POLICY FORUM: CANCER

Preventing Cervical Cancer

Joanna M. Cain and Mary K. Howett

The introduction 50 years ago of the Papanicolaou smear for detecting premalignant changes in the cervix has decreased the incidence of invasive cervical cancer in countries where Pap smears and subsequent treatment of premalignant disease are readily available to women (*1, 2*). In the United States, there has been a 74% decline in the incidence of invasive cervical cancer between 1955 and 1992. The American Cancer Society predicts that there will be 12,800 U.S. cases of cervical cancer diagnosed through Pap smears and 4600 deaths this year (*3*). As with many diseases, the poor and disenfranchised develop cervical cancer disproportionately. The women who die from cervical cancer are usually those who have never had a Pap smear or who have long intervals between Pap screening. Cervical cancer causes about 250,000 deaths annually worldwide, with women in developing countries accounting for 80% of these deaths (*4*).

There is now compelling evidence that infection of the cervical epithelium with human papillomavirus (HPV) increases the risk of premalignant lesions and progression to cervical cancer. HPV testing, microbicidal agents that kill HPV, and vaccines to protect against HPV infection are new strategies to detect and prevent cervical cancer. When, where, and how to implement these strategies and whether they will have an impact in the developing world where the incidence of cervical cancer is highest are questions that still need to be answered. Problems with implementing HPV testing include: greater cost, restricted availability, treatment of lesions once a positive test is obtained, psychological consequences of a positive HPV test in the absence of disease, and the potential for overtreatment because of a high rate of false positives. On the other hand, HPV testing is rapid in an appropriately equipped laboratory and can even be performed on vaginal swabs that women collect at home and then send to the laboratory for analysis (*5*).

Screening for Cervical Cancer

Among women who have never been screened for cervical cancer, random colposcopy (microscopic examination of the cervix) reveals that 1 to 3% will have lesions in the cervical epithelia (although most of these are premalignant) (*6*). The Pap smear test analyzes changes in the appearance of a smear of cervical epithelial cells. Recent improvements in Pap screening include the introduction of thin-layer smears and automated reading of smears (*7, 8*).

HPV testing has been introduced in the United States, Europe, and Asia as an adjunct to Pap screening to detect virus in Pap smears that appear abnormal but do not show premalignant changes (termed ASCUS). The most recent HPV diagnostic test (Hybrid Capture II HPV DNA Assay, Digene Corp.) uses hybridization and a cocktail of HPV-specific probes to detect and type (high-risk versus low-risk) HPV. This sensitive assay has an average cost of $60 per test compared to $20 to $40 per test for the Pap smear. A positive HPV test determines those women who should undergo further examination by colposcopy.

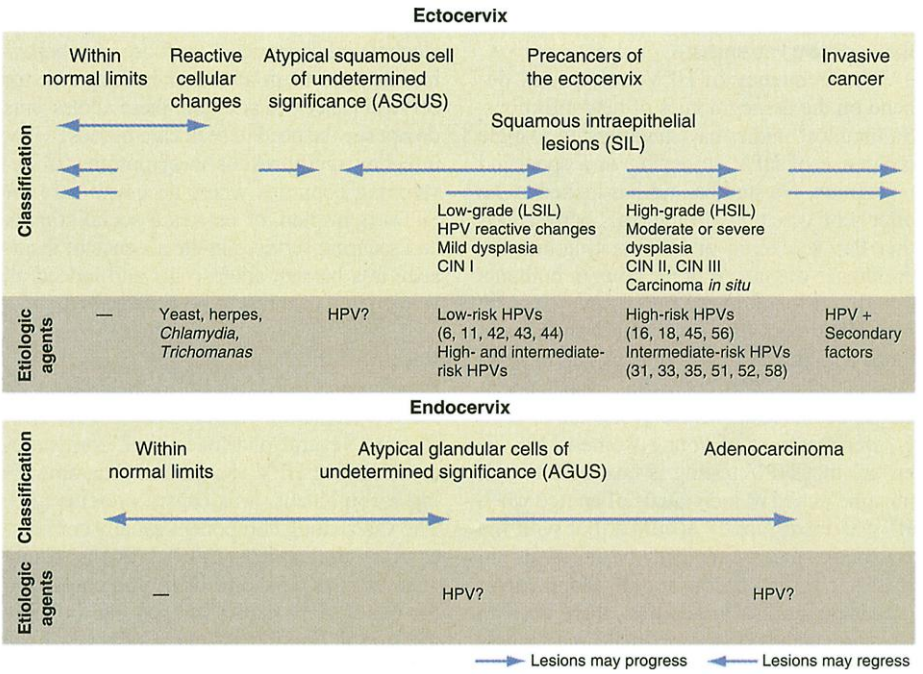
Although HPV testing could be used on its own as a primary screening tool, a positive HPV test does not confirm actual disease (either premalignant or malignant). Thus, HPV testing yields more false positive results when used independently of Pap screening (*5–7*). For example, in a South African study (*5*), vaginal swabs collected by women at home and tested for HPV yielded a false positive rate of 17.1% (95% CI, 15.1% to 19.3%) for the HPV test versus 12.3% (95% CI, 10.5% to 14.2%) for Pap screening ($p < 0.001$).

HPV Infection

HPV is acquired at a rapid rate during the initiation of sexual activity, primarily in the teen years (*9*). Testing of cervical tissue for HPV DNA confirms that HPV infection in women is a sexually transmitted disease (STD) of high incidence—HPV prevalence is about 25% to 39% of the sample group depending on age and geographic location (*6, 10*). Most of these women will have normal Pap smears, will not be aware of their HPV status, and will be asymptomatic for HPV infection.

A women's first inkling of HPV infection may be the report of abnormal cells on her Pap smear. The result of infection can be clearance of the virus, persistence with no disease, or development of a continuum of epithelial lesions that become increasingly abnormal. Low-grade lesions spontaneously regress, persist, or move into the continuum toward high-grade lesions (see the table, above). High-grade lesions rarely regress spontaneously and are likely to progress to carcinoma if not removed through surgery or laser ablation. Of all women who have a cervical lesion on a Pap smear that subsequently tests positive for HPV, only 1% will develop cervical cancer.

There are more than 100 HPV subtypes of which about 20 have oncogenic potential (see the table). Analyses of high-grade lesions by PCR consistently identify HPV 16 and 18 as the principal "high-risk" subtypes. HPV 6, 11, and others are considered "low-risk" and predominate in genital warts but are often found in low-grade lesions.



The authors are in the Departments of Obstetrics and Gynecology; Microbiology and Immunology, The Pennsylvania State University, College of Medicine MB103 HOSPITAL, Hershey, PA 17033, USA. E-mail: jcain@psghs.edu

Pros and Cons of HPV Screening

The availability of HPV testing raises the question of how and when it should be used for cost-effective screening. Failure to detect HPV infection does not change the follow-up procedure because new infections may occur in the future. Detection of a low-risk HPV subtype still mandates regular follow-up because even low-risk subtypes can be found in cancers, and re-infection with a high-risk subtype is possible. Likewise, detection of a high-risk subtype requires regular follow-up and would not *per se* mandate more aggressive surgical ablation, except in circumstances where further screening and evaluation might be limited (*6*), or concurrent diseases or infections (such as HIV) increase risk. Thus, except for ASCUS samples where failure to detect HPV may prevent an unnecessary colposcopy, it is currently unclear how HPV testing will alter the usual course of clinical care for a positive Pap smear.

The frequency of HPV testing will depend on the demographics of new infections. So far, most studies have investigated a single incidence of HPV screening in a specified population. No study as yet has looked at the effects of variations in intervals between either Pap screening or HPV testing and the preference of one test or the other or both in a broad and longitudinal population. Even in high-risk populations, greater than 70% of those with positive HPV screens will have no detectable disease (*6*). A major issue in cervical cancer screening is the avoidance of costly overtreatment of young women (*12*). To ensure that HPV testing is cost effective, it must be aimed at individuals of an age when HPV is most rapidly acquired, but with the knowledge that the majority of infections are readily cleared without the development of precursor lesions. In addition, there need to be more studies on the optimal time for follow-up and clinical treatment after a positive Pap or HPV test.

As more sophisticated strategies for screening (for example, HPV testing of Pap smears) are developed, education of the public will be crucial. Without education, there is the potential for harm if women assume that absence of high-risk HPV subtypes implies no future risk of infection or a natural protection against cervical cancer. The individual who tested negative at 15 or 25 years of age may well be positive at age 40. The acquisition of new sexual partners and exposure to new infections does not stop as individuals age, although HPV testing in women over 35 is more likely to identify persistent rather than transient infections. An assumption that a positive HPV test implies the presence of cervical cancer is equally as harmful.

The psychological impact of a positive HPV test and the possibility of cervical cancer has not been fully explored. Sensitizing even informed women to every subsequent variation in normal menstrual cycles as though they augured the onset of cancer is a concern. There is already a stigma attached to women with STDs. Leaving women with both a worry about developing cancer and a social stigma, often without adequate longitudinal access to care, is an unacceptable outcome for a test intended to detect disease. That women could be either overtreated at a young age with the potential for hysterectomy, or underserved because of a sense of false security, should be a strong cautionary note in the propulsion of HPV testing into the mainstream of cervical cancer screening.

As cervical cancer prevention strategies evolve, a big challenge will be that the prepubescent and adolescent girls most likely to need access to screening are those least likely to seek care (*13*). The risky behaviors of adolescents—sexual intercourse and the use of alcohol and cigarettes—are those very behaviors that put them at higher lifelong risk for cervical cancer. In addition, these adolescents do not see the need to seek care because HPV infection rarely results in symptoms. In developing countries where access to care for STDs is limited, or carries a social stigma, and securing services in the absence of insurance is a barrier, adolescents and indeed all women will continue to be underserved.

Vaccination

Preteens and teens will be a logical target for future vaccination efforts to prevent HPV infection. Several pharmaceutical companies are mounting HPV vaccination programs using recombinant virus capsid proteins (*14*). The vaccinating component usually comprises virus-like particles (VLPs), that is, empty virus capsids devoid of DNA and containing the major HPV capsid antigen and possibly the minor capsid antigen. Because of the exquisite antigenic specificity of HPV capsid antigens, there is unfortunately no cross protection. Thus, immunity against each HPV subtype requires vaccination with VLPs specific for that subtype. Most vaccines use a VLP cocktail of common HPV subtypes. For example, a cocktail including VLPs for HPV 16, 18, 31, and 45 could potentially prevent 75% of cervical cancers (*15*). However, the exact nature of the immune response required for protection is unknown. If the vaccine prevents certain subtypes from infecting individuals, it is possible that other subtypes will quickly fill the void. Phase I and II clinical trials of candidate VLP vaccines are in progress and should answer some of these questions.

Microbicidal Drugs

An additional approach to HPV prevention is the use of microbicidal agents to block or inactivate the virus. Currently, there are not any effective, commercially available, microbicides that can do this. Condoms have been reported to provide only partial protection against HPV transmission. Effective abrogation of HPV infection of human epithelial xenografts by alkyl sulfate microbicides has been reported (*16*) but further clinical testing of these preventative agents is needed. The immunostimulant Aldara has been used to ablate HPV-associated anogenital warts. Topical vaginal microbicides are practical, female-controlled, and inexpensive agents for prevention of STDs including HPV. Topical microbicides may be especially attractive in developing countries where vaccine delivery is economically challenging. As with vaccination, microbicides must be culturally acceptable with education to encourage use.

Conclusions

Education of the general public and cost effectiveness are the keys to success for new strategies to combat cervical cancer. HPV testing may reduce costs by identifying a low-risk group for less frequent screening. But there is no proof that the savings from HPV testing are greater than the expenses associated with increased screening of women identified as high-risk by a positive HPV test. Furthermore, Pap smears are already underused. Even in the United States where Pap screening is routine, more than half of the new cervical cancer patients have not had a Pap smear within 3 years. Thus, the likelihood that a new screening strategy would be more widely adopted requires careful investigation. In developing countries where Pap smears are either underused or not available, there may be a place for HPV testing as a primary screening method. But our view is that right now the primary concern should be consistent availability and use of Pap screening for women worldwide together with adequate follow-up of individuals with positive Pap smears.

References

1. R. Bergstrom and P. Sparen, *Br. J. Cancer* **81**, 159 (1999).
2. P. Sasieni and J. Adams, *BMJ* **318**, 1244 (1999).
3. American Cancer Society, *Cancer Facts and Figures, 2000* (Atlanta, Georgia, 2000).
4. W. M. Schoell *et al.*, *Semin. Surg. Oncol.* **16**, 203 (1999).
5. T. C. Wright *et al.*, *JAMA* **283**, 81 (2000).
6. K. J. Syrjanen, in *Papillomavirus Reviews: Current Research on Papillomaviruses*, C. Lacy, Ed. (Leeds University Press, Leeds, UK, 1996), pp. 189–205.
7. M. Schiffman *et al.*, *JAMA* **283**, 87 (2000).
8. A. Brown and A. Garber, *JAMA* **281**, 347 (1999).
9. M. L. Hutchinson *et al.*, *Cancer* **87**, 48 (1999).
10. J. J. Carter *et al.*, *J. Infect. Dis.* **174**, 927 (1996).
11. L. O. Eckert *et al.*, *Infect. Dis. Ob/Gyn.* **7**, 158 (1999).
12. M. Van Ballegooijen *et al.*, *Br. J. Cancer* **76**, 651 (1997).
13. C. A. Ford *et al.*, *JAMA* **282**, 2227 (1999).
14. M. E. Sherman *et al.*, *Diagn. Cytopathol.* **18**, 5 (1998).
15. F. X. Bosch *et al.*, *J. Natl. Cancer Inst.* **87**, 796 (1995).
16. M. K. Howett *et al.*, *Antimicrobial. Agents and Chemo.* **43**, 314 (1999).