Preventing Cervical Cancer Globally

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Abstract

Cervical cancer is one of the leading causes of cancer and cancer-related deaths among women worldwide. More than 85% of cases and deaths occur in the developing world where the availability of effective screening is limited. In this issue of the journal, Pierce and colleagues (beginning on page 1273) describe a novel technique using a high-resolution microendoscope (HRME) to diagnose cervical dysplasia. This perspective reviews the limitations of existing cervical cancer screening methods currently in use in low-resource settings and the potential for HRME imaging to contribute to cervical cancer prevention in the developing world. Cancer Prev Res; 5(11); 1257–9. ©2012 AACR.

Cervical cancer was previously the leading cause of cancer-related death among women in the United States. However, the incidence and mortality has decreased by approximately 70% over the past 40 years. This decline is largely due to the introduction of the Papanicolaou (Pap) smear in 1941, which has led to a systemic effort to detect early cervical cancer and precancerous lesions (1). The Pap smear has been associated with a sustained reduction in cervical cancer incidence and mortality. In stark comparison, cervical cancer continues to be the first or second leading cause of cancer and cancer-related death among women in developing countries (2). This inequity is largely due to the lack of early detection programs, which in turn can be ascribed to a lack of appropriate screening tools for resource-limited settings.

Virtually, all cases of cervical cancer are caused by persistent infection with high-risk types of the human papillomavirus (HPV; ref. 3). The discovery of HPV as the infectious etiologic agent of this disease led to the development of effective preventive vaccines that have been commercially available since 2006 (4, 5). The Centers for Disease Control and Prevention (CDC) recommends vaccination of girls and boys between the ages of 11 and 12 years before the onset of sexual activity. Although these vaccines hold the promise to further reduce the incidence of cervical cancer, the uptake of HPV vaccination has been poor. Recent reports have shown that less than one-half of eligible children in the United States undergo HPV vaccination, with fewer than 30% of those initiating vaccination completing the 3 vaccine series (6, 7). Economic, political, and logistical barriers, particularly in developing countries, have limited the development of universal mass screening programs. In addition, the existing vaccines do not cover all high-risk HPV types, so routine cervical cancer screening will still be necessary, even for women who have been vaccinated. Cervical cancer screening will therefore remain necessary for the foreseeable future.

Current approaches for cervical cancer prevention in developed countries include cytologic screening with a Pap test, often in combination with HPV testing, or with HPV testing alone. Patients with abnormal results undergo colposcopy with directed biopsies of abnormal appearing areas. If clinically significant precursor lesions are identified, ablative (e.g., cryotherapy) or excisional procedures [e.g., loop electrosurgical excision procedure (LEEP), or cold knife conization] are conducted. Although these algorithms are effective in preventing cervical cancer, they are expensive, cumbersome, and require high-level infrastructure and well-trained personnel. In addition, they require 3 separate patient visits with the communication of test results between visits.

There is therefore a significant need for alternative solutions to support screening for cervical cancer, particularly in developing countries where resources are limited. Ideal characteristics of such a program include: (i) a low-cost test that can be conducted in a primary health care facility by a trained nurse or paramedical staff; (ii) minimal technology or training is required to conduct, process, or interpret the test result; (iii) test results are immediate or available within a few hours; and (iv) screening and treatment is conducted at the same visit. To meet these criteria, single visit “see-and-treat” approaches have been explored, particularly with visual inspection with acetic acid (VIA) and cryotherapy. VIA consists of a trained healthcare provider examining the cervix with the naked eye before and after the application of acetic acid. Whitening of the epithelium is indicative of a precancerous lesion, and ablation with
cryotherapy can be immediately conducted at the same visit. The sensitivity of VIA to detect cervical dysplasia and cancer in low-resource settings has been shown to be similar to standard colposcopy but with a lower specificity (8–12).

Another possible alternative to Pap testing in low-resource settings is high-risk HPV DNA testing. Sankaranarayanan and colleagues (13) conducted a randomized trial of 131,746 women between the ages of 30 and 59 years in rural India. Patients were randomized to either a single lifetime screening test using 1 of 3 screening methods [cervical cytology, VIA, or HPV testing by Hybrid Capture 2 (HC2; Qiagen)] or standard-of-care treatment consisting of cervical cancer health education. At 8-year follow-up, women who underwent a single HPV test versus standard-of-care had a 50% reduction in cervical cancer incidence and cervical cancer mortality. However, there were no significant differences in cervical cancer incidence or mortality in the groups screened by cytology or VIA compared with standard-of-care (13).

While these HPV testing results are promising, the currently available HPV tests pose several challenges for low-resource settings. They are expensive ($50–$100 per test in the United States), require infrastructure for processing, and there is a waiting time of 1 or more days for results. However, a rapid-result HPV test (careHPV; Qiagen) is currently undergoing evaluation. It is lower in cost and provides results within a few hours. Qiao and colleagues (14) recently conducted a cross-sectional study of 2,388 women of ages 30 to 54 years in China. Each study participant underwent HPV testing using traditional testing methods (HC2), HPV testing using the rapid-result testing (careHPV), as well as VIA. Colposcopy with directed biopsies was conducted in all patients as the reference standard. There were no significant differences in the detection of cervical intraepithelial neoplasia (CIN2/3) or cancer between the 2 HPV testing methods. Both methods were noted to be superior to VIA. In addition, the authors compared provider-collected cervical samples with patient self-collected vaginal samples and noted no significant differences in the sensitivity and specificity. These findings and others (15) show promise for the potential use of rapid-result HPV testing as a primary screening method, particularly in the developing world. As HIV coinfection with HPV has been associated with increased cervical cancer risk especially in developing countries (16), high-risk HPV testing and screening may help to reduce the burden of CIN in HIV-infected women through prevention and early intervention (17).

However, the low specificity of both HPV testing and VIA can lead to false positive results, resulting in the overtreatment of many benign conditions, which do not increase cervical cancer risk or require intervention. This overtreatment increases the cost of such prevention programs and results in unnecessary concern for patients. In settings where colposcopically directed biopsies and histopathologic review are not feasible, diagnostic methods that add specificity to these screening methods by better identifying patients requiring cryotherapy or other intervention is highly desirable.

In this issue of the journal, Pierce and colleagues describe a novel cervical visualization technique that can be used as part of a "see-and-treat" approach (18). The technique uses a low-cost, high-resolution microendoscope (HRME) imaging system to evaluate epithelial cell morphology. Proflavine, a topical contrast agent, is applied to the cervix in a manner similar to the application of acetic acid in colposcopy. The tip of a small fiber optic probe is then placed directly onto the cervical epithelium, and the fluorescence from the proflavine-stained epithelium is transmitted back to the HRME unit and displayed on a laptop computer screen. Morphologic features typically evaluated by pathologists including nuclear crowding, pleomorphism, and nuclear-to-cytoplasm (N/C) ratio are assessed in vivo in real-time. Image analysis software is then used to quantify nuclear morphology parameters and to calculate N/C ratio.

The authors describe a pilot study evaluating this technique in 174 women in rural China. All patients underwent HPV testing, VIA, colposcopy, and HRME imaging. Cervical biopsies were obtained in all patients with abnormalities noted on colposcopy. Of the 174 women in the study, 69 were noted to have abnormalities on colposcopy, but only 12 (17%) showed high-grade disease (CIN2 or greater) on biopsy. HRME imaging correctly classified all 12 high-grade areas (100%) as abnormal and correctly classified 38 of the remaining 57 (67%) as normal. Furthermore, when patients were stratified on the basis of a positive high-risk HPV DNA test, HRME imaging correctly identified 100% of the patients with CIN2 or greater. Of the 30 patients with a positive high-risk HPV DNA test but no histologic evidence of disease, only 6 patients (20%) were incorrectly identified as abnormal on HRME imaging.

The findings from this study suggest that HRME imaging could provide a complementary technique to existing cervical cancer screening methods in resource-limited settings. HRME was noted to improve the specificity of current cervical visualization techniques, such as VIA or colposcopy, potentially leading to more accurate identification of patients needing cryotherapy or other treatment. The study results also support the potential use of HRME imaging as a first-step diagnostic tool following a positive high-risk HPV screening test.

As the authors state, the study was limited by a study design not reflective of the intended use of HRME imaging as an adjunctive diagnostic tool to triage patients with a positive HPV screening test or lesion noted on VIA. Furthermore, the required training methods and learning curve for use of this technology were not assessed. It remains unclear what level of training and personnel are required to conduct HRME. However, the study provides excellent preliminary data for this novel technique that can potentially be incorporated into "see-and-treat" protocols. The strengths of the study include that it was conducted in rural China, showing the feasibility of using...
this tool in resource-limited settings. Furthermore, each patient underwent VIA, colposcopy, and HRME imaging by the same practitioner, and histopathologic correlation with biopsy was obtained for all abnormalities noted on VIA or colposcopy. If the earlier described performance characteristics are validated in a large clinical trial, HRME imaging may prove to be an important tool to add to cervical cancer screening and prevention efforts in the developing world, where they are needed most.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References
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