

Human Papillomavirus

To Screen or Not to Screen

THE SEXUALLY active are faced with an epidemic of genital human papillomavirus (HPV) infection. The presence of this virus in the female genital tract correlates with an increased risk for the development of cervical dysplasia and invasive cancer. Despite intense research into this fascinating area, which will likely unfold the mysteries of cancer genesis, clinicians are faced with several immediate problems. As more evidence links the presence of HPV in the female genital tract with cervical cancer, efforts to detect HPV at earlier stages appear to help predict which women are at risk of cervical cancer.

See also pages 1239 and 1250

Unfortunately, the basic problem with HPV infection is that most infected individuals are asymptomatic and the virus cannot be cultured. Clinicians are therefore forced to rely on indirect methods of detecting HPV. Traditionally, the Papanicolaou test has yielded one mechanism for detecting HPV-induced changes: the examination of exfoliated cervical cells. Despite global evidence that populations undergoing cervical Papanicolaou's test experience much lower rates of deaths due to cervical cancer, the effectiveness of this time-honored screening method has come into question.¹ False-negative results, incorrect interpretation of results, and the lack of widespread availability are among the numerous issues plaguing the claim of Papanicolaou's test to public health success. Indeed, nearly one third of all women dying of cervical cancer have had a normal Papanicolaou's test result within the preceding 3 years!² Accordingly, efforts to detect HPV infection at earlier, asymptomatic phases have empirical appeal.

The studies by Reed et al³ and Zazove et al⁴ in this issue of the ARCHIVES support this basic "sooner-is-better" strategy from different perspectives. The study by Reed et al investigates a group of "lower-risk" women and correlates such patient factors as symptoms, demographics, and sexual practices with women who are at increased risk of HPV infection and therefore more likely to be at risk of cervical cancer. The study by Zazove et al

investigates different HPV detection methods in this same population, with a similar outcome. Both of these studies suggest that identifying women with HPV infection at earlier stages helps address the lack of sensitivity and the potential false-negative results of traditional screening with the Papanicolaou test.

Despite demonstrating this statistical advantage, the clinician is forced to ask whether identifying these women and intervening at earlier, asymptomatic stages of infection will favorably alter their outcomes. Despite the high correlation of cervical HPV infection with cervical cytologic changes, the majority of cervical HPV infections among these women appear to either spontaneously regress or remain stable. A smaller portion of infections will progress to dysplasia or cancer. The best test to help clinicians treat these patients has not yet been developed, ie, a method to determine which patients have HPV infections that are prone to progress and which will develop a less cancer-prone relationship with their lifelong viral infection.

The data presented by Reed et al imply that questioning about or "verbal screening" for newly identified risk factors may enhance the clinician's ability to identify individuals who warrant earlier intervention such as colposcopy with biopsy. Clinicians routinely incorporate inquiry about clinical symptoms into their evaluation of individual patients. Indeed, the question regarding the presence of itching, odor, or vaginal swelling can be easily applied to practice with little effort and at virtually no cost or inconvenience. However, it ultimately remains to be seen whether the cost of screening women with ultrasensitive polymerase chain reaction technology will ultimately improve outcomes, ie, prevent cervical cancer, in a cost-effective manner.

Unfortunately, although the finding of HPV infection in the female genital tract suggests a higher risk status when these women are compared with a noninfected cohort, the simple presence of the virus is still not a predictor of outcomes. Given the high prevalence of HPV infection in women suggested by this and other data that, as demonstrated, depend on the sensitivity of the viral screen being used, one wonders whether ultrasensitive methods such as polymerase chain reaction for detecting

HPV will ultimately prove to be of practical, predictive value for clinicians. This dilemma is reminiscent of the early "fibrocystic breast data" that correlated the presence of breast cancer (a common cancer) with a preexisting fibrocystic breast disease (a common condition). The clinical relevance, however, became moot when it was realized that nearly 40% of all women have some degree of fibrocystic disease. Indeed, if 40% of all women have "something" and most of them are asymptomatic, is it a "disease" at all?

Given the current trends in the HPV epidemic, it may be that a majority of the sexually active will eventually be exposed to HPV and that very early detection may yield a very poor predictive value despite the high cost of widespread application for some of these detection methods. Accordingly, it may not be the presence of HPV that is the issue but possibly the expression of HPV within a given individual. Clinicians must still rely on those screening methods that detect the expression of the HPV viral genome, such as the abnormal results of the Papanicolaou test, the cervigram, or visible changes of the cervix, to decide which patients should undergo the colposcopy-directed biopsy.

Despite the intellectual passion to determine a better or more precise method of detecting preneoplastic cervi-

cal disease, the issue for the clinician still remains much more fundamental. Nearly half of all women who die of cervical cancer have not had even a single Papanicolaou's test within 10 years preceding their deaths! In what way can precious resources be best used to address this dismal observation? The ultimate screening test for cervical cancer has yet to come along. Careful questioning regarding newly identified risk factors may help, but stressing healthy behavior and overall access to care currently is, and may likely remain, the most valuable tool to us as clinicians.

Gary R. Newkirk, MD
University of Washington
Spokane

1. Koss LG. The Papanicolaou test for cervical cancer detection: a triumph and a tragedy. *JAMA*. 1989;261:737-743.
2. Dunn JE Jr, Schweitzer VK. The relationship of cervical cytology to the incidence of invasive cervical cancer and mortality in Alameda County, California, 1960 to 1974. *Am J Obstet Gynecol*. 1981;139:868-876.
3. Reed BD, Zazove P, Gregoire L, Gorenflo DW, Lancaster WD, Ruffin MT IV. Factors associated with human papillomavirus infection in women encountered in community-based offices. *Arch Fam Med*. 1993;2:1239-1248.
4. Zazove P, Reed BD, Gregoire L, et al. Presence of human papillomavirus infection of the uterine cervix as determined by different detection methods in a low-risk community-based population. *Arch Fam Med*. 1993;2:1250-1258.