

New Considerations in Controlling Human Papillomavirus Infection

An estimated 20 million Americans are currently infected with human papillomavirus (HPV), and an additional 5.5 million are believed to become infected each year. Although most cases of HPV infection appear to resolve naturally, persistent infections, especially with HPV strains 16, 18, 31, and 45, are of special concern because they are strongly associated with the development of cervical cancer. Slowing HPV infection rates and minimizing associated morbidities are essential but difficult goals to achieve.

Two new studies suggest why. The first finds that the temporal link between HPV infection and the development of cervical neoplasia is rather loose, thus limiting the prognostic power of clinical inferences drawn from characterizing a woman's HPV status at a single point in time.¹ The second finds that risk factors for acquiring HPV are distinct from those for developing low-grade squamous intraepithelial lesions (LSILs).² While the attribution of specific risks to specific conditions is certainly important, the finding that cigarette smoking (which now appears to be increasing in young women) plays a role in the development of LSILs but not in HPV acquisition only underscores the challenges that lie ahead.

NATURAL HISTORY OF HPV

Woodman et al¹ performed a longitudinal cohort study of 1,075 women who had only recently become sexually active and thus were unlikely to already be infected with HPV. The young women, ages 15 to 19, were recruited from a Birmingham (UK) health center between 1988 and 1992. A cervical smear and serum sample were obtained from each participant at study entry and every six months thereafter, as were social, sexual, and behavioral risk-factor profiles. All participants were cytologically normal and HPV negative at enrollment. Women in whom a cytologic abnormality developed during the study were referred for colpo-

scopic assessment. Treatment was begun when there was evidence of progression to high-grade cervical intraepithelial neoplasia (CIN).

At three years' follow-up, 407 women had become infected with HPV, predominantly HPV type 16. The three-year cumulative risk of infection with HPV of any type was 44%. More than half of the HPV-positive women (246, or 60%) presented with an abnormal smear during follow-up; from this subset, 28 developed high-grade CIN. The likelihood of developing high-grade CIN was greatest among women infected with HPV type 16. The risk of high-grade CIN from HPV 16 infection was greatest six to 12 months after first exposure but was highly variable (Table 1).

Table 1. Likelihood of cervical intraepithelial neoplasia with HPV 16 infection

Time since first exposure (months)	Relative hazard ratio (95% CI)
Unexposed	1.00
≤ 6	5.98 (1.33 – 26.85)
6 – 12	18.02 (5.50 – 59.03)
12 – 18	14.22 (3.76 – 53.86)
> 18	2.60 (0.75 – 8.99)

HPV, human papillomavirus; CI, confidence interval.

Adapted from Woodman et al.¹

Attempts to correlate low-viral-load and high-viral-load samples with cytologic abnormality raised more questions than answers. For example, although cytologic abnormalities were more likely in samples containing high viral loads, viral load was found to wax and wane over the course of infection, thus providing little prognostic value. Adding further complexity was the finding that five women who progressed to high-grade CIN consistently tested negative for HPV.

Table 2. Risk factors

Covariate	Relative hazard ratio (95% CI)	P value
For incident HPV infection		
Rate of new partners per month since last visit	10.10 (3.24 – 31.50)	< .001
History of herpes simplex virus infection	3.54 (1.37 – 9.10)	.009
History of vulvar warts	2.73 (1.27 – 5.87)	.01
Current use of oral contraceptives	0.49 (0.28 – 0.86)	.01
For cervical low-grade squamous intraepithelial lesions		
HPV infection		
< 1 year	7.40 (4.74 – 11.57)	< .001
1 – 2 years	10.27 (5.64 – 18.69)	< .001
2 – 3 years	6.11 (1.86 – 20.06)	.003
> 3 years	4.48 (0.61 – 32.98)	.14
Daily cigarette smoking	1.67 (1.12 – 2.48)	.01

HPV, human papillomavirus; CI, confidence interval.
Adapted from Moscicki et al.²

RISK FACTORS FOR HPV AND LOW-GRADE LESIONS

To determine whether behavioral and biologic risk factors for LSILs are simply risk factors for HPV infection, Moscicki et al² tracked the development of HPV infection in a group of 105 HPV-negative women and the development of LSILs in a group of 496 women who tested positive for HPV. Data on demographic, behavioral, and clinical risk factors were collected at baseline and prospectively every four months (or every six months for those who remained HPV negative). Investigative procedures that were employed included cervical cytology, samples from which were later tested for HPV DNA; face-to-face interviews; and colposcopic examination. The young women, ages 13 to 21, were recruited from one of two family planning clinics in the San Francisco Bay area. Median

follow-up was 50 months.

At outcome, 54 of the women who had been HPV negative had acquired the virus. (Ten of them developed LSILs.) Risk factors for HPV infection were as follows: having new sexual partners each month since the last visit, having a history of herpes simplex virus infection, and having a history of vulvar warts. Current use of oral contraceptives was shown to have a protective effect; those who used them were about half as likely as those who did not to have an HPV-positive status. Table 2 lists the relative hazard values for each of these associations.

Among the women who were HPV positive at baseline or during follow-up, 109 presented with LSILs. However, as this number suggests, the majority of women who were HPV positive did not develop LSILs within the follow-up period. Despite this

finding, the most prominent risk factor for LSIL development was HPV infection. The likelihood of LSIL was shown to be greatest in women who had remained HPV positive for one to two years. Daily cigarette smoking was identified as an independent risk factor for LSIL but not for HPV infection. None of the variables identified as risk factors for HPV infection were found to alter the likelihood of LSIL development. 🦋

REFERENCES

1. Woodman CBJ, Collins S, Winter H, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet*. 2001;357:1831-1836.
2. Moscicki AB, Hills N, Shiboski S, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. *JAMA*. 2001;285:2995-3002.