Recent Evidence on Cervical Cancer Screening in Low-Resource Settings

In September 2009, the Alliance for Cervical Cancer Prevention (ACCP) partners summarized and shared key findings and recommendations for effective cervical cancer screening and treatment programs in low-resource settings. Among their findings were the following:

- The most efficient and effective strategy for detecting and treating cervical cancer precursors in low-resource settings is to screen using either visual inspection with acetic acid (VIA) or human papillomavirus (HPV) DNA testing and then to treat using cryotherapy.
- The use of HPV DNA testing followed by cryotherapy results in a greater reduction in the incidence of cervical cancer precursors than the use of other screen-and-treat approaches.
- When conducted by competent providers, cryotherapy is a safe way of treating precancerous cervical lesions and results in cure rates of at least 85 percent.

The current fact sheet presents evidence from selected reports of screening and treatment that have been published since the paper cited above was written, in both low- and high-resource regions. This recent information continues to support the use of HPV DNA technologies and—until low-cost versions are available for use in developing countries—the use of visual inspection methods for cervical cancer screening. Cryotherapy continues to perform well for treating precancerous lesions in low-resource settings, although the cure rate is not as high as that found in clinical trials in developed countries.

Cervical cancer incidence and mortality update

New estimates of worldwide and regional cancer incidence and mortality published by the World Health Organization in the GLOBOCAN 2008 report confirm the prediction that the numbers for cervical cancer would continue to climb, especially in developing countries. The estimated annual incidence in the less-developed countries of the world is now more than 450,000 and the mortality more than 240,000. Using GLOBOCAN 2002 figures, more than 80 percent of deaths from cervical cancer worldwide were estimated to be in developing countries; in GLOBOCAN 2008, it was 88 percent; and by 2030, it is predicted to be at least 98 percent.

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In spite of this discouraging trend, studies reviewed here bring promising news: they demonstrate good results for the feasibility and accuracy of screening technologies that are alternatives to resource-intensive Pap smears. When used in comprehensive prevention programs that include HPV vaccination of girls and young adolescent females before exposure to HPV, timely screening with HPV testing or visual inspection, along with appropriate treatment, can slow the loss of lives from cervical cancer.
**HPV types in women with normal cytology**

In order to provide baseline values for the prevalence of HPV types worldwide, a meta-analysis of HPV DNA screening studies on more than a million women with normal cytology was recently published: the studies spanned five continents and almost 15 years. These data are important for evaluating the potential impact of prophylactic HPV vaccines, which are now licensed in more than 100 countries. The authors found that although the prevalence of HPV types varied somewhat across countries, types 16, 18, 31, 52, and 58 were consistently among the 10 most common in all regions, which is similar to previous findings. A limitation of the analysis is that more than 85 percent of women tested were from Europe and North America.

**HPV types in cervical cancer cases**

Baseline values for HPV type prevalence in cases of cervical cancer are important because these can reveal whether the types in cancers are changing as more of the population is vaccinated and whether new vaccines are targeting the correct types. A meta-analysis looked at papers published between 1990 and 2010 on more than 30,000 cervical cancer cases. The most common HPV types found, in order of decreasing prevalence, were HPV 16 (57 percent), 18 (16 percent), 58 (4.7 percent), 33 (4.6 percent), 45 (4.5 percent), 31, 52, and 35. In addition, more specimens than in previous studies showed infection with several HPV types, probably both because tests have become more sensitive and more types are now included in laboratory protocols. The authors caution that it is increasingly difficult to attribute a given cancer case to a specific HPV type. About 38 percent of the cases studied were from East Asia, while 6.5 percent were from Africa.

Findings of another report, this one on about 9,000 cervical cancer specimens, came from women in 38 countries in Europe, North America, South and Central America, Asia, Africa, and Oceania. The most common HPV types, found in 91 percent of the cancers, were 16 (61 percent), 18 (10 percent), 45 (6 percent), 31, 33, 52, 35, and 58. Ninety percent of the specimens came from Europe, Asia, South and Central America; only 6 percent were from Africa.

**Reports on the accuracy of screening methods**

Investigators continue to evaluate screening technologies in meta-analyses, randomized clinical trials, and cervical cancer prevention programs. The new evidence adds support for the use of HPV DNA testing as the primary technology for cervical cancer screening, both in high-resource areas and in developing countries. Despite this evidence, significant barriers to widespread use of HPV DNA testing stand in the way, both in high- and low-resource areas. In high-resource countries, changing the paradigm of frequently repeated Pap smears will require educating providers and patients as well as changing the current guidelines, while in low-resource regions, cost remains a deterrent. For low- and middle-income countries, studies of visual screening confirm that these methods offer a low-cost, effective option until affordable HPV DNA technologies become more widely available.
Accuracy of screening methods

Sensitivity and specificity

In order to assess whether a screening method is correctly identifying precancerous lesions, all women in a study should be tested using a “gold standard” as well as the screening methods in question. The gold standard for cervical lesions is usually colposcopically-directed biopsy, followed by histological analysis. Colposcopy is the examination of the cervix under magnification and bright lighting to identify visible clues suggestive of abnormal tissue. Biopsies can be taken of areas that appear abnormal, or if abnormalities are not evident, a sampling technique can be used.

Sensitivity is the proportion of true positives (lesions defined by histological diagnosis) that are correctly identified by the screening method. For example, a screening method that identifies as positive eight out of ten lesions diagnosed by histology has a sensitivity of 80 percent.

Specificity is the proportion of negatives that are correctly identified. A method with a high specificity ensures that healthy women are not given treatment.

Verification bias

The sensitivity and specificity of screening methods in clinical trials are calculated as explained above. However, in observational studies, typically only screen-positive women receive further testing (e.g., histological analysis). This results in a potential “verification bias” and associated over-estimation of screening test sensitivity.

This happens because some of the women who were negative on the screening test may have had lesions, but were never tested with the gold standard. Thus the number of true positives may be underestimated.

Another type of verification bias occurs when only women with abnormal colposcopy results have biopsies and histological analysis. Studies have indicated that colposcopy can miss 20 to 30 percent of cases of CIN2/3.*

Meta-analysis of VIA studies

The authors of a meta-analysis9 on the accuracy of VIA concluded that it has been shown to be a simple, low-cost, and efficient alternative to cytologic testing in low-resource areas. They found 57 studies that met their criteria, and chose 26 of these for the primary analysis. In these, histology was performed on all women (thus eliminating verification bias) and the results showed 80 percent sensitivity and 92 percent specificity (see box) for VIA. The majority of the women screened were between 25 and 65 years of age. Study region, capacity of screener, or size of the study population did not affect accuracy.

Meta-analysis of studies comparing HPV DNA testing, VIA, and cytology

A recent report10 from mainland China concluded that HPV DNA testing is highly sensitive and moderately specific for cervical intraepithelial neoplasia 3 or worse (CIN3+; CIN3 is the usual immediate precursor to invasive cervical cancer), with consistent results across study sites and age groups. This paper reviewed reports of more than 30,000 women from population-based screening studies done between 1999 and 2008, with the aim of assessing whether HPV DNA testing could be applied to cervical cancer screening programs in China. About 75 percent of the women tested were between the ages of 30 and 50 years. The studies used concurrent HPV DNA testing, liquid-based cytology, and VIA; women positive for any test were referred for colposcopy and biopsy. Even though not every woman had a biopsy, verification bias (see box) was stated to be low because every woman had three screening tests. Sensitivities of HPV DNA testing, cytology, and VIA were, respectively, 98, 88, and 55 percent, while specificities were 85, 95, and 90 percent.

Clinical trial evaluating HPV DNA testing and VIA

A clinical trial in South Africa assessed VIA and HPV DNA testing and concluded in 2005 that both approaches were safe and resulted in a lower prevalence of high-grade cervical cancer precursor lesions compared with delayed evaluation, at both 6 and 12 months.11 HPV DNA testing followed by treatment with cryotherapy performed better than VIA plus cryotherapy in women in the trial, who were aged 35 to 65 years.

A large clinical trial in South Africa showed that, after 3 years, HPV DNA testing plus treatment had reduced the occurrence of CIN3+ by more than 77 percent, and that VIA plus treatment reduced it by 38 percent, compared with a control group.

A 2010 follow-up\textsuperscript{12} to the earlier report provides important information on the longer-term efficacy of these screening strategies. After 36 months, researchers found that HPV DNA testing plus treatment had reduced the occurrence of CIN3+ by more than 77 percent, and that VIA plus treatment reduced it by 38 percent, compared with a control group. Sensitivities for HPV DNA and VIA were 90 percent and 53 percent, respectively, and specificities were 83 percent and 78 percent. Because HPV DNA testing correctly identified both positive and negative women more often than VIA, using this test for screening was associated with less undertreatment as well as less overtreatment than VIA.

The efficacy of a screen-and-treat program is influenced not only by accuracy of the screening test but also by the ability of the treatment, in this case cryotherapy, to eliminate CIN2+ lesions identified by screening. While cryotherapy was highly successful in this trial, eliminating 75 to 77 percent of CIN2+ lesions, this was lower than previously reported 85 to 90 percent cure rates for clinical trials in developed countries and for less rigorous studies in developing regions.\textsuperscript{7} The authors noted that in their South Africa trial, women underwent four separate examinations and that this rigorous assessment may explain the (more accurate) finding of lower performance for cryotherapy.

The investigators concluded that, with the development of an inexpensive HPV DNA test, HPV DNA screening, followed by treatment when necessary, is an attractive option for cervical cancer prevention in low-resource settings.

\textit{Observational studies of visual inspection screening programs}

Bangladesh has no organized screening program, but recently the government decided to expand opportunistic VIA screening, making it one of the first countries to introduce VIA for its national cervical cancer screening program.\textsuperscript{13} A report on this program\textsuperscript{14} announced that more than 100,000 women over 30 years of age had been screened, with a VIA positivity rate of less than 5 percent—a very low rate, which was attributed to extensive training and to the predominantly Muslim population.

Of the women screened, results were available for only about 2,200 who attended a particular clinic. These women, who all had positive VIA results, subsequently had repeat VIA by gynecologists at the clinic: only about half of the women were found to have positive VIA results at this second visit. The authors also noted a problem with the treatment of screen-positive women: only half of those with high-grade precancers received treatment. This rate could be improved by offering treatment immediately following colposcopy rather than waiting for histopathology results (which is standard practice in the country). While the program has many challenges, these early efforts mark a significant forward step in cervical cancer prevention in this country.

Two studies in Africa\textsuperscript{15,16} evaluated the feasibility of using two visual inspection methods for cervical cancer screening and assessed their performance in the field; the methods were VIA and visual inspection with Lugol’s iodine (VILI). Women in the studies were between 25 and 59 years of age, with at least 73 percent younger than age 45. The studies, in Tanzania and Angola, found that it is feasible to set up visual inspection screening programs in low-resource countries, the services are safe and well accepted, and health workers can be trained to accurately screen women for cervical cancer and precancer. The programs also established platforms to train health workers and doctors for the future.
The reported sensitivity in the Tanzania study for VIA (for CIN2/3 lesions) was 61 percent and the specificity 98 percent; in Angola the numbers were 71 percent and 94 percent. For VILI in Tanzania, sensitivity was 94 percent and specificity 97 percent; in Angola the sensitivity was 88 percent and specificity 69 percent. In both studies, colposcopy was performed on all participants, but histology was done only for women with abnormal colposcopy results (about 4 to 6 percent of total study participants). This could have increased the reported sensitivities of the tests.

Positivity rates appear low in these populations, around 4 to 7 percent, except for a 32 percent positivity rate for VILI in Angola. Investigators noted that many test providers were not able to distinguish the color changes seen in VILI-positive cases from irrelevant conditions such as ectropion or inflammation, in spite of repeated training. This may be a limitation of VILI in these settings. Another challenge identified in the studies was providing appropriate treatment. In the Tanzania study, only 21 of 33 women with CIN2/3 received treatment, while in the Angola study, 374 women were treated with cryotherapy or loop electrosurgical excision procedure (LEEP), yet only about 20 percent of these had subsequently confirmed CIN2/3.

Studies in high-resource countries

A publication on results of HPV DNA testing in Denmark provides information about the long-term efficacy of this method; the study followed more than 7,000 women for over 13 years.\(^\text{17}\) The women were 20 to 29 years of age at enrollment. Investigators found that being positive for HPV 16 carries the highest risk for progression to high-grade cervical lesions. Women who had normal cytology but were positive for HPV 16 at baseline had a 27 percent chance of developing CIN3+ within 12 years of follow-up, and for women with HPV 16 at two exams 2 years apart, the risk was 47 percent.

In contrast, only three percent of women who had a negative HPV DNA test for 13 high risk types developed CIN3+ within the timeframe of the study, indicating that frequent screening of these women may be unnecessary. The researchers found that although infection with some types, such as HPV 53, 56, 59, and 68, were prone to persist for 2 years, they did not lead to lesions during the entire follow-up period.

A study in Italy\(^\text{18}\) investigated the efficacy of HPV DNA testing for CIN and cervical cancers and supported the use of stand-alone HPV DNA testing as a primary screening test, especially for women aged 35 years and older. This randomized clinical trial of more than 90,000 women showed a significantly greater efficacy for HPV DNA testing than for cytology for preventing invasive cancers. In addition, HPV DNA testing provided better and earlier detection of CIN2+. Among women aged 25 to 34 years, HPV DNA testing resulted in overdiagnosis of regressive CIN2, so further research is needed for best management of younger women who are HPV positive.

Cost-effectiveness of HPV DNA testing

A study in Mexico, a middle-income country, set out to determine the incremental costs and outcomes of different HPV DNA testing strategies when compared with Pap smears for cervical cancer screening.\(^\text{19}\)
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Studies continue to report good results with vaginal self-sampling for HPV DNA testing. In both high- and low-resource regions, the accuracy of testing on self-collected specimens is nearly as high as that for clinician-collected specimens and continues to improve, with sensitivities in the range of 80 to 86 percent. Studies in high-resource settings have found that providing self-sampling kits to women who do not attend regular cytological screening increases their participation, and that these populations frequently have a high rate of HPV positivity.

One study investigated the use of HPV DNA testing to determine success of treatment after cryotherapy. Here, self-collected vaginal samples had a lower sensitivity (55 percent) than clinician-collected cervical samples (85 percent) when women were tested 6 months after cryotherapy. The reason for this difference is unknown, but a possible explanation put forward by the investigators is that tissue destruction caused by cryotherapy may result in exfoliation of cervical cells with a low viral load into the vagina. This might result in vaginal samples with a viral load too low to be detected by the self-sampling method.

Screening HIV-positive women

Addressing the health needs of women living with HIV/AIDS presents special challenges, including that of screening for cervical cancer. These women are at increased risk of HPV infection, and thus, of developing cervical cancer, an AIDS-defining condition. While the current document cannot review this topic in detail, studies are available with information on whether there is a need for specific screening guidelines for HIV-positive women. Some studies have investigated the time to HPV infection after incident HIV infection and others have begun to investigate the effect of treatment of CIN on subsequent risk of acquiring HIV. Because women with HIV/AIDS are living longer with the availability of highly-active anti-retroviral therapy, these questions have become more urgent, and ongoing studies will help to address them.
Summary

- Recent meta-analyses show that the most common cervical HPV types in women with normal cytology are similar worldwide, as are the types associated with cervical cancer. These findings are important for evaluating the impact of the current prophylactic vaccines as well as for developing new vaccines. A limitation of the studies is the small number of women tested in some low-resource countries.

- In evaluating screening methods, many of the studies reviewed here concluded that HPV DNA testing alone should eventually become the primary test in women aged 30 years or older and that high-risk HPV-negative women have an extremely low risk of developing cervical cancer in the 5 to 10 years after screening. HPV DNA testing has the additional advantage of cost-effectiveness, gained from lengthening the screening interval for HPV-negative women. The screening interval is lengthened because the test detects a very high percentage of cervical abnormalities, leaving very few that need to be found at subsequent screenings. This long interval also provides confidence that HPV DNA testing will be more effective than other methods for one-time screening in low-resource environments.

- While the sensitivity of visual inspection methods is not as high as that of HPV DNA testing and results are more variable across studies, most investigations have found that the sensitivity is as high as or higher than that of cytology.

- VIA can be implemented in many low-resource areas, whereas cytology, with its requirements for significant infrastructure, cannot.

- Until low-cost HPV DNA testing becomes more widely available for developing countries, visual inspection methods, especially VIA, provide a reliable and effective means for reducing the burden of cervical cancer.

References


