Do Our Current Cervical Cancer Control Strategies Still Make Sense?

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The dramatic decrease in cervical cancer mortality seen over the last 50 years is the result of cervical cancer control programs conceived and established prior to understanding the importance of human papillomavirus (HPV) in the development of both benign and malignant neoplastic cervical lesions. At present in the United States, cervical cancer control is achieved by routine cytologic screening to identify women with Pap smears showing "low- or high-grade squamous intraepithelial lesions (SIL)/carcinoma in situ (CIS)" or repeated "atypical squamous cells of undetermined significance (ASCUS)." Women with SIL/CIS and repeated ASCUS are referred for diagnostic colposcopy (examination of the cervix through a magnifying lens) and biopsy. Those with biopsy-confirmed cervical intraepithelial neoplasia grade 2 or 3 (CIN 2-3) and frequently those with CIN grade 1 (CIN 1) undergo ablative treatment of the transformation zone (area on the cervix originally surfaced by columnar epithelium that has undergone squamous metaplasia). Close follow-up of women with ASCUS only is also deemed important by many clinicians. This relatively aggressive approach to cervical cancer control is based on the hypothesis that invasive cervical cancer is preceded by an intraepithelial stage termed carcinoma in situ, which, unless detected and eradicated in a timely fashion, evolves into invasive cervical cancer within an average time span of 10-20 years. Referral of women with low-grade SIL (LGSIL) for colposcopy, biopsy, and close follow-up or treatment is based on acceptance of the idea [proposed almost 30 years ago by Richart and Barron (1)] that CIS evolves from CIN 1 (and perhaps from ASCUS) and that CIN 1, CIN 2, and CIN 3/CIS represent a morphologic and biologic continuum of progressive, consecutive stages in the development of invasive cancer. This high rate of progression of CIN 1 lesions has recently been questioned (2). Most recent natural history studies [reviewed in (3)] suggest that fewer than 30% of the women with CIN 1 (who had not had a biopsy or who had not been treated) will develop CIN 3. It has become clear that many CIN 1 lesions are simply self-limited cervical infections with either high- or low-risk types of HPV. Data presented by Park et al. (4) support this idea. The realization that the majority of low-grade CIN appears to spontaneously resolve, along with the high costs incurred by follow-up of all women with ASCUS and LGSIL, has prompted a search for alternative methods for management of women with these lesions. The possible use of DNA assays in the management of women with LGSIL or ASCUS is now being explored a search for alternative methods for management of women with these lesions. The possible use of DNA assays in the management of women with LGSIL or ASCUS is now being explored.
management by 1) immediate colposcopy and biopsy (the approach of many practitioners in the United States), 2) follow-up by cytology alone (the practice in Canada and many European nations), and 3) referral for colposcopy and biopsy on the basis of detection of high-risk types of HPV DNA. Park et al. (4) suggest that testing for the monoclonality of CIN 1 lesions may also be useful in the triage of women with low-grade Pap smear abnormalities.

However, data from a number of recent studies examining the role of HPV infection in the development of cervical epithelial pathology suggest that it may be necessary to consider a much more basic revamping of both our view of the pathogenesis of CIN 3 and invasive cervical cancer as well as our overall approach to detection of CIN 2-3.

Our study (5) examining the development of biopsy-confirmed CIN 2-3 in relationship to cervical HPV infection shows that CIN 2-3 is a common and early manifestation of cervical infection with high-risk types of HPV. Interestingly, more than 50% of the women who developed CIN 2-3 in this study did so without first developing CIN 1. Furthermore, all women who developed CIN 2-3 did so within 24 months of initial detection of cervical HPV DNA regardless of whether or not they first developed CIN 1, with most CIN 2-3 being detected within the first 6 months of initial detection of high-risk types of HPV.

These data, along with morphologic observations of HPV-transfected epithelial cell cultures (6), suggest that CIN 2-3 lesions may be initially established as such, rather than evolving from CIN 1. At inception, CIN 2-3 lesions might simply be the result of changes associated with infection of metaplastic epithelium by high-risk types of HPV. Whether CIN 1 lesions ever "evolve" into CIN 2-3 is unclear. If CIN 1 and CIN 2-3 are two separate lesions, which, in some women, are established concomitantly, CIN 1 might appear to precede (or evolve into) CIN 2-3 only because CIN 1 lesions are located in areas of the cervix that favor early cytologic detection. CIN 2-3 lesions are more likely to occur higher in the cervical canal (7) and, therefore, may be harder to detect. If CIN 2-3 is the only real cervical cancer precursor lesion and ASCUS and CIN 1 are not on the biologic pathway to cancer, it may be most cost-effective to develop cervical cancer-control strategies on the basis of identification of women with high-risk types of HPV and to ignore the presence or absence of ASCUS or LSIL.

In our ongoing cohort studies examining women with various cytologic findings at study entry, we find that risk of developing CIN 2-3 is independently associated with detection of high-risk HPV DNA but not with ASCUS or LSIL. Cuzick et al. (8) screened 1985 women presenting for routine Pap smears by both cytology and HPV DNA assay and referred for colposcopy and biopsy those with either high levels of HPV DNA or cytologic abnormality. The sensitivity and positive predictive value of any abnormal cytologic finding for biopsy-confirmed CIN 2-3 was only 56% and 35%, respectively, while the sensitivity and specificity of HPV DNA assay for the identification of women with CIN 2-3 was 75% and 42%, respectively. The results of these studies, the increasing costs, and the medical and legal problems associated with Pap screening, along with the ongoing development of sensitive, specific, reproducible, and quantitative HPV assays that are appropriate for nonresearch settings, make it important to undertake studies examining the question of whether HPV testing, cytology, or a combination of these two assays will provide the most cost-effective approach to cervical cancer control.

References

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