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Risk Factors for Non–Human Papillomavirus (HPV) Type 16/18 Cervical Infections and Associated Lesions Among HPV DNA–Negative Women Vaccinated Against HPV-16/18 in the Costa Rica Vaccine Trial

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Background. Factors that lead human papillomavirus (HPV) infections to persist and progress to cancer are not fully understood. We evaluated co-factors for acquisition, persistence, and progression of non–HPV-16/18 infections among HPV-vaccinated women.

Methods. We analyzed 2153 women aged 18–25 years randomized to the HPV-vaccine arm of the Costa Rica HPV Vaccine Trial. Women were HPV DNA negative for all types at baseline and followed for approximately 11 years. Generalized estimating equation methods were used to account for correlated observations. Time-dependent factors evaluated were age, sexual behavior, marital status, hormonally related factors, number of full-term pregnancies (FTPs), smoking behavior, and baseline body mass index.

Results. A total of 1777 incident oncogenic non–HPV-16/18 infections were detected in 12 292 visits (average, 0.14 infections/visit). Age and sexual behavior–related variables were associated with oncogenic non–HPV-16/18 acquisition. Twenty-six percent of incident infections persisted for ≥1 year. None of the factors evaluated were statistically associated with persistence of oncogenic non–HPV-16/18 infections. Risk of progression to Cervical Intraepithelial Neoplasia grade 2 or worst (CIN2+) increased with increasing age (*P* for trend = .001), injectable contraceptive use (relative risk, 2.61 [95% confidence interval, 1.19–5.73] ever vs never), and increasing FTPs (*P* for trend = .034).

Conclusions. In a cohort of HPV-16/18–vaccinated women, age and sexual behavior variables are associated with acquisition of oncogenic non–HPV-16/18 infections; no notable factors are associated with persistence of acquired infections; and age, parity, and hormonally related exposures are associated with progression to CIN2+.

Keywords. HPV infection; incidence; persistence; progression; CIN2+; HPV vaccine.

Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections. Most women become infected at some point in their lives, but infections are transient and typically clear within a few months to 2 years. A small fraction of women with persistent, oncogenic HPV infections are at risk of development of high-grade precancerous lesions that may progress to cervical cancer if untreated [1, 2]. Approximately 70%–75% of all cervical cancers worldwide are caused by oncogenic HPV types 16 and 18 and the remaining cancers are caused by HPV types 31/33/35/39/45/51/52/56/58/59 [2].

Several viral (eg, viral load, HPV genotypes) and nonviral (eg, smoking, oral contraceptive use, increased number of full-term pregnancies [FTPs]) co-factors have been associated with HPV persistence and progression [1]. However, our understanding of these co-factors and of the natural history of HPV infection is largely driven by studies of HPV-16/18 [2, 3].

Available HPV vaccines (bivalent, quadrivalent, and nonavalent) have the potential to eliminate oncogenic HPV-16/18 infection and associated cervical disease. Evidence from high-income countries indicates that after the introduction of the bivalent and quadrivalent vaccines, the incidence of HPV-16/18 infections is reduced [4]. In some populations, the incidence of the nonvaccine HPV types 31/33/45 has also

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declined, suggesting cross-protection, specifically for the bivalent vaccine [4, 5]. We postulate that HPV infections have independent natural histories; thus, it is important to study whether the natural history of non–HPV-16/18 infections that occur in vaccinated populations differ from that previously observed for HPV-16/18 infections. In the present study, we evaluated risk factors for acquisition, persistence, and progression of non–HPV-16/18 infections in a population of HPV-negative women aged 18–25 years who received the bivalent HPV vaccine.

METHODS

We investigated this research question in women randomized to the HPV-16/18 vaccine arm of the Costa Rica Vaccine Trial (CVT). To be included in this analysis, women had to be HPV DNA negative for all types at baseline (to approximate an adolescent/naive population at vaccination [2153 of the 3727 women in the HPV arm]) and received at least 1 dose of the bivalent HPV vaccine. Women were actively followed for acquisition, persistence, and progression over a period of approximately 11 years.

CVT Study Design

CVT (NCT00128661) is a community-based, double-blind, randomized clinical trial aimed to investigate the safety and efficacy of the HPV-16/18 AS04-adjuvanted vaccine (Cervarix; GlaxoSmithKline Biologicals, Rixensart, Belgium) in the prevention of cervical precancers. The trial methodology has been published elsewhere [6]. In brief, 7466 consenting women aged 18–25 years were randomized 1:1 to receive 3 doses of Cervarix (treatment arm) or hepatitis A vaccine (Havrix, GlaxoSmithKline Biologicals, Rixensart, Belgium; control arm). At enrollment and annual follow-up visits, women provided a serum sample and sexually active women also had a pelvic examination to collect exfoliated cervical cells for cytology and HPV DNA infection determination. Women were followed for 4 years in the blinded phase, referred to as CVT. Women were provided cervical cancer screening via cytology with HPV triage of atypical squamous cells of unknown significance [7]. See Supplementary Methods for more information.

After the 4-year visit of CVT, women were invited to participate in an unblinded long-term follow-up (LTFU) study to evaluate the long-term risks and benefits of the prophylactic HPV vaccine over a decade. Detailed rationale and methods for LTFU are published elsewhere [7]. Approximately 80% (2919/3687) of the eligible HPV-vaccinated women were enrolled in the LTFU study. Clinician-collected cervical samples were obtained in years 7, 9, and 11. Once every 2 years, women underwent HPV DNA detection and cervical cancer screening, although more often if clinically indicated [7, 8] (see Supplementary Methods for more details).

During the 11 years of follow-up, women referred to colposcopy had a biopsy taken for histological evaluation. Women with histological Cervical Intraepithelial Neoplasia grade 2 or worst (CIN2+) lesions or with worrisome virologic patterns were treated by loop electrosurgical excisional procedure. Protocols were approved by the United States National Cancer Institute and the Costa Rica institutional review boards [6, 7].

HPV DNA Detection and Genotyping

Cervical specimens collected during the first 4 years of CVT and the early years of LTFU were tested at Delft Diagnostics Laboratory (Netherlands) using broad-spectrum polymerase chain reaction (PCR)–based HPV DNA testing using the SPF10 DNA enzyme immunoassay (DEIA) system and the LiPA25 line detection system [6, 9, 10]. If HPV DNA results from SPF10 DEIA were positive and LiPA25 was negative for HPV-16/18, specimens were tested for the presence of HPV-16 and HPV-18 using type-specific PCR primer sets [10]. Specimens collected during the later years of the LTFU study were tested at the National Cancer Institute Cancer Genomics Research Laboratory using a next-generation sequencing assay (TypeSeq). TypeSeq detects viral DNA for 51 HPV genotypes [11]. SPF10-LiPA25 and TypeSeq results had a 93.1% positive agreement for detecting any oncogenic HPV type; the agreement for non–HPV-16/18 oncogenic types ranged from 71.4% (HPV-59) to 100% (HPV-58), and no difference in vaccine efficacy was observed when using either test to define outcomes [12]. HPV determination was based on SPF10-LiPA25 for the initial 4 years of the study and on SPF10-LiPA25 or TypeSeq results thereafter. At some timepoints, a woman had HPV results available from both testing methods, SPF10-LiPA25 and TypeSeq. In these cases, we selected the most common method used at that timepoint and the less common method only when it was the sole option. Thus, the primary testing used was SPF10-LiPA25 for year 7 and TypeSeq for years 9 and 11 and intervening clinical management study visits. Sensitivity analyses that utilized alternative approaches to HPV classification yielded comparable results (data not shown).

Outcomes

An incident (acquisition) HPV infection was defined as a type-specific cervical HPV infection that was not present/detected at the previous scheduled visit (years 1, 2, 3, 4, 7, 9, and 11). Note, there could be multiple incident infections within a woman at a given visit. Persistence of an HPV infection was defined as the incident HPV infection persisting for at least 1 year, with the second detection at least 300 days after incidence without an intervening negative test. Progression was defined as the occurrence of CIN2+ histological diagnosis at a visit with a persistent infection.

Exposures

At each scheduled study visit, women responded to a structured questionnaire that included socioeconomic indicators, smoking, sexual and reproductive history, and contraceptive use [6, 7]. Factors for acquisition, persistence, and progression of non–HPV-16/18 infections included age, sexual behavior (age at first sexual intercourse [AFI], lifetime number of sexual partners [LNSP], monthly frequency of sex, marital status), contraceptive use (oral contraceptives [OC], injectable contraceptives, condoms, and other infrequent [<5%] contraceptive methods), number of FTPs, smoking behavior (status, intensity, age of initiation), and body mass index (BMI). BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2). All of these exposures were considered time-dependent in the analyses, except for BMI (measured at enrollment).

Statistical Analysis

We first evaluated the relationship between risk factors and incidence of infection. We categorized each risk factor (eg, for age, we used 18–21, 22–25 years, etc) and then report the corresponding number of scheduled visits (eg, number of visits where the woman was 18–21 years old) and the number of incident infections occurring at those visits. Moreover, we reported the relative risk (RR) of acquiring an incident infection for each category. To calculate the RR, we created a dataset with 121 296 rows ≈ number of women × number of scheduled visits × number of infection types. Scheduled visits included follow-up visits at years 1, 2, 3, 4, 7, 9, and 11 (ie, not accelerated screening or colposcopy visits). We estimated the RRs using generalized estimating equations (GEEs) with incident infection as the dependent variable, the risk factor as the independent variable, subject as the cluster, an independent working correlation matrix, and a log-link function [13]. The risk factor was included as a continuous variable to obtain *P* values for trend (P_{trend}). Our "base" models were adjusted for HPV type and our "adjusted" models also adjusted for assay type (SPF10-LiPA25/TypeSeq), visit protocol (CVT/LTFU), missed previous visit (yes/no), time since last HPV test, age, smoking, OC use, AFI, LNSP, frequency of sex, number of FTPs, and marital status.

We next evaluated the relationship between risk factors and persistence of an infection. We report the number of incident infections that occurred at scheduled visits (years 1, 2, 3, 4, 7, 9, and 11, excluding accelerated screening and colposcopy visits) within each category and then report the proportion of those infections that persisted for ≥1 year. While a persistent infection needed to be identified in a scheduled visit, we used both scheduled visits and accelerated screening visits to confirm persistence. We used GEEs to estimate the RR of persistence. Our dataset was restricted to incident infections that occurred at least 300 days prior to the final visit and was the first of its type. Our "base" models had no adjustments and our "adjusted" models adjusted for assay type at both incident (ie, visit with incident infection) and test visits (eg, first visit >300 days after incidence), visit protocol, missed visit prior to incident-visit, time between incident and test visits, number of visits between the incident visit and test visit, time between incident visit and its prior visit, age, smoking, OC use, AFI, LNSP, frequency of sex, number of FTPs, and marital status.

Finally, we evaluated the relationship between risk factors and progression to CIN2+. Following the above ideas, we report the number of visits where there was a persistent infection and the proportion of those visits where there was also a CIN2+ lesion (ie, progression). For this analysis, we included all visits with a persistent infection—that is, a persistent infection can be identified at a scheduled visit or at an accelerated screening visit. Women were truncated at their first CIN2+ lesion. We truncated follow-up at the time of treatment, as treatment of lesions interrupts their natural history. We used GEEs to estimate the RR but, because of the limited number of CIN2+ lesions, we only adjusted for age, number of oncogenic HPV persistent infections, and duration of the longest oncogenic HPV infection present.

We present acquisition, persistence, and progression models for oncogenic non–HPV-16/18 infections (types 31/33/35/39/45/51/52/56/58/59) in the main text and models for acquisition and persistence for "any" non–HPV-16/18 infections (oncogenic non–HPV-16/18 types and HPV-6/11/34/40/42/43/44/53/54/66/70/74/68/73) in Supplementary Tables 1 and 2. We tested numerous relationships, and therefore a significance threshold of $P = .05$ can only be considered suggestive evidence of a relationship. All reported *P* values are 2-sided. Statistical analyses were conducted using PROC GENMOD in SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Determinants of Acquisition of Oncogenic Non–HPV-16/18 Infections

We evaluated the relationship between risk factors and acquisition of HPV infection (Table 1). During the 11 years of follow-up in 2153 vaccinated women, we detected 1777 incident oncogenic non–HPV-16/18 infections during 12 292 visits (average, 0.14 HPV infections/visit). The risk of oncogenic non–HPV-16/18 acquisition decreased with increasing age ($P_{trend} < .001$) and risk of acquisition increased with increasing AFI ($P_{trend} < .001$) and with increasing LNSP ($P_{trend} < .001$). Unmarried women had twice the risk of oncogenic non–HPV-16/18 acquisition as married women (RR, 2.08 [95% confidence interval {CI}, 1.81–2.38] vs no).

Table 1. Determinants of Acquisitionof Oncogenic Non–Human Papillomavirus 16/18 Infections

Characteristics	No. of Visits	% of Visits	No. of Incident Infections	Average No. of Incident Infections per Visit	Unadjusted RR[a] (95% CI)	Adjusted RR[b] (95% CI)
Age, y						
18–21	1941	15.8	297	0.153	0.99 (.82–1.20)	2.47 (1.81–3.36)
22–25	3967	32.3	573	0.144	0.96 (.82–1.13)	1.83 (1.42–2.36)
26–29	3640	29.6	513	0.141	0.96 (.83–1.12)	1.37 (1.14–1.66)
30–37	2744	22.3	394	0.144	Reference	Reference
P value for trend					.89	<.001
Sexual behavior (among sexually active)						
AFI, y						
≤15	2695	25.2	367	0.136	0.70 (.60–.81)	0.71 (.59–.84)
16–17	2932	27.4	465	0.159	0.84 (.73–.96)	0.91 (.78–1.05)
≥18	5089	47.5	945	0.186	Reference	Reference
P value for trend					<.001	<.001
LNSP						
1	4002	32.6	428	0.107	Reference	Reference
2–3	3850	31.3	712	0.185	1.78 (1.54–2.06)	1.67 (1.43–1.95)
≥4	2869	23.3	637	0.222	2.13 (1.84–2.47)	2.07 (1.74–2.48)
P value for trend					<.001	<.001
Monthly frequency of sexual intercourse since last visit						
≤1	1173	11.2	230	0.196	1.40 (1.16–1.67)	0.77 (.62–.95)
2–4	2490	23.7	502	0.202	1.45 (1.26–1.67)	1.01 (.87–1.18)
5–9	2716	25.9	393	0.145	1.04 (.90–1.20)	0.97 (.84–1.13)
≥10	4129	39.3	589	0.143	Reference	Reference
P value for trend					<.001	.097
Married/living as married						
Yes	7213	59.0	829	0.115	Reference	Reference
No	5018	41.0	933	0.186	1.65 (1.47–1.84)	2.08 (1.81–2.38)
Contraceptive use (among sexually active)						
Use of oral contraceptives						
Never	1512	15.6	302	0.200	Reference	Reference
Ever	8181	84.4	1299	0.159	0.79 (.68–.93)	1.12 (.95–1.33)
Use of injectable contraceptives						
Never	4802	50.4	865	0.180	Reference	Reference
Ever	4721	49.6	736	0.156	0.89 (.79–1.01)	1.15 (.99–1.33)
Use of condoms						
Never	2762	31.0	379	0.137	Reference	Reference
Ever	6155	69.0	1074	0.174	1.32 (1.14–1.53)	1.03 (.88–1.20)
Use of other contraceptive method[c]						
Never	8732	82.6	1494	0.171	Reference	Reference
Ever	1840	17.4	251	0.136	0.81 (.69–.95)	0.87 (.73–1.04)

Table 1. Continued

Characteristics	No. of Visits	% of Visits	No. of Incident Infections	Average No. of Incident Infections per Visit	Unadjusted RR[a] (95% CI)	Adjusted RR[b] (95% CI)
No. of full–term pregnancies						
0	4479	36.4	678	0.151	Reference	Reference
1–2	6524	53.1	909	0.139	0.92 (.81–1.05)	0.85 (.73–.99)
≥3	1289	10.5	190	0.147	0.99 (.81–1.20)	1.11 (.88–1.40)
P value for trend					.49	.78
Smoking behavior						
Smoking status						
Never smoked	10 539	85.7	1425	0.135	Reference	Reference
Ever	1753	14.3	352	0.201	1.45 (1.26–1.67)	1.03 (.88–1.20)
Among smokers, No. of cigarettes/wk						
1–5	729	42.4	163	0.224	Reference	Reference
6–20	613	35.6	108	0.176	0.82 (.62–1.09)	1.00 (.75–1.33)
>20	378	22.0	73	0.193	0.74 (.54–1.01)	0.70 (.50–.97)
P value for trend					.050	.057
Among smokers, age at smoking initiation, y						
≤14	222	12.7	30	0.135	0.53 (.35–.80)	0.58 (.38–.87)
15–18	787	44.9	144	0.183	0.74 (.57–.96)	0.63 (.48–.82)
≥19	744	42.4	178	0.239	Reference	Reference
P value for trend					.001	.001
BMI at enrollment						
Underweight (<18.5 kg/m^2)	925	7.5	176	0.190	1.29 (1.04–1.59)	1.20 (.99–1.46)
Normal (18.5–24.9 kg/m^2)	6761	55.0	1019	0.151	Reference	Reference
Overweight (25–29.9 kg/m^2)	2846	23.2	361	0.127	0.85 (.73–.98)	0.92 (.79–1.07)
Obese (≥30 kg/m^2)	1760	14.3	221	0.126	0.84 (.69–1.02)	0.93 (.76–1.14)
P value for trend					.001	.067

Abbreviations: AFI, age at first sexual intercourse; BMI, body mass index; CI, confidence interval; LNSP, lifetime number of sexual partners; RR, relative risk.

[a]Unadjusted model controls for human papillomavirus (HPV) type.

[b]Adjusted model includes HPV type, assay type (includes all combinations of assay prior to incident infection and assay of incident infection; SPF10–LiPA25/TypeSeq for each), visit protocol (Costa Rica Vaccine Trial/long-term follow-up), missed previous visit (yes/no), time since last HPV test (using a 4 degrees of freedom [*df*] cubic spline of log[time]), visit age (using a 4 *df* cubic spline of age), smoking, oral contraceptive use, AFI, LNSP, monthly frequency of sexual intercourse since last visit, number of full-term pregnancies, and marital status.

[c]Diaphragm, sponge, spermicide, intrauterine device, and others.

Table 2. Determinants of Persistence of Oncogenic Non–Human Papillomavirus 16/18 Infections

Characteristics	No. of Incident Infections	No. of Persistent Infections	% of Infections That Persist	Unadjusted RR (95% CI)	Adjusted RR[a] (95% CI)
Age, y					
18–21	265	63	23.8	0.74 (.55–.98)	0.81 (.53–1.25)
22–25	506	113	22.3	0.69 (.54–.88)	0.81 (.57–1.15)
26–29	433	118	27.3	0.84 (.67–1.07)	0.97 (.74–1.26)
30–37	251	81	32.3	Reference	Reference
P value for trend				.009	.28
Sexual behavior					
AFI, y					
≤15	284	75	26.4	1.03 (.81–1.30)	1.12 (.85–1.47)
16–17	390	99	25.4	0.99 (.80–1.22)	0.99 (.79–1.25)
≥18	781	201	25.7	Reference	Reference
P value for trend				.88	.49
LNSP					
1	374	95	25.4	Reference	Reference
2–3	597	154	25.8	1.02 (.81–1.28)	1.00 (.79–1.27)
≥4	484	126	26.0	1.02 (.81–1.30)	0.96 (.73–1.26)
P value for trend				.84	.76
Monthly frequency of sexual intercourse since last visit					
≤1	198	58	29.3	1.19 (.89–1.59)	1.21 (.88–1.68)
2–4	407	107	26.3	1.07 (.85–1.34)	1.08 (.84–1.38)
5–9	325	83	25.5	1.04 (.80–1.34)	1.00 (.78–1.29)
≥10	476	117	24.6	Reference	Reference
P value for trend				.25	.29
Married/living as married					
Yes	666	173	26.0	Reference	Reference
No	780	200	25.6	0.99 (.82–1.19)	0.98 (.78–1.22)
Contraceptive use (among sexually active)					
Use of oral contraceptives					
Never	263	70	26.6	Reference	Reference
Ever	1039	272	26.2	0.98 (.77–1.25)	0.89 (.69–1.14)
Use of injectable contraceptives					
Never	714	184	25.8	Reference	Reference
Ever	591	154	26.1	1.01 (.84–1.22)	0.88 (.70–1.12)
Use of condoms					
Never	320	83	25.9	Reference	Reference
Ever	839	220	26.2	1.01 (.81–1.26)	1.01 (.79–1.29)
Use of other contraceptive method[b]					
Never	1241	327	26.4	Reference	Reference
Ever	193	44	22.8	0.87 (.65–1.15)	0.78 (.57–1.06)

Table 2. Continued

Characteristics	No. of Incident Infections	No. of Persistent Infections	% of Infections That Persist	Unadjusted RR (95% CI)	Adjusted RR[a] (95% CI)
No. of full–term pregnancies					
0	579	138	23.8	Reference	Reference
1–2	723	188	26.0	1.09 (.89–1.33)	1.05 (.83–1.33)
≥3	153	49	32.0	1.34 (1.02–1.78)	1.07 (.75–1.53)
P value for trend				.059	.68
Smoking behavior					
Smoking status					
Never smoked	1178	316	26.8	Reference	Reference
Ever	277	59	21.3	0.79 (.62–1.01)	0.86 (.67–1.11)
Among smokers, No. of cigarettes/wk					
1–5	123	18	14.6	Reference	Reference
6–20	93	25	26.9	1.84 (1.10–3.07)	1.65 (.97–2.81)
>20	55	13	23.6	1.62 (.87–3.01)	1.54 (.80–2.94)
P value for trend				.051	.074
Among smokers, age at smoking initiation, y					
≤14	20	7	35.0	1.55 (.67–3.60)	2.76 (1.29–5.89)
15–18	111	19	17.1	0.76 (.47–1.21)	0.91 (.55–1.53)
≥19	146	33	22.6	Reference	Reference
P value for trend				.87	.15
BMI at enrollment					
Underweight (<18.5 kg/m^2)	141	48	34.0	1.37 (1.06–1.78)	1.46 (1.11–1.92)
Normal (18.5–24.9 kg/m^2)	826	205	24.8	Reference	Reference
Overweight (25–29.9 kg/m^2)	307	71	23.1	0.93 (.73–1.18)	1.04 (.81–1.33)
Obese (≥30 kg/m^2)	181	51	28.2	1.14 (.87–1.48)	1.20 (.91–1.58)
P value for trend				.44	.78

Abbreviations: AFI, age at first sexual intercourse; BMI, body mass index; CI, confidence interval; LNSP, lifetime number of sexual partners; RR, relative risk.

[a]Adjusted model includes assay (includes all combination of assay of prior incident infection assay of incident infection, and first assay after 300 days—the assay used to declare persistence; SPF10–LiPA25/TypeSeq for each), number of tests between incident and persistent infection (0, ≥1), time between test prior to incident infection and incident infection (using a 3 degrees of freedom [*df*] cubic spline of log[time]), time between test for incident infection and first test after 300 days (using a 3 *df* cubic spline of log[time]), visit protocol (Costa Rica Vaccine Trial/long-term follow-up), missed previous visit (yes/no), visit age (using a 3 *df* cubic spline of age), smoking, oral contraceptive use, age at first sexual intercourse, LNSP, monthly frequency of sexual intercourse since last visit, number of full-term pregnancies, and marital status.

[b]Diaphragm, sponge, spermicide, intrauterine device, and others.

Table 3. Determinants of Progression to Cervical Intraepithelial Neoplasia grade 2 or worst (CIN2+) of Oncogenic Non–Human Papillomavirus 16/18 Persistent Infections

Characteristics	No. of Persistent Infections	No. of Visits With a Persistent Infection	No. of Visits With a Persistent Infection and CIN2+	Proportion Visits With Progression	Unadjusted RR (95% CI)	Adjusted RR[a] (95% CI)
Age, y						
18–21	50	47	0	0.000	0	0
22–25	215	190	2	0.011	0.15 (.04–.63)	0.16 (.04–.63)
26–29	273	252	12	0.048	0.69 (.35–1.34)	0.71 (.37–1.36)
30–37	340	317	22	0.069	Reference	Reference
P value for trend					.001	.001
Sexual behavior (among sexually active)						
AFI, y						
≤15	196	177	6	0.034	0.88 (.37–2.09)	0.79 (.34–1.84)
16–17	233	216	14	0.065	1.67 (.85–3.29)	1.70 (.86–3.36)
≥18	449	413	16	0.039	Reference	Reference
P value for trend					.89	.90
LNSP						
1	149	140	7	0.050	Reference	Reference
2–3	375	341	12	0.035	0.70 (.29–1.70)	0.67 (.28–1.59)
≥4	354	325	17	0.052	1.05 (.46–2.37)	0.79 (.35–1.79)
P value for trend					.69	.76
Monthly frequency of sexual intercourse since last visit						
≤1	112	97	4	0.041	0.81 (.28–2.29)	0.78 (.28–2.21)
2–4	267	240	10	0.042	0.81 (.38–1.72)	0.81 (.38–1.70)
5–9	173	159	6	0.038	0.74 (.30–1.79)	0.71 (.29–1.71)
≥10	309	293	15	0.051	Reference	Reference
P value for trend					.59	.56
Married/living as married						
Yes	444	426	23	0.054	Reference	Reference
No	431	377	13	0.034	0.64 (.34–1.21)	0.71 (.38–1.33)
Contraceptive use (among sexually active)						
Use of oral contraceptives						
Never	117	108	2	0.019	Reference	Reference
Ever	719	662	33	0.050	2.69 (.65–11.10)	1.74 (.42–7.14)
Use of injectable contraceptives						
Never	396	367	7	0.019	Reference	Reference
Ever	434	397	27	0.068	3.57 (1.63–7.78)	2.61 (1.19–5.73)
Use of condom						
Never	179	173	7	0.040	Reference	Reference
Ever	619	564	27	0.048	1.18 (.54–2.61)	1.21 (.52–2.79)
Use of other contraceptive method[b]						
Never	737	673	31	0.046	Reference	Reference
Ever	129	122	5	0.041	0.89 (.36–2.20)	0.75 (.30–1.85)

Table 3. Continued

Characteristics	No. of Persistent Infections	No. of Visits With a Persistent Infection	No. of Visits With a Persistent Infection and CIN2+	Proportion Visits With Progression	Unadjusted RR (95% CI)	Adjusted RR[a] (95% CI)
No. of full–term pregnancies						
0	288	256	4	0.016	Reference	Reference
1–2	463	435	21	0.048	3.09 (1.10–8.64)	2.03 (.74–5.60)
≥3	127	115	11	0.096	6.12 (2.06–18.20)	3.03 (1.01–9.08)
P value for trend					<.001	.034
Smoking behavior						
Smoking status						
Never smoked	704	646	25	0.039	Reference	Reference
Ever	174	160	11	0.069	1.78 (.92–3.41)	1.71 (.91–3.23)
Among smokers, No. of cigarettes/wk						
1–5	77	74	5	0.068	Reference	Reference
6–20	56	49	3	0.061	0.91 (.27–3.07)	0.56 (.16–1.91)
>20	30	27	1	0.037	0.55 (.07–4.35)	0.24 (.06–.93)
P value for trend					.57	.064
Among smokers, age at smoking initiation, y						
≤14	19	17	0	0.000	0	0
15–18	47	47	0	0.000	0	0
≥19	108	96	11	0.115	Reference	Reference
P value for trend					NA	NA
BMI at enrollment						
Underweight (<18.5 kg/m^2)	102	92	4	0.043	0.98 (.36–2.71)	1.23 (.44–3.39)
Normal (18.5–24.9 kg/m^2)	499	452	20	0.044	Reference	Reference
Overweight (25–29.9 kg/m^2)	175	167	9	0.054	1.22 (.60–2.49)	1.13 (.56–2.29)
Obese (≥30 kg/m^2)	102	95	3	0.032	0.71 (.22–2.29)	0.60 (.18–1.94)
P value for trend					.85	.42

Abbreviations: AFI, age at first sexual intercourse; BMI, body mass index; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worst; LNSP, lifetime number of sexual partners; NA, not applicable; RR, relative risk.

[a]Adjusted model includes visit age (using a 3 degrees of freedom cubic spline of age), time of the longest oncogenic human papillomavirus (HPV) incident persistent infection (above or below the median infection length of 643.5 days), and number of oncogenic HPV persistent infections at that visit (1 vs >1).

[b]Diaphragm, sponge, spermicide, intrauterine device, and others.

None of the contraception methods evaluated were statistically associated with oncogenic non–HPV-16/18 acquisition, except for suggestive evidence of a relationship with injectable contraceptive use (RR, 1.15 [95% CI, .99–1.33] ever vs never). Smoking status was not associated with oncogenic non–HPV-16/18 acquisition but among smokers, there was a slight reduction in acquisition with increasing smoking intensity (P_{trend} = .057) and a slight increase in risk with increasing age at smoking initiation (P_{trend} = .001). We found a statistically insignificant decrease in risk of infection with increasing BMI at enrollment (P_{trend} = .067). Similar associations were obtained for the acquisition of "any" non–HPV-16/18 infection (Supplementary Table 1).

We further explored the combined relationship between AFI, LNSP, and acquisition of oncogenic non–HPV-16/18 infections. We observed positive associations for both AFI and LNSP within strata of the other, suggesting independent effects (data not shown).

Determinants of Persistence of Oncogenic Non–HPV-16/18 Incident Infections

We evaluated the relationship between risk factors and persistence in 1455 qualifying infections (Table 2); we did not have sufficient follow-up time to define persistence for 322 incident oncogenic non–HPV-16/18 infections. Twenty-six percent (375/1455) of oncogenic non–HPV-16/18 incident infections persisted for 1 year or longer. After adjusting for OC use, sexual behavior variables, marital status, and number of FTPs, none of the factors evaluated had statistically significant associations with persistence. We noted a suggestive evidence of a relationship between OC use (RR, 0.89 [95% CI, .69–1.14] for ever vs never), injectable contraceptive use (RR, 0.88 [95% CI, .70–1.12] for ever vs never), other contraceptive method use (RR, 0.78 [95% CI, .57–1.06] for ever vs never), and persistent oncogenic non–HPV-16/18 infections. Although there was not a linear trend with age at smoking initiation or increasing smoking intensity, the risk of persistence was approximately 3-fold higher for smoking initiation at ≤14 years (vs ≥19 years) and approximately 1.5-fold higher in underweight women (vs normal weight). Similar associations were obtained for the persistence of "any" non–HPV-16/18 infections (Supplementary Table 2).

Determinants of Progression to CIN2+ of Oncogenic Non–HPV-16/18 Incident Persistent Infections

We evaluated the relationship between risk factors and progression to CIN2+ at 878 follow-up visits with at least 1 persistent infection (Table 3). There were 36 visits with both a persistent infection and CIN2+ diagnosis. After adjusting for number of persistent oncogenic HPV infections and time of the longest oncogenic infection, the risk of progression to CIN2+ increased with increasing age (P_{trend} = .001). In the models that further adjusted by age, the use of injectable contraceptives was associated with a 2.6-fold (95% CI, 1.19–5.73) increase in the risk of progression to CIN2+ and OC use with a nonsignificant 1.7-fold increase in risk of progression to CIN2+ (95% CI, .42–7.14) as compared to never users. There was a significant trend of increased risk of progression to CIN2+ with an increased number of FTPs (P_{trend} = .034). No apparent associations with progression to CIN2+ were observed for smoking or sexual behavior variables, marital status, condom use, other contraceptive methods, or BMI.

Although limited by the number of CIN2+ cases, to explore whether observed effects for age, injectable contraceptives, and FTPs were independent of each other, we evaluated models in which we mutually adjusted for these variables. The effect of age remained after control for injectable contraceptives and FTPs (P_{trend} = .013). The effects of injectable contraceptives and FTPs were evident after control for age but were no longer statistically significant (although patterns remained comparable to those shown in Table 3) upon further control for each other (P = .05 for injectable contraceptive use; P_{trend} = .41 for FTPs).

Finally, we explored risk of progression of persistent HPV-31/35/52/58 to CIN2+ and obtained similar results (data not shown), as these were the most frequent persistent infections (30 of the 36 visits had both a persistent HPV-31/35/52/58 infection and CIN2+ diagnosis). We were unable to evaluate the risk of progression by other specific HPV types because of small sample sizes (Supplementary Table 3).

DISCUSSION

Much of what we know about the factors associated with acquisition, persistence, and progression of HPV infections is driven by our understanding of HPV-16/18 among unvaccinated women. We evaluated factors associated with acquisition, persistence, or progression of cervical oncogenic non–HPV-16/18 infections in the absence of HPV-16/18, among a cohort of >2000 HPV DNA–negative women vaccinated against HPV-16/18 and followed for 11 years. Our results are consistent with previous work showing that sexual behavior variables determine acquisition of oncogenic non–HPV-16/18 infections; identified no sociodemographic, behavioral, or exogenous factors to be associated with persistence of newly acquired infections; and importantly noted that hormonal/reproductive factors were significantly associated with risk of progression to precancer among women with persistent infections.

With respect to acquisition of non–HPV-16/18 oncogenic infections, our findings largely support previous work among unvaccinated populations that demonstrated a strong association between sexual behavior and HPV acquisition [14–16], and declining acquisition with increasing age [14–20]. Specifically, we found that increasing LNSP and living as unmarried increased the risk of oncogenic non–HPV-16/18

acquisition. Surprisingly, we note that early AFI was associated with a reduced risk of acquisition, which contrasts with previous studies that consistently observed those with earlier AFI to have an increased risk of HPV acquisition. To fully explore this association, we stratified AFI by LNSP and confirmed that the reduced risk associated with early AFI was observed within each stratum of LNSP, thus confirming that the observed association with AFI was not explained by LNSP. Early AFI can be a marker of risky behaviors; thus, one could speculate that increased HPV exposure at young ages among those who initiate sexual activity earlier would lead to a better ability to control infections that occur in later years. Replication of this finding is needed before drawing strong conclusions.

Even though we evaluated nearly 1500 incident oncogenic non–HPV-16/18 infections and 26% of these infections persisted ≥1 year, none of the risk factors evaluated were consistently associated with persistence of incident infections. We observed significant increases in risk of persistence for women who initiated smoking early and women who were underweight. However, in the absence of an effect for current/past smokers and a lack of a dose-response relationship for either smoking or BMI, we interpret these results with caution. Further corroborations from additional prospective studies are required before drawing any conclusions. Of note, we were unable to evaluate the host's immunological responses or viral characteristics as a determinant of oncogenic non–HPV-16/18 persistence in our study. It is likely that such responses/characteristics play a role on whether an HPV infection persists or clears [1].

Our findings with respect to factors associated with progression were notable. We found that, independent of age, the number of FTPs had the strongest and most consistent associations with progression to CIN2+, with a significant dose response and RRs increasing to 3 (for any oncogenic non–HPV-16/18) for women who reported >2 FTPs. We also observed that, independent of age, ever use of injectable contraceptives was associated with 2.6-fold increase in the risk of cervical precancer and, although not statistically significant, it is interesting to note that OC use was associated with a near 2-fold increase in risk of cervical precancer. Due to limited numbers, we were unable to fully evaluate whether effects of injectable contraceptives and number of FTPs were independent of each other. These findings, which suggest that endogenous and exogenous hormonal factors are important determinants of progression of persistent oncogenic incident non–HPV-16/18 infections, are largely consistent with studies in which the majority of CIN2+ cases were caused HPV-16/18 [21–30]. More specifically, multiple prevaccination era studies reported a dose-response relationship between pregnancies and cervical precancer/cancer [25, 28–31]. However, studies of unvaccinated women that evaluated the association between hormonal contraceptive use and cervical precancer/cancer yielded mixed results, with some studies showing positive associations [21–26] but others not [27, 32–34].

Possible biological explanations for these findings should be considered. Increased hormonal levels and impaired immune response during pregnancy might facilitate HPV exposure or enhance the role of HPV in cervical carcinogenesis; also, cervical trauma during delivery may explain the increased risk of precursor lesions and cervical cancer [29–31, 35–41]. It is unclear how hormonal contraceptive use might affect HPV acquisition or persistence, but published work points to a promoting effect of estrogens on the cervical carcinogenesis process initiated by HPV infection [21, 26, 33].

Smoking is an established HPV cofactor for the development of precursor lesions and cervical cancer [1]. We did not observe smoking to be associated with progression of persistent oncogenic non–HPV-16/18 infections, perhaps due to the small proportion (16%) of women who reported being ever smokers in our study.

Major strengths of this work are the sample size and follow-up, at ages when HPV acquisition rates are high. Another important strength is our ability to exclude women with prevalent infections at enrollment. This cohort allowed us to investigate the influence of risk factors on each stage in the natural history from HPV acquisition to persistence to progression to CIN2+. Despite the large sample size of our cohort, we were limited by the modest number of incident CIN2+ cases that developed during follow-up and were unable to evaluate individual or phylogenetically related groupings of HPV types. Nonetheless, we found that the most frequently persistent oncogenic HPV types in incident CIN2+ cases were HPV-31/35/52/58 (α-9 group) and HPV-39/59/68 (α-7 group), which have been frequently associated with cervical cancer [42]. Finally, we were unable to evaluate immunological responses to infection or viral characteristics that might be important determinants of persistence/progression.

In conclusion, our results revealed that age and sexual behavior variables are associated with the acquisition of oncogenic non–HPV-16/18 infections; there are no behavioral/modifiable factors that strongly affect the risk of persistence of acquired infections; and age, parity and hormonally related exposures are associated with the progression of persistent infections to CIN2+. Results from our study may be generalizable to women without evidence of previous HPV exposure at time of vaccination with the bivalent HPV vaccine, a target group of adolescent/naive populations for whom vaccination could have the most impact. As more countries adopt HPV vaccination, understanding the co-factors for persistence and progression of oncogenic non–HPV-16/18 infections becomes more relevant, because current vaccines do not provide protection against all oncogenic HPV types that can cause cervical cancer.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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