

NATURAL HISTORY OF CERVICOVAGINAL PAPILLOMAVIRUS INFECTION
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AND ROBERT D. BURK, M.D.**ABSTRACT**

Background Genital human papillomavirus (HPV) infection is highly prevalent in sexually active young women. However, precise risk factors for HPV infection and its incidence and duration are not well known.

Methods We followed 608 college women at six-month intervals for three years. At each visit, we collected information about lifestyle and sexual behavior and obtained cervicovaginal-lavage samples for the detection of HPV DNA by polymerase chain reaction and Southern blot hybridization. Pap smears were obtained annually.

Results The cumulative 36-month incidence of HPV infection was 43 percent (95 percent confidence interval, 36 to 49 percent). An increased risk of HPV infection was significantly associated with younger age, Hispanic ethnicity, black race, an increased number of vaginal-sex partners, high frequencies of vaginal sex and alcohol consumption, anal sex, and certain characteristics of partners (regular partners having an increased number of lifetime partners and not being in school). The median duration of new infections was 8 months (95 percent confidence interval, 7 to 10 months). The persistence of HPV for ≥ 6 months was related to older age, types of HPV associated with cervical cancer, and infection with multiple types of HPV but not with smoking. The risk of an abnormal Pap smear increased with persistent HPV infection, particularly with high-risk types (relative risk, 37.2; 95 percent confidence interval, 14.6 to 94.8).

Conclusions The incidence of HPV infection in sexually active young college women is high. The short duration of most HPV infections in these women suggests that the associated cervical dysplasia should be managed conservatively. (N Engl J Med 1998;338:423-8.)

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GENITAL infection with human papillomavirus (HPV) is one of the most common sexually transmitted diseases, its prevalence in young women ranging from 20 to 46 percent in various countries.¹⁻⁵ The effect of this infection on public health is compounded by the recognized causal relations between genital HPV infection and cervical dysplasia and cervical cancer.⁶⁻⁸ Information about the natural history of HPV infection, however, is limited. Although there are numer-

ous cross-sectional studies of its prevalence,^{1,3,4,9} the probability of acquiring this infection and the risk factors for it are not known. Some studies have concluded that genital HPV infection is mainly transient, but they were based on small numbers and only two points in time.¹⁰⁻¹⁴ Specific types of HPV are associated with cervical cancer,¹⁵ but whether these high-risk types have natural histories that are different from those of other types not associated with cervical cancer is unknown. This prospective study was conducted to address these questions.

METHODS

Through campuswide advertisements, we recruited and enrolled 608 female students from a state university in New Brunswick, New Jersey. As reported previously, their mean (\pm SD) age was 20 ± 3 years, and the racial and ethnic distribution was 57 percent white, 13 percent Hispanic, 12 percent black, and 18 percent other.¹ The prevalence of HPV infection at base line was 26 percent. The women were followed at six-month intervals for a maximum of three years. At each visit, a questionnaire on lifestyle and sexual behavior was completed, and cervicovaginal lavage was done.^{16,17} A pelvic examination, including a Pap smear, was performed at base line and annually thereafter. The 608 women were seen a total of 2971 times (median, 5 visits each) during an average of 2.2 years of follow-up (maximum, 3.4 years). The median number of months between two consecutive follow-up visits was 6 (range, 3 to 24), and 89 percent of the follow-up visits were completed within 5 to 7 months after the previous visit. The study protocol was approved by the institutional review board of the Albert Einstein College of Medicine, and informed consent was obtained from all the women.

Detection of HPV DNA

Exfoliated cervicovaginal cells were obtained by lavage for determination and typing of HPV by the polymerase chain reaction (PCR) and Southern blot hybridization as previously described.^{11,16,17} The HPV DNA fragments amplified by PCR that did not hybridize to any type-specific probes were considered to represent "uncharacterized" HPV types. A sample was considered positive for HPV if either the PCR or the Southern blot assay was positive, and negative if both assays were negative. No lavage samples were obtained during 14 of the 2971 visits, and the samples from another 63 visits were Southern blot-negative without PCR

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results; hence, the samples from 77 visits (3 percent) had indeterminate HPV results.

HPV types determined by PCR and Southern blot assay were combined into two groups: "high-risk" types known to be associated with cervical cancer (types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and W13b) and all other types.¹⁵ Sixteen of the 296 women (5 percent) in whom HPV DNA was ever detected had fluctuations in type — i.e., negativity for a specific type flanked by positivity. In the data analyses, these fluctuations were treated as loss of infection and then reinfection with that specific type.

Statistical Analysis

We estimated the cumulative probabilities of acquiring and losing an incident HPV infection and having an incident cytologic abnormality by the Kaplan–Meier method. The time of the event was estimated as the midpoint between visits. All P values presented are two-sided.

For the non-type-specific incidence of HPV, the results in the 399 women who were HPV-negative at base line and who had at least one follow-up visit were analyzed. Time-dependent proportional-hazards regression analysis was performed to identify independent risk factors for incident HPV infection. The incidence of a specific HPV type was analyzed in the women who at base line were either HPV-negative or positive for other types.

For the duration of HPV infection, data on the 175 women who had a new HPV-type-specific infection and at least one subsequent follow-up visit were analyzed. A woman was considered to have a persistent infection if at least one of the types continued to be detected at subsequent visits. For the duration of infection with a specific type of HPV, only the women with a new infection of that type were included. To identify risk factors for persistent HPV infection, a generalized linear regression model with a generalized estimating-equation approach was used.^{18,19} The HPV results of every two consecutive visits of a woman were grouped as a pair, as previously described.⁶ The outcome was classified as persistence when at least one of the types detected at the previous visit was detected at the next visit, and as resolution when none of the types from the previous visit were detected at the next visit. Because the majority of follow-up visits were completed within the 6-month intervals, this analytic approach defined persistent HPV infection as infection with the same type or types for ≥6 months.

For analysis of the incidence of squamous intraepithelial lesions, the 443 women whose HPV status was known and who had normal Pap smears at base line, excluding atypia, and at least one follow-up visit were included. The relation between HPV infection and the incidence of squamous intraepithelial lesions was examined by time-dependent proportional-hazards regression analysis.

RESULTS

Incidence of HPV

The cumulative 36-month incidence of HPV infection in the women who were HPV-negative at base line was 43 percent (95 percent confidence interval, 36 to 49 percent). The incidence tended to decrease with time; it was 20 percent in the first 12 months, as compared with 14 percent and 9 percent in the second and third 12-month periods, respectively.

The 20 types of HPV for which the 24-month cumulative incidences were ≥2 percent are listed in Table 1. The incidences of HPV types 51, 66, 16, PAPI55, 6, 18, and 59 were the highest (≥4 percent). The mean (±SD) 24-month cumulative inci-

TABLE 1. CUMULATIVE 24-MONTH INCIDENCE AND MEDIAN DURATION OF INFECTION WITH SPECIFIC TYPES OF HPV IN COLLEGE WOMEN.*

HPV TYPE	CUMULATIVE 24-MONTH INCIDENCE†	MEDIAN DURATION†	NO. WITH INFECTION/NO. AT RISK	NO. IN WHOM INCIDENT INFECTION RESOLVED/NO. AT RISK
	% (95% CI)	mo (95% CI)		
51‡	8 (6–11)	7 (6–12)	43/529	29/36
66	7 (5–10)	6 (6–7)	38/529	26/28
16‡	7 (4–9)	11 (7–12)	38/514	18/25
PAPI55	7 (4–9)	7 (6–11)	35/526	25/28
6	5 (3–7)	6 (6–7)	29/531	22/23
18‡	4 (3–6)	12 (6–17)	22/525	11/17
59‡	4 (2–5)	6 (5–7)	19/527	14/14
53	3 (2–5)	8 (6–11)	21/521	16/19
61	3 (2–5)	15 (6–17)	17/529	10/13
52‡	3 (1–4)	7 (6–11)	15/531	11/13
39‡	3 (1–4)	6 (5–11)	13/530	11/11
73‡	3 (1–4)	11 (10–14)	15/527	9/12
58‡	3 (1–4)	6 (6–∞)§	13/528	6/9
PAP291	3 (1–4)	6 (6–7)	15/529	13/14
AE7	3 (1–4)	16 (11–22)	13/532	5/9
31‡	2 (1–4)	6 (6–13)	12/529	10/11
54	2 (1–4)	9 (6–20)	13/533	7/10
33‡	2 (1–4)	7 (6–8)	10/536	6/7
45‡	2 (1–4)	6 (5–12)	10/531	8/9
35‡	2 (1–3)	6 (5–7)	9/536	9/9

*The 20 types of HPV with the highest 24-month cumulative incidences (≥2 percent) are shown. Not shown are HPV types 11, 26, 32, 34, 40, 42, 55, 56, 67, 68, 70, AE2, AE6, AE8, and W13B, because their incidence was <2 percent. The total type-specific incidence is presented, although the incidence of a particular type tended to be lower among women who were HPV-negative at base line than among those who were HPV-positive with a different type. CI denotes confidence interval.

†The cumulative 24-month incidence and median duration of HPV infection were obtained by the Kaplan–Meier method. Confidence intervals for the median durations were derived with the use of the SAS statistical package²⁰ and by the methods described in Brookmeyer and Crowley.²¹

‡This type is high risk.

§The upper limit of the 95 percent confidence interval was not obtainable for HPV type 58.

dence of the 16 high-risk types of HPV was 3±2 percent, as compared with 2±2 percent among the 19 other HPV types, excluding the uncharacterized types (P=0.26).

An increased risk of incident HPV infection was associated with younger age, membership in a racial or ethnic minority group, and increased frequency of alcohol consumption (Table 2). The risk of HPV detection at a given visit was associated with the numbers of vaginal-sex partners both in the previous 6 months and in the previous 7 to 12 months. The women who had had at least one regular partner since the previous visit had an increased likelihood of acquiring an HPV infection if the partner was sexually promiscuous or not currently in school, or

TABLE 2. RISK FACTORS FOR INCIDENT HPV INFECTION IN COLLEGE WOMEN.

Risk Factor*	ADJUSTED RELATIVE RISK (95% CI)†	P VALUE
Time-independent variables		
Age (per additional yr)	0.9 (0.8–0.9)	0.001
Racial or ethnic group		
White, Asian, and others	1.0	
Hispanic	2.1 (1.2–3.7)	0.009
Black	4.4 (2.7–7.2)	<0.001
Time-dependent variables‡		
Frequency of alcohol consumption		
<1 time/mo	1.0	0.005§
1–3 times/mo	1.3 (0.9–2.1)	
≥4 times/mo	2.0 (1.2–3.1)	
No. of male vaginal-sex partners in previous 6 mo¶		
0–3	1.0	
≥4	3.6 (1.8–7.2)	<0.001
No. of male vaginal-sex partners in previous 7–12 mo¶		
0	1.0	<0.001§
1	1.7 (0.9–3.2)	
2–3	3.0 (1.6–5.8)	
≥4	4.2 (1.5–11.5)	
Had anal sex with any regular partners	1.6 (1.1–2.4)	0.03
Total frequency of vaginal sex with all regular partners		
<2–6 times/wk	1.0	
≥2–6 times/wk	1.5 (1.1–2.3)	0.02
No. of lifetime sexual partners of main regular partner**		
1	1.0	<0.001§
2–5	5.8 (2.1–16.0)	
≥6	10.1 (3.6–28.4)	
Main regular partner was currently in school**	0.6 (0.4–0.9)	0.01
Had at least one regular partner††	1.0 (0.5–1.9)	0.96

*The following variables were not significant in multivariate time-dependent proportional-hazards analysis: income; lifestyle; use of cigarettes, recreational drugs, and oral contraceptives; number of casual sex partners (sexual contact for <1 month); number of regular sex partners (≥1 month); number of new regular sex partners; frequency of oral sex and sex under the influence of alcohol or drugs; postcoital bleeding; sex during menstruation; use of vaginal douche; and use of condoms during vaginal sex.

†CI denotes confidence interval.

‡All time-dependent variables refer to the period since the previous visit unless otherwise specified.

§P value is for linear trend.

¶Number of sexual partners was normalized to a six-month period (i.e., the number of partners between two visits was divided by the number of months between two visits and multiplied by 6).

||The frequency of vaginal sex since the last visit was coded as “none,” “1–5 times,” “1 time per month,” “2–3 times per month,” “1 time per week,” “2–6 times per week,” or “daily” in the questionnaire, and it was converted to the number of times per month by using the median frequency of each category. The total frequency of vaginal sex was the sum of the frequencies with all regular partners.

**If there were multiple regular partners, the most recent male partner with whom the woman had the most frequent sexual encounters and the longest relationship was considered to be the main regular partner.

††This is a dummy variable so that every woman, with or without a regular partner, could be entered into the regression model. All relative risks related to the characteristics of and sexual activities with the regular partner or partners were interpreted as risk estimates among women with at least one regular partner since the previous visit.^{1,22}

if the woman and her partner were having anal sex or a high frequency of vaginal sex.

Duration of HPV Infection

The median duration of HPV infection was 8 months (95 percent confidence interval, 7 to 10). By 12 months after the incident infection, 70 percent of the women were no longer infected, and by 24 months only 9 percent continued to be infected. The five types of HPV associated with the longest median duration of infection were AE7, 61, 18, 16, and 73 (Table 1).

The risk factors for persistent HPV infection of ≥6 months were older age, infection with multiple types of HPV, and infection with a high-risk type at the previous visit (Table 3). A woman with a newly acquired HPV infection was unlikely to have the same infection six months later; the longer an infection persisted from previous visits the more likely it was to continue to persist. Cigarette smoking was protective against persistent infection.

Incidence of Squamous Intraepithelial Lesions

Thirty-one incident cases of squamous intraepithelial lesions were diagnosed by cytology, of which two were high-grade lesions. The women who had been HPV-positive at base line were three times as likely to have an incident squamous intraepithelial lesion as the HPV-negative women (95 percent confidence interval, two to seven times; P<0.001) (Fig. 1). All the women were HPV-positive when the lesions were detected, and 81 percent had also tested positive at the previous six-month visit. The risk of the development of squamous intraepithelial lesions was associated with having had an HPV infection for at least six months, particularly a persistent infection with a high-risk type (Table 4).

DISCUSSION

The average annual incidence of HPV infection in this cohort of college women was 14 percent. Including the 26 percent who were HPV-positive at base line, about 60 percent of the women were infected with HPV at some time during the three-year period of the study, revealing the high risk of exposure to HPV for both heterosexual men and women in a college environment.

A woman’s risk of incident HPV infection was defined by her age, behavior, and the men with whom she associated sexually. Although the age range in this cohort was narrow, the older women had a lower risk of acquiring HPV infection than the younger women, perhaps because of acquired immunity to HPV from past exposure.²³ In addition to the transmission of HPV by vaginal sexual relations, the increased risk associated with anal sex or a high frequency of alcohol consumption may be a proxy for the risks associated with other forms of sexual be-

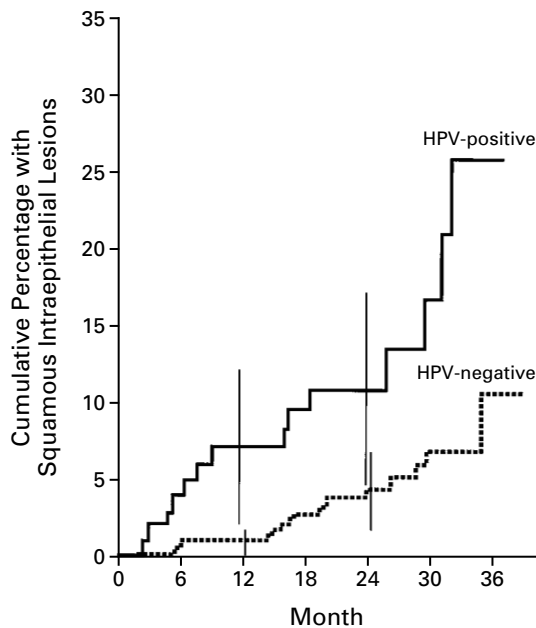
TABLE 3. RISK FACTORS FOR PERSISTENCE OF HPV INFECTION FOR ≥6 MONTHS IN COLLEGE WOMEN.*

RISK FACTOR	ADJUSTED ODDS RATIO (95% CI)	P VALUE
Age (per additional yr)	1.1 (1.1–1.2)	0.05
No. of cigarettes smoked/day since previous visit		
None	1.0	0.003‡
≤5	0.8 (0.5–1.3)	
>5	0.3 (0.2–0.7)	
Status of HPV infection at previous visit‡		
New infection	1.0	
Already persistent for 6 mo	2.3 (1.4–3.8)	0.001
Already persistent for >6 mo	3.1 (1.8–5.6)	<0.001
Infection of unknown duration	1.4 (0.9–2.2)	0.19
Multiple types detected at previous visit	4.1 (2.7–6.3)	<0.001
High-risk types detected at previous visit	1.5 (1.1–2.2)	0.03

*Results were obtained from a time-dependent generalized linear regression model with a generalized estimating-equation approach.^{18,19} CI denotes confidence interval.

‡P value is for linear trend.

‡HPV results of two consecutive visits were grouped as a pair. An infection at the previous visit was classified as a new infection if the HPV types had not been detected at previous visits, as a continual type-specific persistent infection if at least one of the types had been detected six months or more than six months before, or as an infection of unknown duration if the most recent visit was the base-line visit or no information from previous visits was available.



NO. OF WOMEN AT RISK

HPV-positive	102	83	68	21
HPV-negative	341	322	262	102

Figure 1. Cumulative Percentages of College Women with Incident Squamous Intraepithelial Lesions among Those Who Were HPV-Positive and HPV-Negative at Base Line.

Vertical bars represent 95 percent confidence intervals.

TABLE 4. RELATIVE RISK FOR THE ASSOCIATION BETWEEN CONTINUAL HPV INFECTION AND THE DEVELOPMENT OF SQUAMOUS INTRAEPITHELIAL LESIONS.*

HPV STATUS	RELATIVE RISK (95% CI)	P VALUE
HPV-negative at the previous or current visit	1.0	
HPV-positive at both visits†	20.9 (8.6–51.0)	<0.001
With different HPV types	14.7 (4.5–48.3)	<0.001
Non-high-risk types at current visit	9.6 (1.9–47.6)	0.006
High-risk types at current visit	22.2 (5.5–89.5)	<0.001
With the same HPV types	25.5 (10.2–63.7)	<0.001
Non-high-risk types	6.9 (1.4–34.1)	0.02
High-risk types	37.2 (14.6–94.8)	<0.001

*Results were obtained from univariate time-dependent proportional-hazards regression analysis. Continual HPV infection was determined by the HPV results at two consecutive visits — the current visit when a Pap smear was taken and the previous six-month visit. CI denotes confidence interval.

†Women who were HPV-positive at both visits were subclassified according to whether they had continual infection of different types or of the same type and whether high-risk types were involved. The relative-risk estimates were obtained from separate univariate analyses for each classification, with the women who were HPV-negative at one or both visits as the reference group.

havior that were not measured. The detection of incident HPV infection was associated with having four or more vaginal-sex partners in the previous six months. However, there was a direct relation between the detection of HPV infection and the number of vaginal-sex partners in the previous 7 to 12 months. These findings suggest a delay in the detection of HPV infection, perhaps related to the time required for the virus to replicate in cervicovaginal cells after infection.^{3,24}

Several studies of prevalent HPV infection have concluded that HPV is mainly a transient infection.^{2,10-12,14,25-27} The results of this study were similar for incident infections. Infection with high-risk types of HPV and older age were risk factors for persistent HPV infection.^{12,25} The etiologic role of high-risk HPV types, as well as the peak incidence of cervical cancer in women more than 40 years old,^{15,28} may be explained by the long duration of infection in older women infected with high-risk types. Persistent infection in turn may increase the risk for the development and persistence of squamous intraepithelial lesions, as shown in this and previous studies.^{6,25} The association between persistent infection and multiple types of HPV suggests that women who have multiple types might have certain characteristics — e.g., deficient immune responses to HPV — that predispose them to persistent infection.²⁹ In fact, women who are immunosuppressed by infection with the human immunodeficiency virus are at increased risk for infection with multiple types of HPV.³⁰

A woman was likely to lose her existing HPV infection if it was newly acquired, and the longer an infection persisted the more difficult it was to lose it. The probability of losing an incident HPV infection in the first 6-month period was 31 percent, and in the second 6-month period it was 39 percent; if an infection did not resolve in the first 12 months, the probability of its resolving in the third 6-month period dropped considerably, to 11 percent. This pattern is similar to the regression and persistence patterns of squamous intraepithelial lesions.^{31,32}

Previous studies have implicated cigarette smoking as a risk factor for cervical cancer^{33,34} whereas it was protective against persistent HPV infection in this and another study.¹² The protective mechanism of smoking, whether it is a biologic or a confounding effect, is unknown.

Among the 35 types of HPV, the incidence of infection with the high-risk types was similar to the incidence with the other types. Nevertheless, types 16 and 18, which have the strongest association with cervical cancer,¹⁵ were the only two types included in the top quartiles for both incidence and duration.

We found a relation between incident squamous intraepithelial lesions and continuous HPV infections (both type-specific and non-type-specific), which had been suggested in previous studies.^{12,17} Whereas type-specific infections prolong the duration of squamous intraepithelial lesions,^{6,25} repeated non-type-specific infections are associated with multiple episodes of squamous intraepithelial lesions, and both increase the chances that squamous intraepithelial lesions will be detected by periodic Pap smears.

Since some women could have acquired and lost an HPV infection between two six-month visits, this study may have underestimated the incidence and overestimated the duration of HPV infection. The trend of high incidence and short duration was therefore a conservative representation of the natural history of HPV infection in young women. However, we do not know whether these data apply to other populations, particularly older women.

Finally, clinicians who treat adolescent girls and young women should consider that HPV infection is mainly short-lived. Hence, the manifestation of HPV, particularly a low-grade squamous intraepithelial lesion, often undergoes spontaneous regression.^{25,32,35} Moreover, whether aggressive surgical treatments for squamous intraepithelial lesions cure HPV infection or interrupt its transmission is not known. Current data on the natural history of HPV infection and its associated lesions suggest that conservative management, such as follow-up without ablative therapy, may be indicated in young women with low-grade squamous intraepithelial lesions associated with transient HPV infection.

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