Preventing Cervical Cancer Globally by Acting Locally: If Not Now, When?

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Invasive cervical cancer remains an important public health problem as a leading cause of cancer-related death in women in many developing countries (1) (http://globocan.iarc.fr/). Despite the promise of a highly efficacious prophylactic human papillomavirus (HPV) vaccine (2–4), HPV vaccination will not prevent approximately 30% of invasive cervical cancer nor does it treat preexisting...
infections and precancerous lesions, and it requires cold chain delivery and is expensive to administer. Even if vaccines were made available at a greatly reduced cost and widespread vaccination could be rapidly implemented globally (which is not possible in the near-to-mid term), the primary prevention of invasive cervical cancer by prophylactic HPV vaccination would not be realized for another 30 or more years, during which time an estimated 20 million additional cervical cancers will occur in less developed countries (1) (http://globocan.iarc.fr/). Therefore, secondary prevention, that is, screening and treatment of precancerous lesions, will be needed for a long time to come.

In this issue of the Journal, Denny et al. (5) present long-term follow-up results of a randomized controlled trial to compare carcinogenic HPV DNA testing with visual inspection of the cervix after acetic acid staining (VIA) as the primary screen for precancerous cervical lesions in a screen-and-treat strategy that eliminates the need for confirmation by biopsy. This landmark study was conducted in a low-resource setting where such strategies are needed to prevent the majority of invasive cervical cancer. The authors made the following observations: 1) HPV testing with immediate cryotherapy of HPV DNA–positive women prevented 72.5% of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and 77.4% CIN grade 3 or worse (CIN3+) over 36 months, more than the percentages of CIN2+ and CIN3+ prevented by the VIA-based screen-and-treat approach (31.0% and 38.1%, respectively); 2) The sensitivity for 3-year cumulative CIN2+ was statistically significantly greater for HPV testing vs VIA (90% vs 53%, respectively), whereas the specificity was virtually identical (83% vs 78%, respectively); 3) Cryotherapy was 75%–77% effective at ablating CIN2+ lesions; and 4) Cryotherapy of HPV-positive women non-statistically significantly increased the incidence of HIV infection. Importantly, Denny et al. have demonstrated that a simplified screen-and-treat prevention program that is based on HPV DNA screening, which eliminates costly and time-consuming colposcopically directed biopsy for diagnosis, can effectively and rapidly reduce precancerous lesions in a low-resource setting.

The superior performance of HPV DNA testing compared with VIA in a screen-and-treat program is predicted by studies (6–13) that have shown that HPV DNA screening is more sensitive for detection of precancerous lesions and early-stage cancers compared with VIA or cytology. A highly sensitive test, as demonstrated in
In countries that lack the capacity for surgical treatment or cancer screening, the risk of developing cervical cancer for women can be treated will be useful but not perfect. The efficacy of treating their lesion. All visual assessments of the cervix, colposcopic examination as typically practiced (28) is less accurate than commonly realized for determining if treatment is warranted. Many precancerous lesions detected and treated are CIN2, an equivocal precancerous diagnosis that often regresses without therapy because it represents an admixture of CIN3 (22–24) and acute HPV infections that will never become invasive cervical cancer. Finally, restriction of screen-and-treat programs to the proper age range would decrease overtreatment. HPV DNA testing works best for women aged approximately 30–35 years or older, or women at least 15–20 years older than the median age of sexual initiation in the population. In this age group, cervical cancer is still preventable, and a greater proportion of the detected HPV infections are likely to be persistent and strongly linked to the eventual development of cancer compared with transient infections found in younger women (25).

With the advent of accurate low-cost HPV DNA testing (16), we can anticipate offering low-income women a highly sensitive screen once or twice in a lifetime. The exact strategy used will vary. In this South African trial (5), nurses collected the specimens and treated screen-positive women with cryotherapy after a visual triage that determined indication for cryotherapy. The menu of secondary prevention options, each with trade-offs of effectiveness, costs, and acceptability, will include which test to use (as more become available), which sampling method, and the management of HPV DNA–positive women and their treatment (Figure 1). Substituting pelvic examinations with self-collection of a cervicovaginal specimen [albeit with some loss of sensitivity (26)] might reduce programmatic costs, clinic burden, and visit times while increasing screening coverage. Some countries will demand a high level of diagnostic accuracy before treatment. However, colposcopic evaluation with biopsy diagnosis is limited by the availability of trained colposcopists (27) and pathologists; more fundamentally, a single colposcopic examination as typically practiced (28) is less accurate than commonly realized for determining if treatment is warranted. When advanced diagnostic services are in short supply, it may be easier to establish and maintain a reliable treatment threshold based on an objective biomarker (eg, p16INK4A immunohistochemical staining) instead of a morphologic assessment (29).

More than a quarter million women continue to die each year from cervical cancer; we cannot justify waiting for HPV vaccines nor insist on replicating unsustainable first-world screening strategies. As demonstrated in the South African trial (5), a simplified program of HPV screen and treat could effectively reduce the population risk of cervical cancer, including women already infected with HIV (30). With low-cost accurate HPV screening tests coming online, cervical cancer prevention is becoming more effective, affordable, and feasible for low-resource settings. Future research should focus on the development of low-cost, topical therapeutics to simplify treatment.
Nevertheless, we are now poised to implement large-scale prevention programs to reduce the unequal burden of invasive cervical cancer with the prevention tools that are now available to us. All that missing is the political will and the monetary investment to do so.

References


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