

# Concurrent and Sequential Acquisition of Different Genital Human Papillomavirus Types

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Coinfection with multiple types of genital human papillomavirus (HPV) has been reported, but how frequently it occurs and whether prior infection with specific HPV types inhibits subsequent infection by related types are not known. To address this, 518 women were followed for an average of 2.9 years, and behavioral information and cervical and vulvovaginal swabs for HPV DNA assay were obtained at 4-month intervals. A polymerase chain reaction-based method was used to detect types frequently found in cervical cancers (HPV 16, 18, 31, and 45) and in genital warts (HPV 6 and 11). Concurrent acquisition of multiple types occurred more often than expected by chance. However, no 2 types were more or less likely to be acquired concurrently than any other 2 types. When considering sequential acquisition of HPV types, we found that risk of acquiring a new HPV type was not decreased among those with prior infection by a phylogenetically related or unrelated type (hazard ratio [95% confidence interval], 1.0 [0.4–3.0] and 1.3 [0.8–2.1], respectively).

The study of genital human papillomavirus (HPV) has intensified since the identification of an HPV type 16 genome in cervical carcinoma tissue [1, 2]. A causal relationship has been clearly established between specific HPV types and cervical cancer [3], and >90% of cervical cancers are positive for HPV DNA [4]. HPV types commonly found in cervical carcinomas and considered to be oncogenic include HPV 16, 18, 31, and 45. [4, 5]. Types rarely found in cancers include HPV 6, 11, 42, 43, and 44 [5]. Other types (HPV 33, 35, 39, 51, 52, 56, 58, 59, and 69) are also considered to be oncogenic but are detected less frequently in cervical cancers [4].

Genital HPV infection is largely asymptomatic; it is also highly prevalent among young, sexually active populations [6–8]. Although detection of infection by multiple genital HPV types has been observed [9, 10], little is known about the frequency of coinfection, or whether certain HPV types are more or less likely to be acquired together. Similarly, the extent to which prior HPV infection reduces risk for subsequent infection by phylogenetically related types (that is, HPV 6 and 11, HPV 16 and 31, and HPV 18 and 45 [11]) or unrelated types is not known. In vitro and epidemiologic studies suggest that the hu-

moral immune response to HPV is largely type specific [12, 13], but studies of natural infection by different HPV types have not yet been reported.

Here, we report on coinfections of HPV types in a cohort study of university women. We considered both concurrent and sequential infections. Our main goal was to determine whether persons infected with a specific genital HPV type were at less risk than those not infected with this specific type for acquiring a phylogenetically related type.

## Materials and Methods

*Study population and data collection.* Female students 18–20 years old were recruited from the University of Washington, Seattle, for participation in an ongoing cohort study of the acquisition and natural history of genital HPV infections. Methods of recruitment and data collection for the study have been described elsewhere [13]. Briefly, young women were recruited by letters of invitation mailed to a random sample of 18–20-year-old female university students. Those who responded were eligible if they planned to stay in the area for  $\geq 3$  years and were able to provide informed consent. Six hundred three subjects were enrolled between 1990 and 1997. Study visits were scheduled for every 4 months, and, at each visit, a standardized interview was administered, to obtain information on new sex partners (categorized as  $\geq 1$  new partners reported at the same or at a previous visit), cumulative number of partners at time of visit (categorized as 1–2, 3–9, and 10+ partners), and sex partner characteristics (age of partner, length of pre-coital acquaintanceship, and number of partners of the partner). In addition, each woman received a standardized physical examination, which included collection of separate cervical and vulvovaginal Dacron-tipped swab specimens for HPV DNA analysis by a polymerase chain reaction (PCR)-based method.

*HPV DNA analysis of specimens.* The PCR amplification and

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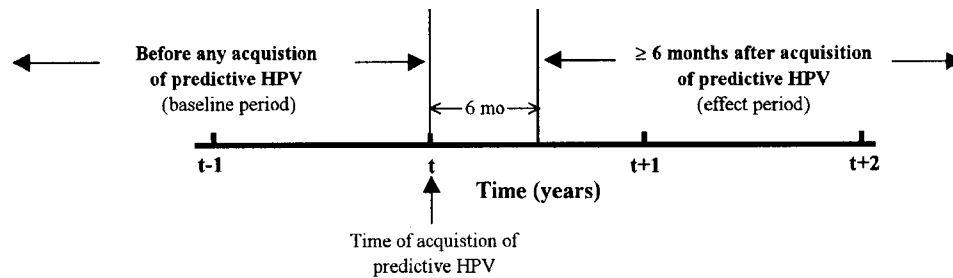
The protocol was reviewed and approved by the University of Washington Institutional Review Board. All participants provided written informed consent.

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**Figure 1.** Schematic diagram showing the times that defined the presence or absence of prior acquisition of predictive human papillomavirus (HPV) type in the analyses of sequential associations.

dot blot hybridization methods we used have been described elsewhere [14]. One-fiftieth of each genital swab sample was amplified in duplicate with the consensus primers MY09, MY11, and HMB01. Each sample was also amplified with human  $\beta$  globin primers as a control. The products of these amplifications were then probed with a biotin-labeled generic probe designed to detect most genital HPV types. Specimens found to be positive by generic probe were then tested with individual and mixtures of biotin-labeled, type-specific oligonucleotide probes, to determine the presence of HPV types 6, 11, 16, 18, 31, 45, and 56 and the following type mixtures: 33, 35, and 39; 40, 42, 53, and 54; and 51, 52, 55, and 58. Samples hybridizing with the generic probe but with none of the type-specific probes were classified as positive for uncharacterized genital HPV types. This report is focused on those HPV types most strongly linked to clinically important outcomes: HPV 6 and 11, which cause genital warts, and HPV 16, 18, 31, and 45, which are the types most commonly detected in invasive cervical cancer.

Because we were interested in acquisition of genital HPV infection and not strictly cervical infection, PCR test results for the cervical and vulvovaginal specimens were combined. Most women (78%) who acquired HPV 6, 11, 16, 18, 31, or 45 infection had a cervical specimen (with or without a vulvovaginal specimen) that was positive for the specific HPV type or types.

**Statistical analysis.** For all analyses, visits before the first reported episode of vaginal intercourse were excluded. Acquisition (incidence) of a given HPV type was defined for each subject to be the first positive result for that type after an observed negative result. Positive initial visits for a subject were assumed to be prevalent infections, and we assumed that the subject was not at risk for acquisition of that type. Thus, women had to have  $\geq 2$  visits, to contribute an acquisition. Potential confounding factors, including age, number of new sex partners ( $\geq 1$  new partners reported within the preceding 8 months), cumulative number of partners at each visit, and partner characteristics (age, length of pre-coital acquaintanceship, and number of partners of the partner), were evaluated in the adjusted models. Other factors, including contraceptive use, cigarette smoking, race/ethnicity, and presence of other sexually transmitted infections, were not associated with acquisition of genital HPV infection and were not evaluated in the adjusted models. All analyses were performed by S-Plus version 3.4, release 1 (MathSoft, Seattle).

**Concurrent associations.** The observed number of visits associated with 0, 1, 2, 3, 4, 5, or 6 acquisitions of different HPV types

were compared with counts that would be expected if the acquisitions were independent. Expected counts were based on mean counts over 1000 simulations of data by using the same number of observations per person and the same number of prevalent infections (i.e., positive at entry) as in the actual data. Data were simulated on the basis of observed incidences per visit of each type. We assumed that acquisitions of different types were independent.

To examine possible associations between concurrent acquisition of pairs of specific types, odds ratios (ORs) for acquisition of each type by acquisition of each other type at the same visit were obtained with separate logistic regressions [15]. The resulting OR gave the increase or decrease in the odds of finding at a visit that a patient had acquired a particular type if, at the patient's same visit, we knew that another particular type had been acquired. Both unadjusted and adjusted regressions were performed, and ORs were obtained.

We hypothesized that all the adjusted ORs came from an underlying common OR (not necessarily 1.0) versus the alternative that  $\geq 1$  were actually different. To test this hypothesis, all pairwise differences between log ORs were calculated, and the standard error of the difference was estimated. These quantities were then used to test the hypothesis of a common underlying OR. If no difference was found, then the common underlying OR can be estimated by the geometric mean of the individual ORs.

**Sequential associations.** To examine possible time-delayed associations between acquisitions of the different types, we defined an "outcome" HPV type and "predictive" HPV type for each comparison. The outcome HPV type was the type whose incidence was treated as the dependent variable in the analysis. We examined whether the incidence of the outcome HPV type was associated with previous acquisition of another HPV type, which, in these analyses, was called the predictive HPV type and was treated as the independent variable. Three time periods relative to the predictive HPV type were defined (figure 1): (1) before any acquisition of the predictive type (the baseline period); (2)  $\geq 6$  months after acquisition of the predictive type (the effect period); and (3) 0–6 months after acquisition of the predictive HPV type (the inconclusive period). All observations that occurred before first detection of a predictive HPV type were included in the baseline period. All observations that occurred  $\geq 6$  months after first detection of the predictive type were included in the effect period. The inconclusive period included observations made during the first 6 months after initial detection of the predictive type. It was important to create the inconclusive period, to reduce the possibility of misclassifying

**Table 1.** Incidence of different human papillomavirus (HPV) type-specific infections among the study population.

HPV type	Observed	Incidence		Positive at some visit, <sup>a</sup> n (%)
		Person-years at risk	Incidence per 100 person-years	
HPV 16	54	1191	4.7	84 (16.2)
HPV 18	35	1289	2.7	49 (9.5)
HPV 31	26	1322	2.0	33 (6.4)
HPV 45	8	1348	0.6	14 (2.7)
HPV 6	41	1256	3.3	54 (10.4)
HPV 11	4	1369	0.3	9 (1.7)
All typed infections <sup>b</sup>	200	899	22.2	241 (46.5)
All typed infections plus uncharacterized infections <sup>c</sup>	231	832	27.8	281 (54.2)

<sup>a</sup> A total of 518 subjects were included in the study.

<sup>b</sup> Includes the following types: 6, 11, 16, 18, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, and 58.

<sup>c</sup> Uncharacterized infections defined as positive using the HPV generic probe but not positive when the specific type or type mix probes were used.

infections acquired concurrently as acquired sequentially and to allow sufficient time for a potentially protective immune response to develop after acquisition of a predictive HPV type. An immune response to HPV infection appears to take more than a couple of months to develop [13].

To obtain hazard ratios (HRs) for time-delayed associations between each pair of types, separate Cox regressions with time-varying covariates were performed for each type as outcome by each other type as predictor [16]. In each of these regressions, the outcome was acquisition of the outcome HPV type. The main exposure was the time period relative to acquisition of the predictive HPV type, as described above. The resulting HR gave the increase or decrease in the chance of seeing acquisition of the outcome type at any visit if we knew that the predictive type was acquired  $\geq 6$  months before that visit. We performed both adjusted and unadjusted regressions. In addition to adjusting data for recent new partners and the cumulative number of partners, we also adjusted for the acquisition of any HPV type that was not the outcome type. Unadjusted and adjusted regressions were also performed on data combined across the comparisons on the basis of all closely related pairs: HPV 16 after HPV 31; HPV 31 after HPV 16; HPV 18 after HPV 45; HPV 45 after HPV 18; HPV 6 after HPV 11; and HPV 11 after HPV 6. For these analyses, the Cox models were stratified by outcome type. Because each person could potentially contribute multiple predictors and outcomes to this analysis, we made adjustment for correlation of outcomes within each person [17]. Regressions were performed in the same way on data combined across all remaining comparisons (that is, between pairs not closely related) and on data across all possible comparisons.

**Results**

*Study population and HPV types.* Of the 603 women enrolled in the study, 86% completed 1 year of follow-up and 77% completed 2 years; 518 reported vaginal intercourse either before enrollment or at some time during study follow-up. Visits for subjects after becoming sexually active for the first time

numbered 4018. Of these, 79 visits (2%) were missing HPV DNA results because the patients' samples of cellular material were unsatisfactory, leaving 3939 visits among 518 women for analysis. Among these women, the mean follow-up time was 34.3 months, the mean number of visits per person was 8.3, and the median time between visits was 4.3 months. The mean cumulative number of partners was 3.7, and the mean number of new partners per person-year was 0.6. Incidence rates for the different HPV types during follow-up ranged from 0.3% (HPV 11) to 4.7% (HPV 16) per person-year (table 1). The overall incidence rate for any genital HPV type among those who were HPV DNA negative at enrollment was 27.8% per person-year. Percentages of subjects ever positive for the different HPV types at some time during the study ranged from 1.7% (HPV 11) to 16.2% (HPV 16).

*Concurrent acquisition of different HPV types.* Observed and expected counts for visits with 0–6 different HPV type acquisitions suggested that women were more likely to experience coinfection with multiple types than would be expected if acquisitions were independent. For example, 2.8 visits by women newly coinfecting by 2 HPV types were expected, whereas 17 such visits were observed ( $P < .01$ ). Similarly, 0 visits by women with recent acquisition of 3 HPV types were expected, and 2 such visits were observed ( $P < .01$ ) (table 2).

Estimates for the 6 type-by-type unadjusted ORs for HPV types 6, 16, 18, and 31 ranged from 5.8 to 20.7 (table 3). Too few women acquired HPV type 11 or 45 at the same visit to obtain meaningful type-by-type ORs. After adjustment for recent new partner and cumulative lifetime number of partners, the ORs obtained for concurrent acquisition (relative to acquiring only 1 of the 2 types) remained elevated and ranged from 3.3 to 12.2 (table 3).

To explore whether some pairs of HPV types were more highly associated than others, all pairwise differences between the 6 adjusted log ORs were calculated ( $n = 15$ ). None of the 15 differences was found to be statistically significant, leading

**Table 2.** Per visit observed and expected counts of acquiring 0–6 genital infections with human papillomavirus (HPV) types 6, 11, 16, 18, 31, and 45.

No. of concurrent acquisitions	Observed	Expected
0	3790	3771.2
1	130	164.9
2	17 <sup>a</sup>	2.8
3	2 <sup>a</sup>	0
4	0	0
5	0	0
6	0	0

<sup>a</sup> Statistically significantly greater than expected ( $P < .01$ ) by simulation. Expected counts were based on mean counts of 1000 simulations of data, with the same number of observations per person and the same number of people starting the observation period with prevalent infections as in the actual data. Simulations assumed that acquisitions of different types of HPV were independent and were based on observed per visit incidence of each type.

**Table 3.** Concurrent acquisition of human papillomavirus (HPV) types according to number of visits by women who either acquired or did not acquire HPV types 6, 16, 18, or 31.

HPV acquired	HPV acquired					
	HPV 16		HPV 18		HPV 31	
	Yes	No	Yes	No	Yes	No
<b>HPV 18</b>						
Yes	5	17	—	—	—	—
No	46	3242	—	—	—	—
OR (95% CI)	20.7 (7.3–58.6)		—		—	
OR <sub>adj</sub> (95% CI)	12.2 (4.2–35.8)		—		—	
<b>HPV 31</b>						
Yes	3	18	2	21	—	—
No	52	3257	29	3510	—	—
OR (95% CI)	10.4 (3.0–36.5)		11.5 (2.6–51.4)		—	
OR <sub>adj</sub> (95% CI)	5.8 (1.6–21.0)		5.9 (1.3–27.0)		—	
<b>HPV 6</b>						
Yes	5	29	2	37	4	34
No	45	3139	31	3315	20	3445
OR (95% CI)	11.3 (4.0–34.6)		5.8 (1.3–25.0)		20.3 (6.6–62.4)	
OR <sub>adj</sub> (95% CI)	7.3 (2.6–20.6)		3.3 (0.7–14.6)		11.6 (3.6–37.2)	

NOTE. OR, odds ratio; CI, confidence interval; OR<sub>adj</sub>, adjusted odds ratio. The total number of visits and total number of visits positive for acquisition of any particular type varied because once a given HPV type was detected the subject was not considered to be at risk for acquiring that type at later visits. Thus, subsequent visits do not appear in the contingency table comparing that type with any other type. Adjustment was made for recent new partners and cumulative lifetime number of partners.

us to calculate a common underlying adjusted OR of 7.0 (95% confidence interval [CI], 5.8–8.4).

Adjustment for age and sex partner characteristics did not substantially affect any of the ORs, so they were not included in the final models. Although age is generally an important predictor of HPV acquisition, the relatively narrow age range of subjects in the study (19–24 years old for 90% of the visits) may have accounted for its lack of importance in the analysis.

*Sequential acquisition of different HPV types.* Observed and expected counts of acquisition for each HPV type >6 months after each of the other types are given in table 4. Most outcome HPV types showed higher-than-expected counts. The outcome HPV types that we hypothesized would show lower-than-expected counts were HPV 16 after HPV 31; HPV 18 after HPV 45; and HPV 6 after HPV 11 (and vice versa). However, among these, none were much lower than would be expected.

Four of the unadjusted HR estimates for each type pair were 0 because no incident infections were observed after the predictive HPV type, but, in each case, the expected count was ≤0.5. The remaining unadjusted HRs for each type pair ranged from 0.6 (HPV 31 after HPV 6) to 8.3 (HPV 45 after HPV 6) (data not shown).

Adjustment for new and cumulative number of sex partners and nonoutcome HPV type acquisition generally shifted the HRs closer to 1.0 (table 5). Although we hypothesized that HRs for sequential acquisition would be <1, most were >1. Adjusted HRs (95% CIs) for sequential acquisition of phylogenetically related pairs were as follows: HPV 31 after HPV 16 (1.2 [0.4–4.3]), HPV 16 after HPV 31 (0.8 [0.1–6.1]), and HPV

45 after HPV 18 (6.3 [0.6–67.7]). A HR of 1.2 for HPV 31 after HPV 16 means that women with prior HPV 16 infection were ~20% more likely to acquire HPV 31 at a subsequent visit than were women who had never acquired HPV 16. The only 2 adjusted HRs with 95% CIs excluding 1.0 were from analysis of HPV 45 after HPV 6 and of HPV 6 after HPV 45. Because these relationships were not hypothesized a priori, we adjusted for multiple testing in a separate analysis [18] and found that the HRs were no longer statistically different from 1.0 at  $\alpha = .05$ .

Combined data from analysis of the most closely related types (HPV 16 after HPV 31; HPV 45 after HPV 18; HPV 6 after HPV 11; and vice versa for each pair) gave an adjusted HR of 1.0 (0.4–3.0). Analysis of the combined data for the remaining pairs of HPV types that were less closely related gave an adjusted HR of 1.3 (0.8–2.1). The adjusted HR for all data combined was 1.3 (0.8–2.0).

## Discussion

Rates of acquiring different HPV types were investigated for evidence of clustering and cross-protection. HPV types 6, 11, 16, 18, 31, and 45 were investigated because these types are associated with important clinical end points: HPV 6 and 11 cause genital warts, and HPV 16, 18, 31, and 45 are the types most commonly detected in invasive cervical cancer. Our results support previous findings of frequent coinfection by >1 HPV type among female populations [9, 10]. Our results extend these earlier observations by including only incident infections in models designed to evaluate both concurrent and sequential acquisition of HPV types.

Interpretation of our findings depends on the assumption that the observed acquisitions were incident infections, not recurrences. Because HPV may be transiently detected, it is possible that subjects could have already had HPV infections that we did not know about before they entered the study. Such

**Table 4.** Observed and expected counts of each outcome human papillomavirus (HPV) type acquired ≥6 months after each predictive type.

Predictive HPV type	Outcome HPV type, observed (expected) counts					
	HPV 16	HPV 18	HPV 31	HPV 45	HPV 6	HPV 11
HPV 16	—	4 (1.2)	3 (1.4)	1 (0.5)	4 (1.8)	0 (0.3)
HPV 18	2 (0.7)	—	2 (0.8)	1 (0.3)	1 (1.4)	0 (0.2)
HPV 31	1 (1.0)	2 (0.5)	—	0 (0.2)	2 (0.5)	0 (0.1)
HPV 45	0 (0.5)	0 (0.3)	1 (0.2)	—	1 (0.3)	0 (0.0)
HPV 6	2 (2.5)	2 (2.0)	1 (1.3)	2 (0.3)	—	0 (0.3)
HPV 11	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.0)	0 (0.1)	—

NOTE. Expected counts were extrapolated from per person-year incidence rates before any acquisition of predictive HPV type. The number of person-years varies with each comparison. Expected counts were based on 13,295–15,951 person-years contributed by 478–508 subjects. Observed counts after acquisition of HPV type 6, 16, 18, or 31 were based on 190–1048 person-years contributed by 12–46 subjects. Observed counts after acquisition of HPV type 11 or 45 were based on 18–165 person-years contributed by 4–8 subjects.

**Table 5.** Acquisition of outcome human papillomavirus (HPV) types  $\geq 6$  months after each predictive HPV type.

Predictive HPV type	Outcome HPV type, adjusted hazard ratio (95% confidence interval)				
	HPV 16	HPV 18	HPV 31	HPV 45	HPV 6
HPV 16	—	2.0 (0.6–6.0)	1.2 (0.4–4.3)	2.6 (0.3–26.9)	1.9 (0.6–5.8)
HPV 18	2.0 (0.5–8.5)	—	1.6 (0.4–7.3)	6.3 (0.6–67.7)	0.7 (0.1–5.2)
HPV 31	0.8 (0.1–6.1)	3.1 (0.7–13.8)	—	0.0 <sup>a</sup>	3.9 (0.9–16.9)
HPV 45	0.0 <sup>a</sup>	0.0 <sup>a</sup>	3.8 (0.4–34.8)	—	9.4 (1.2–74.5)
HPV 6	0.6 (0.2–2.7)	0.5 (0.1–2.3)	0.5 (0.1–3.8)	8.7 (1.3–57.6)	—

NOTE. Adjustment is by recent new partner, cumulative lifetime number of partners, and acquisition of any HPV other than the outcome HPV.

<sup>a</sup> No incident infections were observed in the period  $\geq 6$  months after predictive HPV type.

women could already have had natural immune protection to some types without our being aware of it. However, at entry into the study, the women in this study were young (mean, 19.4 years) and reported few sex partners (median, 1). Also, we know from a separate study of HPV 16 seroprevalence in this cohort [13] that the seroprevalence of HPV 16 antibodies was similar among those who were sexually active and negative for HPV type 16 DNA at enrollment and those who had never been sexually active. Thus it is reasonable to assume that most HPV infections analyzed were indeed incident infections. In addition, “acquisition” was defined as the first detection of a given type, to avoid inclusion of positive tests after false-negative tests. Earlier work by our group examining sequential detection of HPV 16 variants indicates that, during a 3-year interval, very few women are reinfected by the same HPV type [19].

We expected that the proportion of women infected with multiple types of HPV would be higher than predicted by infection rates of the individual types because of common risk factors such as recent and cumulative number of sex partners. After adjustment for these risk factors, acquisition of multiple HPV types still occurred more frequently than expected by chance; however, concurrent acquisition of any 2 HPV types was not significantly more common than concurrent acquisition of any other 2 HPV types. Therefore, among the HPV types that we studied, we found no evidence that any 2 types are more likely to be acquired together than other types. However, a larger study might detect more subtle differences between these type pairings, and it remains to be determined whether evidence might be found for differences between pairs of types other than those we considered.

In this analysis, HPV types observed for the first time at a given visit were considered concurrent incident infections. HPV types acquired at different times during the intervals between visits but both still detectable would be observed as having been acquired at the same time. For 40% of visits associated with HPV incidence, the subjects reported  $\geq 2$  sex partners during the interval since the previous visit. Different HPV types first seen at the same visit could have been acquired separately, and concurrent acquisitions do not necessarily mean that different HPV types were acquired at the same sexual encounter or even from the same sex partner. Interestingly, 17% of visits

by women reporting only 1 sex partner versus 12% of visits by women reporting  $\geq 2$  partners showed acquisition of  $>1$  HPV type during a 4-month interval.

Although none of the HRs in our analyses of sequential acquisitions had 95% CIs that excluded 1.0, most of these HRs were  $>1.0$ . There are several possible explanations for seeing generally elevated estimates for both concurrent and sequential acquisition. The observed associations may be due to a biological mechanism by which the acquisition of 1 type of HPV does, in some way, facilitate acquisition of another type, although we know of no such mechanism. Alternatively, differences in host susceptibility may predispose some subjects more than others to HPV infection in general. Unmeasured sexual behavior or sex partner characteristics, such as frequency of intercourse or number of HPV types in the partner(s), may also be important. Whether host susceptibility or unmeasured characteristics of the partnership(s) explain the association, there was no evidence that particular types were more likely to be acquired together.

On the basis of relationships between the different HPV types [11], the most likely cross-protective effects would be between HPV 16 and HPV 31, HPV 18 and HPV 45, and HPV 6 and HPV 11. Analyses of sequential acquisition of these related types provided no evidence for a strong cross-protective effect. However, these analyses had limited power. Analyses based on the assumption that cross-protection between these types was similar across the related pairs more clearly precluded strong cross-protection. The result of analyses of combined data from all comparisons was similar. Thus, although we could not rule out the possibility of some cross-protection between specific pairs of HPV types 6, 11, 16, 18, 31, and 45, our results were inconsistent, with strong cross-protection generally and with strong cross-protection between closely related pairs.

In an earlier look at this cohort, among 10 women infected with HPV 31 but not with HPV 16, none were seropositive for HPV 16 capsid antibodies at any visit [13]. The lack of significant cross-protection has also been predicted from in vitro studies. Roden et al. [20] have shown that, overall, most HPV genotypes represent separate serotypes, and because most critical HPV-immune determinants (e.g., L1 proteins) are type specific, cross-protection of antibodies between types is not anti-

culated [21, 22]. On the other hand, evidence for some weaker cross-protective reactions between different HPV types along with the stronger same-type protective reactions has been reported in recent *in vitro* studies [12, 23, 24]. Although we found no evidence for strong cross-protection between the HPV types included in our study, it is possible that HPV types not included in our analyses (e.g., HPV 33, 35, 39, and 56) do inhibit subsequent infection with other HPV types.

Our results in a population of young women showed that acquisition of  $\geq 1$  genital HPV type was common and that risk of acquiring a specific HPV type was not substantially decreased among those with prior infection with a phylogenetically related type.

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