

## Persistent HPV infection is associated with a greater risk of developing cervical lesions than a single positive test

Schlecht NF, Kulaga S, Robitaille J, Ferreira S, Santos M, Miyamura RA, Duarte-Franco E, Rohan TE, Ferenczy A, Villa LL, Franco EL. Persistent human papillomavirus infection as a predictor of cervical intraepithelial neoplasia. *JAMA* 2001; 286: 3106–3114.

**OBJECTIVE** To determine the risk of developing cervical lesions in the presence of persistent cervical human papillomavirus (HPV) infection.

**DESIGN** Prospective cohort study.

**SETTING** Community hospital in Sao Paulo, Brazil.

**SUBJECTS** Non-pregnant women (median age of 33 years, range 18–60 years) were recruited in 1993–97 from various clinics in the hospital. Included in this analysis were 1611 women with normal cervical cytology at baseline and HPV typing at the first two follow-up visits. The majority of women were of low income and educational level.

**INTERVENTION** At baseline, every 4 months in the first year, and twice yearly thereafter, cervical specimens were collected for Papanicolaou cytology and HPV testing. Sixty-nine percent of women had complete follow-up over 5 years. Type-specific MY09/11 L1 consensus primer PCR was used for HPV testing. A single expert reviewer interpreted cytologic slides. Assessors were masked to all other test results.

**MAIN OUTCOME MEASURES** Incidence (per 1000 woman-months) of squamous intraepithelial lesions (SIL) by HPV infection status and relative risk (RR, 95% CI) were calculated for the next 4+ years. Cumulative risk of developing SIL over the entire 5

years was estimated using survival analyses, adjusted for age and ethnicity.

**MAIN RESULTS** The incidence of any grade SIL was 0.7 per 1000 woman-months in the 79% of women with negative HPV results on both initial visits (reference group). If HPV was detected at only 1 visit or different HPV types were detected at each visit, the incidence of SIL was 2.3 for HPV types 16 or 18 (2.2% of women, RR 2.7, 95% CI 0.8–8.7) and 3.4 for other types (12% of women, RR 4.2, 95% CI 2.6–6.8). If the same HPV type was detected at both visits, the incidence of SIL was 8.7 for HPV types 16 or 18 (1.5% of women, RR 11.2, CI 5.0–25), 8.3 for other oncogenic types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68) (2.4% of women, RR 9.9, CI 5.2–19), and 3.5 for non-oncogenic types (2.9% of women, RR 4.5, CI 2.0–10). The cumulative risk of any SIL over 5 years of follow-up was 4% with negative HPV results at both visits, 15% with any type HPV at 1 visit (or different types at both visits), 24% with the same, non-HPV16 or 18 types at both visits, and 38% with HPV types 16 or 18 at both visits\*.

**CONCLUSION** In women with baseline normal cervical cytology, the risk of developing cervical lesions in the following 5 years was 2–4-fold greater for women who had persistent oncogenic HPV infection, as measured by two positive HPV tests for the same type 4 months apart, compared to women who were positive for an oncogenic HPV type only once.

\* Estimated from graph in article.

## Commentary

Increasingly, cervical infections with oncogenic types of human papillomavirus (HPV) are accepted as the universal cause of cervical cancer.<sup>1,2</sup> The present study has contributed important data regarding the natural history and clinical significance of HPV persistence.<sup>3</sup>

Oncogenic types of HPV are common, sexually transmitted, cervical pathogens, especially in younger women, and most infections are transient.<sup>3,4</sup> Cervical cancer generally occurs in women aged 40 years or older; therefore, it appears that, as part of the development of cancer, a small percentage of infections established decades earlier must persist. Very few large and rigorous prospective studies of type-specific HPV infection have been reported.

Based on their Brazilian cohort, the authors of the present study measured HPV infection at enrollment and after 4 months of follow-up. Compared to women who were HPV DNA positive at enrollment alone, women with infections persisting for 4 months were at increased risk of subsequent development of cytological squamous intraepithelial lesions (SIL). While the study thereby suggests that persistence is a general property of oncogenicity, the converse was not necessarily true, in that non-oncogenic types like HPV 53 have been observed to persist but carry no risk of high-grade SIL.

The largest cohort studies of HPV infection are only now maturing. Thus, these authors were forced to include as their clinical end-point not only high-grade SIL (HSIL), a good surrogate marker for cancer risk, but also low-grade SIL (LSIL), which is now recognized as the cytologic manifestation of a productive HPV infection. Therefore, it is perhaps not surprising that the longer the duration of the infection, the more likely that a HPV infection was visualized at the microscopic level, i.e., LSIL cytology. Women who were HPV positive at baseline but negative at 4 months may have cleared the infection (and any resultant cytologic abnormality) in the interim. Future follow-up of this cohort and others will yield more direct comparisons of persistent to incident infections, and very valuable risk estimates specific to HSIL and high-grade histologic outcomes. Also, typing of HPV in all of the lesions detected during follow-up will sharpen the estimates of relative risk and positive predictive value.

These authors should be complimented for achieving a very intensive schedule of follow-up on such a large group of women. In this initial analysis, they presented persistence data based on the first two HPV tests at baseline and 4 months. They are able to demonstrate that even 4 months of persistence increases risk of SIL. The 4-month interval represents a short follow-up period to define persistence, because the median time of viral clearance

tends to be approximately 6–8 months.<sup>3,4</sup> The perfect choice of a re-testing interval for clinical use would capture all infections destined to persist and progress to cancer, while permitting clearance of all transient infections. Clinical researchers are currently attempting to define an optimally efficient re-testing interval that would permit the use of HPV testing along with cytology in cervical screening. There is no perfect choice. In our Costa Rican cohort, we have noted that 5-year persistence of oncogenic HPV types is highly associated with progression to HSIL. But clinicians will undoubtedly be unwilling to wait 5 years for clearance in order to gain high positive predictive value. Professional organizations are now considering whether there are sufficient data to recommend optimal time intervals for repeating positive HPV tests in the context of normal cytologic interpretations. Based on accumulated data, a good clinical trade-off (in our personal opinion) might be to re-test HPV positive women at approximately 1 year, paying particular attention to older women because of increasing a priori concern about their higher cancer risk.

In order to assess oncogenic HPV persistence, these authors emphasized careful HPV typing. It is noteworthy that there is no clinical HPV DNA test currently available that provides HPV typing needed to measure the persistence of HPV infections. Research PCR tests are insufficiently reliable. Persistence may represent an extremely useful early indication of risk for high-grade cervical neoplasia, suggesting that new HPV diagnostics are now needed that incorporate HPV typing.

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