95% CI)	P_{trend}
Age (y)												
<25	50	63			41	51			67	114		
25–34	36	38	0.90 (0.64–1.27)		37	44	0.98 (0.70–1.38)		48	82	0.94 (0.74–1.20)	
35–44	19	18	0.95 (0.59–1.54)		21	20	1.12 (0.77–1.64)		30	38	1.03 (0.76–1.40)	
≥45	13	15	1.65 (0.97–2.81)	0.27	14	16	1.62 (0.98–2.67)	0.10	23	31	1.63 (1.14–2.34)	0.05
Ethnicity												
Japanese	13	14			12	14			16	28		
Caucasian	44	47	1.05 (0.66–1.69)		47	58	0.86 (0.54–1.34)		68	105	0.99 (0.71–1.37)	
Hawaiian	12	13	1.06 (0.56–2.00)		14	14	0.94 (0.51–1.71)		18	27	1.02 (0.65–1.59)	
Filipino	6	5	1.06 (0.43–2.59)		5	5	1.22 (0.40–3.69)		8	10	1.12 (0.58–2.14)	
Other	43	55	1.45 (0.88–2.39)		35	40	0.82 (0.51–1.32)		58	95	1.11 (0.79–1.57)	
Income												
<7,500	42	52			29	36			52	88		
7,500–19,999	29	29	0.66 (0.43–1.01)		26	28	1.55 (0.99–2.43)		41	57	0.92 (0.67–1.26)	
20,000–49,999	27	30	1.05 (0.71–1.55)		33	40	0.99 (0.69–1.42)		41	70	0.98 (0.75–1.27)	
≥50,000	13	15	1.00 (0.58–1.72)	0.86	18	20	1.15 (0.75–1.78)	0.93	24	35	1.07 (0.76–1.49)	0.80
Age at menarche												
<12	28	32			33	41			42	73		
12	33	39	1.39 (0.94–2.06)		31	35	0.97 (0.65–1.43)		44	74	1.16 (0.88–1.52)	
13	22	26	0.68 (0.44–1.05)		27	28	0.96 (0.65–1.40)		39	54	0.78 (0.59–1.05)	
≥14	33	36	1.87 (1.23–2.85)	0.19	22	27	0.85 (0.55–1.32)	0.49	41	63	1.27 (0.96–1.69)	0.56
No. pregnancies												
None	50	59			60	72			78	131		
1	32	37	1.00 (0.70–1.42)		20	23	0.59 (0.40–0.86)		39	60	0.77 (0.60–0.99)	
2	12	14	0.85 (0.48–1.52)		11	10	0.63 (0.36–1.10)		17	24	0.72 (0.48–1.07)	
≥3	24	24	0.66 (0.35–1.26)	0.20	22	26	0.65 (0.34–1.23)	0.07	34	50	0.63 (0.40–0.98)	0.02
Age at first sexual intercourse												
<16	23	34			19	21			33	55		
16–17	40	47	0.80 (0.54–1.19)		37	40	1.80 (1.18–2.74)		56	87	1.11 (0.84–1.48)	
18–19	33	29	0.77 (0.46–1.28)		35	47	1.84 (1.21–2.82)		47	76	1.18 (0.86–1.63)	
≥20	22	24	0.78 (0.49–1.25)	0.32	22	23	1.14 (0.71–1.82)	0.56	32	47	0.92 (0.67–1.27)	0.77
No. lifetime sexual partners												
<2	5	4			7	6			9	10		
2–5	42	46	0.71 (0.29–1.75)		36	42	0.82 (0.45–1.50)		59	88	0.79 (0.46–1.35)	
≥6	69	81	0.80 (0.34–1.89)	0.78	67	81	0.66 (0.37–1.19)	0.08	96	162	0.76 (0.45–1.28)	0.44
Oral contraceptive use at baseline												
Never	25	29			21	19			34	48		
Ever	93	105	1.24 (0.86–1.79)		92	112	1.14 (0.78–1.65)		134	217	1.20 (0.93–1.57)	
Past user	42	39	1.43 (0.94–2.18)		45	46	1.03 (0.67–1.59)		65	85	1.23 (0.91–1.66)	
Current user[‖]	51	66	1.14 (0.77–1.68)		47	66	1.24 (0.83–1.84)		69	132	1.18 (0.89–1.57)	
Years of oral contraceptive pill use												
Never used	44	47			42	40			63	87		
<2 y	12	11	1.25 (0.73–2.14)		15	15	0.85 (0.54–1.33)		20	26	1.03 (0.73–1.46)	
2–4 y	23	33	1.24 (0.82–1.86)		22	31	1.08 (0.72–1.62)		32	64	1.16 (0.87–1.56)	
5–9 y	23	24	0.74 (0.48–1.13)		20	25	0.76 (0.50–1.14)		31	49	0.75 (0.56–1.00)	
≥10 y	16	19	0.92 (0.56–1.52)	0.38	14	20	1.09 (0.67–1.78)	0.78	22	39	0.99 (0.69–1.40)	0.36
Hormonal cream use at baseline												
Never	110	124			105	121			157	245		
Past user	4	5	0.86 (0.40–1.84)		5	5	0.69 (0.29–1.60)		6	10	0.78 (0.44–1.36)	
Current user[‖]	4	5	0.51 (0.24–1.08)		3	5	5.05 (2.14–11.90)		5	10	0.90 (0.50–1.61)	
Tobacco smoking history												
Never	79	95			76	94			110	189		
Ever	39	39	0.94 (0.67–1.33)		37	37	0.82 (0.57–1.19)		58	76	0.89 (0.70–1.13)	
Past	20	14	0.60 (0.35–1.01)		20	20	0.99 (0.57–1.72)		33	34	0.76 (0.53–1.09)	

(*Continued on the following page*)

Table 4. Baseline risk factors for clearance of cervical HPV infection (Cont'd)

	High-risk HPV				Low-risk HPV*				Any HPV			
	Subjects† *n* (=128)	Events‡ *n* (=162)	Hazard ratio§ (95% CI)	P_{trend}	Subjects† *n* (=126)	Events‡ *n* (=170)	Hazard ratio§ (95% CI)	P_{trend}	Subjects† *n* (=185)	Events‡ *n* (=332)	Hazard ratio§ (95% CI)	P_{trend}
Current‖	19	25	1.40 (0.95–2.05)		17	17	0.71 (0.47–1.07)		25	42	1.02 (0.77–1.35)	
Alcohol history												
Never	69	81			61	63			95	144		
Ever	49	53	1.07 (0.79–1.45)		52	68	1.14 (0.85–1.53)		73	121	1.12 (0.91–1.37)	
Past	21	17	0.87 (0.54–1.40)		24	27	0.96 (0.66–1.39)		32	44	0.93 (0.70–1.24)	
Current‖	28	36	1.19 (0.84–1.67)		28	41	1.31 (0.93–1.84)		41	77	1.26 (0.99–1.59)	
History of tubal ligation												
No	110	125			103	120			153	245		
Yes	8	9	0.79 (0.42–1.49)		10	11	1.43 (0.85–2.40)		15	20	1.05 (0.69–1.60)	
Condom use at baseline												
No	69	78			73	75			109	153		
Yes‖	49	56	1.19 (0.88–1.60)		40	56	0.93 (0.68–1.26)		59	112	1.07 (0.86–1.32)	
Spermicide use at baseline												
No	99	111			96	106			144	217		
Yes‖	19	23	1.38 (0.88–2.17)		17	25	1.02 (0.69–1.50)		24	48	1.19 (0.89–1.59)	
History of anal sex												
Never	94	104			89	99			133	203		
Ever	24	30	1.30 (0.89–1.90)		24	32	0.60 (0.43–0.84)		35	62	0.90 (0.71–1.15)	
Past	17	22	1.40 (0.94–2.09)		13	18	0.55 (0.36–0.85)		22	40	0.91 (0.67–1.22)	
Current‖	7	8	1.09 (0.54–2.22)		10	13	0.65 (0.43–0.98)		12	21	0.87 (0.62–1.23)	

*Includes undetermined-risk HPV types.
† The number of subjects who completed the questionnaire and at least two clinical visits.
‡ The number of cleared incident HPV infections during the study period.
§Adjusted for age of participants at study entry.
‖Use within the last 4 mo before the first clinical visit.

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