

Adding a Test for Human Papillomavirus DNA to Cervical-Cancer Screening

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It is now clear that virtually all squamous-cell cervical carcinomas contain one of 18 types of human papillomavirus (HPV) DNA, as shown definitively in the article by Muñoz et al. in this issue of the *Journal* (pages 518–527). Although the observation that HPV DNA is routinely detected in cervical cancers is not proof that it has a causal role, the relative risk of cervical cancer associated with high-risk types of HPV is even higher than the risk of lung cancer associated with smoking. Several oncogenes have been identified in high-risk (oncogenic) types of HPV, and the biologic mechanisms of malignant transformation have been increasingly well characterized. Moreover, the observation that the continued presence of transcriptionally active HPV is necessary for the maintenance of cervical-cancer cell lines *in vitro* is consistent with prospective epidemiologic data demonstrating that persistence of infection is necessary for cervical carcinogenesis.

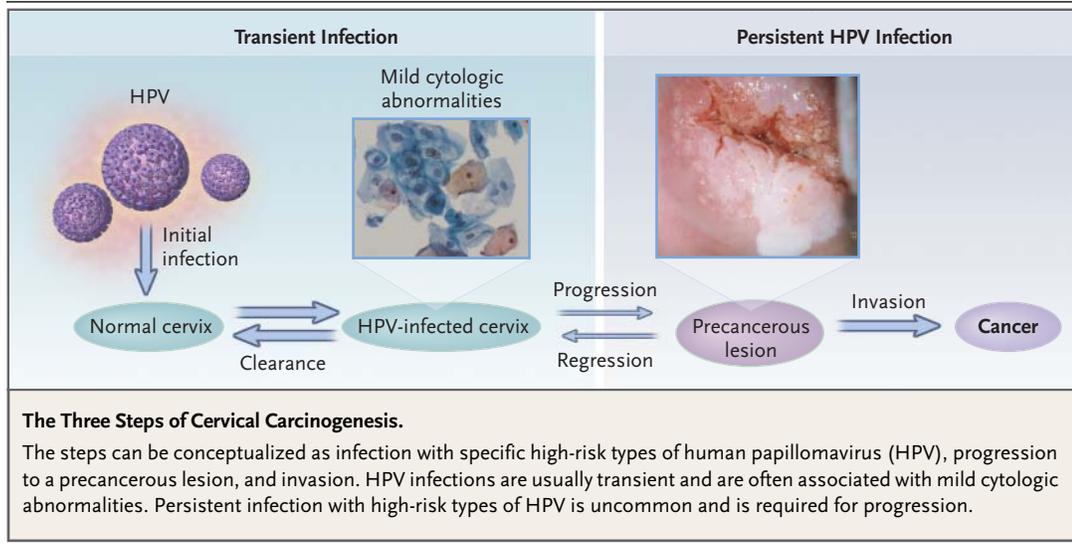
The discovery that persistent, oncogenic HPV infection is necessary for the development of cervical cancer is revolutionizing our approaches to screening and prevention, because an obvious corollary is that the absence of infection means that the risk of cancer is negligible. Encouraging results with a prophylactic HPV vaccine were recently reported in the *Journal*.¹ Molecular testing for HPV is already being incorporated into screening programs that previously relied on cytologic testing (Papanicolaou smears). On the basis of a large randomized, clinical trial, testing for HPV DNA is now recommended for most women with equivocal findings on cervical cytologic analysis (atypical squamous cells of undetermined significance).² In the Atypical Squamous Cells of Undetermined Significance Low-Grade Squamous Intraepithelial Lesion Triage (ASCUSLSIL) Study, a single HPV test identified virtually all women found to have high-grade precancerous lesions during the 24-month study and was more effective than a single colposcopic

examination or two Papanicolaou tests (unpublished data).

Testing for HPV DNA has shown encouraging results in large screening studies and will probably soon receive approval from the Food and Drug Administration for use in conjunction with cytologic analysis in primary screening for cervical cancer in women 30 years of age or older.³ The increased sensitivity achieved with the use of both tests together will allow the interval between screening procedures to be safely extended from the one to two years recommended with cytologic testing to three or more years with the use of the combined tests. Less frequent but effective screening would be especially important for underscreened populations of women, who are at the highest risk for cervical cancer in the United States and elsewhere.

Although there are real benefits to be gained, the incorporation of testing for HPV DNA into primary screening also has a potential for overuse. Although it is natural to want to obtain the maximal protection that a screening test can provide, especially when the target disease is both serious and preventable, focusing on the unobtainable goal of preventing all cases of cervical cancer through widespread HPV DNA testing could have negative consequences. One factor that must be taken into account is the natural history of HPV infection (see Figure).

At present in the United States, most young women become infected with HPV within a few years after they become sexually active. Multiple concurrent and sequential infections with different oncogenic types of HPV are common. These tens of millions of infections are usually transient and clinically nonsignificant, although they frequently produce temporary cytologic changes. Fortunately, few HPV-infected women actually become persistently infected (for example, approximately 10 percent remain infected at five years); it is this smaller group that has a substantial risk (higher than 50



percent) of the development of a high-grade precancerous lesion or cervical cancer if screening is not performed. Thus, the possibility of overuse of HPV DNA testing is particularly problematic for women in their teens and 20s who are likely to have new, transient HPV infections but are unlikely to have cervical cancer because of the long period of latency—years or even decades—between the onset of HPV infection and the development of cancer.

Other forms of overuse are also possible. Excessively frequent use of HPV DNA testing could lead to the classification of large numbers of women as being at high risk even though their infections are destined to resolve. Such misclassification would, in turn, result in considerable anxiety, unnecessary expenditures, and overtreatment, with possible complications. Also, companies that manufacture diagnostic tests might expand the types of high-risk HPV included in their tests from the 13 types currently used to the 18 types described by Muñoz et al. or even more types. Before such expansion occurs, formal evaluations should be undertaken of the tradeoff implicit in screening for more types. The addition of types to the tests might lead to the identification of a small percentage of women at high risk who would otherwise have been missed and might marginally increase confidence that a woman with a negative test truly is at very low risk. However, it would also result in the inappropriate identification of tens of thousands of additional women as being at high risk.

Regardless of how it is implemented, the incorporation of HPV DNA testing into primary screen-

ing will result in informing millions of women with normal Papanicolaou tests that they are at increased risk for cervical cancer. The challenge is to develop clinical strategies that allow us to reap the benefits of HPV DNA testing without unduly alarming or overtreating large numbers of women. Recently introduced guidelines from the American Cancer Society, which recommend that HPV testing be performed no more frequently than every three years in women 30 years of age or older, should help. So, too, should interim guidelines currently under development for the care of women who test positive for HPV DNA but who have negative results on cytologic analysis. However, the greatest challenge will be assuring HPV DNA-positive women that they should not feel unduly alarmed or stigmatized while convincing them of the need for proper follow-up in order to identify those with persistent infection. Achievement of this balance is likely to require a considerable educational effort on the part of clinicians and health educators.

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2. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002;287:2120-9.
3. Sherman ME, Lorincz AT, Scott DR, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. *J Natl Cancer Inst* 2003;95:46-52.