Cervical Cancer Screening: Past, Present, and Future

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ABSTRACT

Introduction: Cervical cancer is the leading cause of cancer deaths in women in the developing world. New technologies have been developed to allow for more rapid, cost-effective, and sensitive cervical cancer screening and treatment.

Aim: The aim of this study was to describe methods for detection and treatment of human papillomavirus (HPV), cervical dysplasia (CD), and cervical cancer. New technologies and updated screening strategies will be emphasized.

Methods: A literature search was conducted using PubMed to identify publications relevant to the subject.

Main Outcome Measure: Sensitivity and cost-effectiveness of new cervical cancer screening methods were the main outcome measures.

Results: HPV and cervical cancer have a significant global impact. Research and innovations related to detection and treatment are key in reducing their burden worldwide.

Conclusion: Screening a woman for HPV and CD can dramatically decrease her risk of dying from cervical cancer. New, rapid, low-cost, HPV testing can allow for high-volume screening for the approximately 1.5 billion women who have never been screened. HPV screening can then be combined with high resolution digital colposcopy to detect CD. In the near future, these colposcopic images will be interpreted by artificial intelligence software. Detected lesions can then be treated easily and effectively with thermocoagulation. This see-and-treat model is a sensitive, efficient, and low-cost vision for the future. **Bedell SL, Goldstein LS, Goldstein AR, et al. Cervical Cancer Screening: Past, Present, and Future. Sex Med Rev 2020;8:28–37.**

Key Words: Cervical Cancer; Human Papillomavirus (HPV); Cervical Dysplasia; Colposcopy; Thermocoagulation

INTRODUCTION

Cervical cancer is the third most common cancer in women worldwide. With continuing improvement in screening methods and vaccination programs in developed countries, the disparity of burden between women in developed countries and women in resource-poor settings becomes even more profound. Currently, >85% of cervical cancer deaths occur in low and middle-income countries. Tragically, cervical cancer is the leading cause of cancer deaths in women of the developing world.[1] However, new technologies have been recently developed to allow for more rapid, cost-effective, and sensitive cervical cancer screening. This article will review the history of cervical cancer screening and will describe these new screening technologies, which have the potential to greatly lower the cervical cancer incidence in the developing world.

Human Papillomavirus

Nearly all cases of cervical cancer can be attributed to infection with human papillomavirus (HPV). HPV types are categorized as low-risk or high-risk strains depending on their oncogenic potential. Low-risk strains of HPV may be asymptomatic or may cause anogenital warts, whereas high-risk strains are oncogenic. Over 99% of precancerous lesions (cervical dysplasia) and cervical carcinomas are caused by high-risk HPV infection.[2] More than 200 strains of HPV have been identified, of which approximately 40 infect the anogenital region.[3] 15–18 of these HPV strains have been classified as high-risk genotypes.[4] Virtually all cervical neoplasias and cancers are attributable to high-risk HPV genotypes, and approximately 70% of all cervical

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cancer cases are attributable to types 16 and 18.[5] Type 16 is responsible for 50% of squamous cell carcinomas and 55−60% of all cervical cancers, whereas type 18 causes about 20% of cervical adenocarcinomas. Other oncogenic strains of HPV include types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, which combined cause 25% of cervical carcinomas.[6] Infection with certain HPV types causes a proportion of cancers of the anus, vulva, vagina, penis, and oropharynx as well.[7]

Almost all cervical cancers are either squamous cell carcinoma or adenocarcinoma.[8] The major steps known to be necessary in cervical carcinogenesis include HPV infection, HPV persistence, progression to dysplasia, and invasion. Steps in the reverse direction are possible, including clearance of HPV infection and regression or resolution of precancerous lesions. Steps of regression and clearance are quite common, making most cervical HPV infections transient and self-limited. It has been shown that approximately 67% of HPV infections will be cleared without intervention within 12 months[9] and over 90% will clear within 2 years.[10] Traditionally, it has been thought that a long-lasting HPV infection causes cervical intraepithelial neoplasia (CIN) in a slow, progressive, and consecutive way; from HPV infected normal tissue to CIN1 (low grade), CIN2 (moderate grade), CIN3/CIS (high grade), and finally cancer. However, recent data suggests that CIN1 may not be necessary for the development of CIN3 and that CIN3 could evolve directly from normal epithelium infected by HPV as described by a "molecular switch" model. In this model, the severity of dysplasia is determined by the degree of methylation of certain genes and this might not progress in a linear fashion.[11] As such, clinically relevant CIN3 may develop fairly rapidly after HPV infection. Therefore, all CIN1 lesions and most CIN2 may not be precursor stages of cervical cancer, but rather the changes of a productive HPV infection. It may then take a decade or more to develop invasive cervical cancer from CIN3. Currently, the standard treatment recommendations following diagnosis of CIN1 include monitoring for progression,[12] whereas treatments for CIN2 and CIN3 include cryotherapy, thermoablation, loop electrosurgical excision procedure (LEEP) and cold knife conization (CKC).[13]

HPV Oncogenesis

HPV consists of a circular, double-stranded genome containing 9 open reading frames.[14,15] The "early" (E) genes control DNA maintenance, replication, and transcription and the "late" (L) genes encode capsid proteins. Proteins E1 and E2 are expressed at high levels early in HPV infection and allow for viral replication within cervical cells. This can lead to low-grade cytological changes on Papanicolaou smears, or low-grade squamous intraepithelial lesions.[16] Viral oncoproteins E6 and E7 are necessary for malignant conversion. E6 proteins bind to the p53 tumor suppressor protein and E7 binds to the retinoblastoma tumor suppressor protein; both of these instances lead to degradation of the suppressor proteins, thereby causing cell proliferation and tumor formation[17] (Figure 1).

HPV Infection and Transmission

Sexual contact is necessary for HPV transmission, and HPV remains the most common sexually transmitted infection in the world. It is most prevalent in teen-aged women and women aged 20−30 years, concordant with timing of first sexual contact.[8] Early age of first sexual intercourse and multiple sexual partners are known risk factors for high-risk HPV infection. Most young women are capable of mounting an effective immune response that clears the HPV infection or decreases the viral load to undetectable levels within 8−24 months.[7] As previously mentioned, over 90% of HPV infections are cleared without intervention by 2 years. Additional known factors that increase the likelihood of HPV persistence include tobacco use, immunosuppression, low socioeconomic status, and long-term use of oral contraceptives.[7,8] Although the vast majority of women with high-risk HPV infection do not develop cancer, persistent infection (>2 years) with high-risk HPV types is widely recognized as the primary causative factor for development of cervical cancer.[5] In an immunocompetent woman, progression to invasive cervical carcinoma typically occurs 10−20 years after primary infection.

HPV Vaccine

There are currently 3 HPV vaccines approved by the U.S. Food and Drug Administration (FDA) to prevent HPV infection: Gardasil, Gardasil 9, and Cervarix. Each of these vaccines protects against HPV genotypes 16 and 18, which collectively cause about 70% of cervical cancers. Both Gardasil vaccines also protect against HPV genotypes 6 and 11, which cause 90% of genital warts. Gardasil 9 also protects against HPV genotypes 31, 33, 45, 52, and 58.[18] As of 2017, Gardasil 9 is the only HPV vaccine available for use in the United States, although Gardasil and Cervarix continue to be used worldwide. The Centers for Disease Control currently recommends vaccination for male and female people ages 9 through 26,[19] although the FDA has recently approved vaccination up through age 45.[20] Those who have undergone vaccination must still be screened for HPV. Additionally, even if an individual has been exposed to HPV, vaccination is still recommended as they can benefit from protection against other HPV types in the vaccine to which they are naïve.

Trials leading to the approval of Gardasil and Cervarix demonstrated that the vaccines are nearly 100% effective in providing protection against both persistent cervical infections and dysplasia caused by HPV types 16 and 18.[18] The trials that led to the approval of Gardasil 9 found it to be nearly 100% effective in preventing cervical, vulvar, and vaginal disease caused by the 5 additional HPV types that it targets.[18] Recent data demonstrates that protection against the targeted HPV genotypes persists for at least 10 years with Gardasil, at least 9 years with Cervarix, and at least 6 years with Gardasil 9.[18]

By 2015, an estimated 47 million women have received the full HPV vaccination series, representing about 1.4% of the world's population. An additional 12 million women were

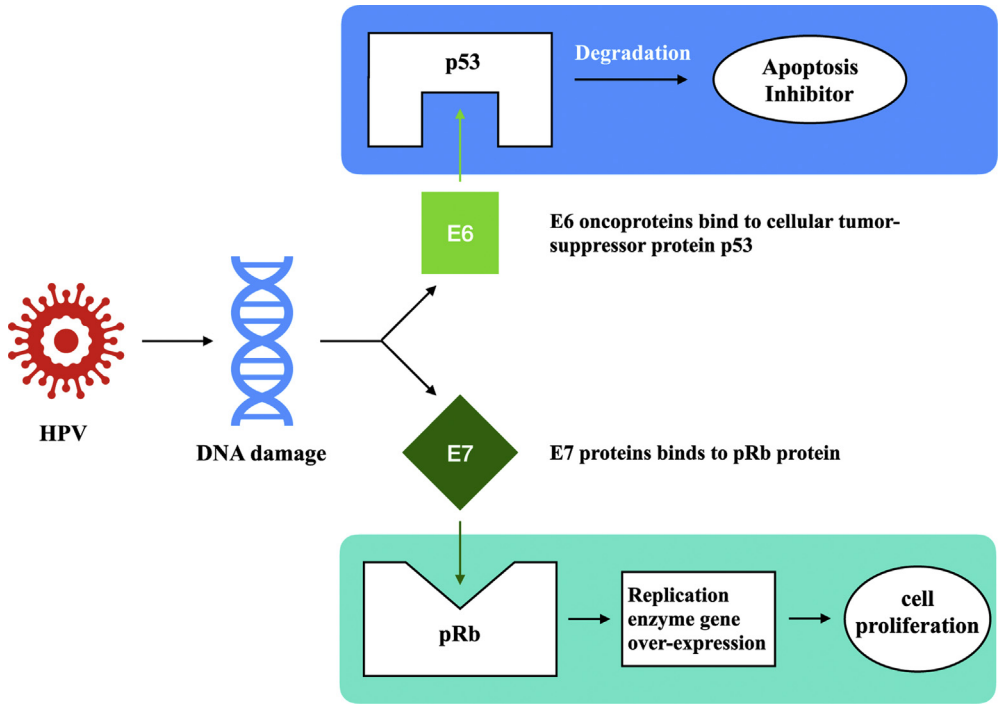

Figure 1. The role of the human papillomavirus genes E6 and E7 in cervical cancer carcinogenesis. Figure 1 is available in color online at www.smr.jsexmed.org.

estimated to have received at least 1 dose of HPV vaccine, thereby accounting for a total of 59 million women globally having received at least 1 dose. Of note, only 1.4 million vaccinated women were from low-income and lower-middle-income countries.[21]

Carrageenan

Recent investigations of the compound carrageenan have demonstrated promising results in its potential to decrease HPV transmission. Carrageenan is a type of sulfated polysaccharide extracted from red algae, and has been shown to be an extremely potent infection inhibitor for a broad range of sexually transmitted viruses, including herpes simplex viruses and some strains of HIV in vitro.[22] Carrageenan acts primarily by preventing the binding of HPV virions to cells. In in vitro studies mimicking an environment similar to the vagina (pH <4.5), carrageenan was found to be active against a range of HPV genotypes that can cause cervical cancer and genital warts. Presently, carrageenan is used as a thickening agent in some commercially available sexual lubricants, lubricated condoms, and infant formula. Clinical trials are needed to determine whether carrageenan-based products are effective as topical agents to prevent genital HPV transmission.[22]

The Papanicolaou Smear and Cytology-Based Cervical Cancer Screening

Early in his medical career, Dr. George Papanicolaou was able to deduce that reproductive cycles of guinea pigs could be predicted by timed examinations of smears of their vaginal secretions. When he began to focus on the cytopathology of the human reproductive system in the 1920s, he was able to replicate this finding and became capable of discerning normal and malignant cervical cells simply by viewing swabs smeared on microscopic slides. Dr. Papanicolaou continued his research with Dr. Herbert Traut, a gynecologic pathologist at the New York Hospital. Their collaborations were eventually published in their landmark book in 1943, *Diagnosis of Uterine Cancer by the Vaginal Smear*. Their writing importantly showed that both normal and abnormal smears of the vagina and cervix could be viewed microscopically and be correctly classified. This procedure is now conventionally known as the Papanicolaou smear. At little cost, relative ease of performance and reproducibility, the Papanicolaou smear quickly became the gold standard in cervical cancer screening.[23]

In the 1990s, advances in cytotechnology led to the development of liquid-based cytology (LBC) products. In contrast to the application of a fixative after a cervical sample is smeared onto a slide (as in a conventional Papanicolaou smear), liquid-based test collection involves sampling and cell transfer to a liquid medium followed by automated processing. Currently, about 80−90% of Papanicolaou tests performed in the United States use liquid-based cytology.[16] Despite multiple theoretic advantages of LBC, including improved cell collection and preparation, filtering of blood and debris, and fewer unsatisfactory results, several studies do not show a considerable difference in sensitivity or specificity for the detection of CIN compared with the conventional Papanicolaou smear. Instead, the benefits

of LBC are restricted to use of a single specimen for concomitant HPV testing and testing for gonorrhea and chlamydial infection in additional to cytology. The American College of Obstetricians & Gynecologists has asserted that both methods are acceptable for cervical cancer screening.[7]

Overall, the Papanicolaou smear has demonstrated consistent specificity (approximately 98%) with estimates of sensitivity being lower and more variable (approximately 55−80%) for detection of CD and invasive cancer.[16,24] Imprecise sensitivity is balanced by repeated screening throughout the majority of a woman's lifetime. Since its introduction, cytology-based cervical cancer screening methods have drastically decreased incidence and mortality rates of cervical cancer. In developed countries with well-established screening programs, and in which women are screened at regular intervals, cytology-based programs have proven to be the single most successful program for cancer prevention.[16] Since its introduction as a screening tool, cervical cancer incidence and mortality has declined by >70% in developed nations.[25,26]

In low-resource settings, however, cytology-based screening programs have proven difficult to implement. It requires electricity for microscopes, supplies to perform the testing, and trained cytopathologists to interpret the results. Moreover, the success of the Papanicolaou smear relies on continued interval screening over time and this proves difficult for populations without a developed infrastructure for testing. Last, patient follow-up among rural populations is challenging as well, as individuals are unable to travel to areas of screening or to return if the Papanicolaou smear shows evidence of dysplasia. In developing countries, meta-analyses of cytology-based screening have demonstrated sensitivity ranges as low as 11%, and specificity as low as 14% for detecting high grade lesions (CIN2 or greater).[27,28] As such, the Papanicolaou smear is less reliable, less cost-effective, and a logistically impractical screening method in many areas worldwide.[29]

Cytology and HPV Co-testing

Recent updates in cervical cancer screening guidelines include the addition of HPV testing to cervical cytology. HPV-DNA testing can be performed on cervical specimens by signal amplification techniques or by nucleic acid amplification with polymerase chain reaction. In 2003, the Hybrid Capture II HPV-DNA Assay (Digene) became the first FDA-approved test for the detection of high-risk HPV. Since then, 4 additional tests have received FDA approval: Cervista HPV HR (Hologic), Cervista HPV 16/18 (Hologic), Cobas HPV test (Roche Molecular Systems), and APTIMA HPV Assay (Gen-Probe).[30]

In 2003, the FDA approved the use of high-risk HPV testing in combination with cytology (or "co-testing") for cervical cancer screening, specifically in women aged 30 and older.[4] Due to a high prevalence of high-risk HPV infection in women under age 30, identification of HPV in women under 30 puts this group at risk for unnecessary overtreatment. As such, HPV testing is not approved for this age group. HPV testing may be collected as a separate specimen or performed from the remaining LBC specimen after the cytology is prepared. The combination of high-risk HPV testing with cytology can increase the sensitivity of a single Papanicolaou test for high-grade neoplasia from 50−85% to nearly 100%.[7,16] Due to a very high negative predictive value for high-grade neoplasia, relatively slow progression of HPV infection to neoplasia and increased cost, co-testing is performed at 5-year intervals, provided both test results are negative.[4] Current guidelines recommend that women aged 21−29 years should be tested with cervical cytology alone, and screening should be performed every 3 years. For women aged 30−65 years, co-testing with cytology and high-risk HPV testing every 5 years is preferred. For this age group, screening with cytology alone every 3 years is considered acceptable.[4,7] The American Society for Colposcopy and Cervical Pathology provides algorithms and regularly updated guidelines for the management of abnormal results.[4]

HPV Testing as Primary Cervical Cancer Screening

In recent years, investigators have studied the utility of HPV testing alone as a primary screening modality. A large U.S.-based study of HPV primary screening, known as the Addressing the Need for Advanced HPV Diagnostics trial, demonstrated that the HPV test had equivalent or superior effectiveness for primary cervical cancer screening as compared to cytology alone.[31] Accordingly, in 2014, the FDA modified the labeling of the Roche Cobas HPV test to include the additional indication of primary cervical cancer screening (HPV primary screening) in women starting at age 25.[32] In this trial, positive specimens underwent HPV genotyping. If a specimen was positive for HPV 16 or 18, colposcopy was performed. If a specimen was negative for HPV 16 and 18, cytology testing was performed reflexively; abnormal results then underwent colposcopy. If cytology results were normal, repeat co-testing was performed in 1 year.[31] Major societies' guidelines continue to support cytology alone and co-testing as recommended options for cervical cancer screening.[4,7] In 2015, the American Society for Colposcopy and Cervical Pathology published interim guidelines for the use of the FDA-approved HPV test for primary cervical cancer screening, stating it may be considered an alternative in women 25 years and older.[33] It has been predicted that primary HPV screening may become the standard screening modality within the next decade.[34] Under this model in the United States, HPV genotyping is performed first. If the patient is positive for HPV 16 or 18, colposcopy is recommended. If the patient is negative for HPV 16 and 18 but positive for another high-risk HPV genotype, reflex cytology is performed. If the cytology shows any epithelial abnormality greater than atypical squamous cells of undetermined significance, colposcopy is recommended. If the cytology is negative, follow-up in 1 year is recommended. If the HPV test is negative, follow-up in 3 years is recommended.[33]

One significant advantage to using HPV testing for primary screening is the potential for simplified collection. Rather than requiring a pelvic examination performed by a trained provider, HPV testing can be performed by the patient via self-swabbing. This might be especially beneficial in low-resource settings.[35] In a meta-analysis performed by Ogilvie et al,[36] the sensitivities and specificities of patient self-sampling compared to those collected by physicians for detecting HPV were comparable (74% and 88% vs 81% and 90%, respectively). Multiple additional studies implemented in various international regions have further found that the majority of women screened are willing to utilize the self-swab method.[37–40] Ogilvie and colleagues[36] note that the ability to screen many more women by way of self-collected samples justifies the small decrease in testing accuracy.

The greatest issue with HPV testing is cost, need for laboratory processing, and time to obtain results. A new variant of the Hybrid Capture II HPV DNA test has been designed to work in low-resource settings[41,42]; the careHPV testing system (QIAGEN, Germantown, MD, USA) is a simple, fast, low-cost, and robust method for HPV testing. It is also semiportable and each careHPV system can run 90 specimens in approximately 3e hours for US $4–6 per specimen. With this relatively rapid HPV testing, patients may await results and undergo visualization of the cervix with acetic acid (VIA) or digital colposcopy (DC) in the same day. Rapid, more sensitive, and low-cost polymerase chain reaction-based HPV testing systems are currently approved in China and Europe and they are awaiting FDA approval (AmpFire; Atila Bio Systems, Mountain View, CA, USA; Figure 2).

The advent of self-swabbing and low-cost, prompt HPV testing allows for rapid, high-volume HPV screening. The authors describe a successful use of the aforementioned model to screen and treat and approximately 3,600 women in regions of the Yunnan province in China with each occurring in 1 week.[43] In this model, HPV genotyping is performed first. Any high-risk HPV-positive result calls for the performance of visualization with DC and on-site treatment of both low and high-grade lesions.[43] This model parallels the current international recommendations from the World Health Organization (WHO).[44] Under these guidelines, if HPV testing is feasible, it is preferred as a primary screening modality over cytology. Any positive high-risk HPV test is then followed by a VIA. If a lesion is present, on-site treatment is recommended.

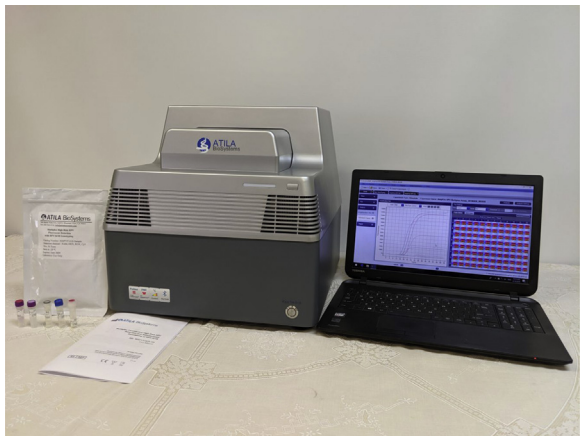

Figure 2. AmpFire human papillomavirus detection system, Atila Biosystems. Figure 2 is available in color online at www.smr.jsexmed.org.

Visualization and Colposcopy Methods

Colposcopy is traditionally a diagnostic, visual inspection procedure that is performed following an abnormal cervical cancer screening test. It involves the use of a colposcope to magnify visualization of the cervix up to 30 times. Typically, the entire cervix is examined with an emphasis on 2 areas: the squamocolumnar junction, or "SCJ," and the transformation zone. The SCJ is the junction between the squamous epithelium and the columnar epithelium of the cervix, generally located at the external cervical os (although with variable positioning). By way of gradual metaplastic processes, glandular cells of this SCJ are continually being replaced by squamous cells, leading to the formation of a dynamic tissue area known as the transformation zone. These are the areas at greatest risk for neoplasia.[45] During colposcopy, the cervix is examined after the application of a solution of 3–5% acetic acid. After approximately 30–90 seconds, the acidic solution dehydrates cells so that squamous cells with relatively large or dense nuclei (such as metaplastic cells, dysplastic cells, and cells infected with HPV) reflect light and thus appear white.[16,46] These are referred to as "acetowhite changes." Additionally, abnormal blood vessels and vascular patterns become easier to visualize against this white background. Similarly, Lugol's iodine can be applied to the cervix, resulting in easier visualization of dysplastic lesions. Lugol's iodine is a compound that will become brown or black when in contact with glycogen, which is present in normal mature squamous epithelium. Precancerous lesions and cancer contain little or no glycogen, due to poor cellular differentiation, and will subsequently turn various shades of yellow after Lugol application.[16] Similarly, normal conditions, such as normal columnar epithelium, atrophic epithelium, and hyperkeratosis (leukoplakia), can also cause negative Lugol's staining, rendering it a relatively nonspecific test. Visualization with a colposcope is then performed and lesions are documented, and a directed biopsy or biopsies are obtained.[16]

Visualization Methods as Primary Cervical Cancer Screening

Due to the limitations of cytology previously discussed, alternative screening methods have been developed. VIA or with visualization with Lugol's iodine (VILI) have arisen as cost-effective, accurate screening methods in resource-poor settings. VIA involves the application of 3–5% acetic acid onto the cervix then looking with the naked eye to identify color changes on the cervix. A positive test includes the visualization of sharp, distinct,

well-defined acetowhite areas. Ideally, VIA requires a private examination area, a good light source, and well-trained health professionals to interpret results. VILI involves a similar setup, with application of 5% Lugol's iodine solution on the cervix. A positive test includes the appearance of dense, mustard-yellow areas of iodine non-uptake. Large-scale studies in different regions in Bangladesh and Africa have demonstrated that the use of VIA and VILI as a primary screening method are safe and feasible to implement.[47–49] Reviews of studies from pooled data on the accuracy of VIA report a sensitivity of 84% (range 66–96%) and a specificity of 82% (range 64–98%) in detecting high-grade dysplasia.[50]

The most comprehensive meta-analysis in which VIA was used as a primary screening modality was performed by Sauvaget et al.[41] The authors examined 57 studies, 26 of which were used in their final analysis. These studies included both high- and low-income countries in hospital and rural settings. Additionally, confirmatory histology was performed, and disease presence was defined as CIN2 or greater (CIN2+). The authors report an overall sensitivity of 80%, specificity of 92%, a positive predictive value of 10%, and a negative predictive value of 99%.[41] Furthermore, they concluded that region, training level of the screening provider, setting, size of study population, and setting had no effect of the accuracy of VIA. The high negative predictive value demonstrated by Sauvaget et al[41] was reproduced by Sankaranarayanan et al[51] in a longitudinal study performed in India. Among 23,000 VIA-negative women screened in this study, only 25 developed cervical cancer within the next 8 years. This suggests that women with VIA-negative screening results are unlikely to develop cervical cancer in the near future.[51]

Compared to the reported sensitivities and specificities of cervical cytology in resource poor settings, VIA may be a more accurate screening method. VIA is also low-cost, safe, and can be performed by a wide range of medical providers owing to its simplicity. Additionally, it requires less infrastructure compared to cytology methods, as results are given immediately without a need for laboratory processing. Limitations of VIA arise among populations where rates of cervicitis are significant. This leads to false-positive results, as infected cervical cells become acetowhite lesions upon application of acetic acid. This may lead to over-treatment and possible infectious complications of different treatment methods.[52–54] VIA also requires a degree of training and visual acuity for the screening provider, is subject to poor lighting, and does not allow for the collection of a permanent image nor pathology for documentation and quality control.

Digital Colposcopy

Recent advances in digital optical technology have allowed for the development of highly portable digital colposcopes. DC has the same advantages of standard colposcopy but, in addition, ultra-high-resolution digital images can be obtained. These images can oftentimes be magnified to higher degrees than a conventional colposcope and may thereby allow for superior visualization of cervical surface morphology. Studies have been performed with the use of digital cameras and even smartphones to capture colposcopy images.[55,56] The Enhanced Visual Assessment System (MobileODT, Israel),[57] for example, utilizes the advanced optics found in Android smartphones that are quite common, even in low-resource countries (Figure 3).

In a prospective cohort study examining cervical cancer screening amongst HIV-positive and HIV-negative women in Cambodia, They et al[56] were able to use DC as a method of colposcopy for HPV-positive women, and were able to distinguish between CIN1 and CIN2-positive lesions consistently and accurately during the study; all women who underwent biopsies had accurate, corresponding colposcopic impressions with DC. Systematic reviews have further concluded that, due to greater magnification capabilities, DC may potentially have improved sensitivity and specificity over VIA[58] (Figure 4).

There are several additional advantages of DC. First, the digital images can be used for both patient and provider education. Second, the images provide permanent documentation, which can be incorporated in an electronic medical record. Third, the images can be reviewed in quality control programs. Fourth, the images can be transmitted electronically so that they can be used in real-time telemedicine consultations with expert colposcopists.[55,59] Last, and perhaps most exciting, studies are currently underway to develop artificial intelligence algorithm software to help interpret the digital colposcopic images to predict in real-time the probability of CIN2-positive lesions.[60] These interpretation algorithms are currently cloud-based, but they may soon be incorporated into the software in the hand-held digital colposcopes.

Treatment Options

As previously mentioned, standard recommendations in the United States following a diagnosis of CIN1 include monitoring for progression with treatment of only persistent lesions (at least 2 years) by way of ablation or excision.[12] Treatments for CIN2 and 3 include ablative or excisional procedures.[13] Ablation procedures include cryotherapy or thermoablation (sometimes referred to as cold coagulation or thermocoagulation). Cryotherapy involves the use of compressed gas (such as carbon dioxide or nitrous oxide) to freeze cervical tissue and cause necrosis. Thermoablation uses heat instead of cold to ablate tissue.[60] Excisional procedures, such as a LEEP or CKC are preferred over ablative therapies if colposcopy is inadequate, CIN2 or greater is present on endocervical curettage, or if the patient has received previous treatment.[12]

Alternatively, the WHO provides screen-and-treat recommendations for women in low-resource settings.[44] By their model, cryotherapy is considered a first-line treatment for those who screen positive and qualify for treatment. Cryotherapy is an option if the entire lesion is visible, the SCJ is visible, the lesion does not cover more than 75% of the ectocervix, and cervical cancer is not suspected. If the lesion extends beyond the

Figure 3. Enhanced Visual Assessment (EVA) System, MobileODT. Figure 3 is available in color online at www.smr.jsexmed.org.

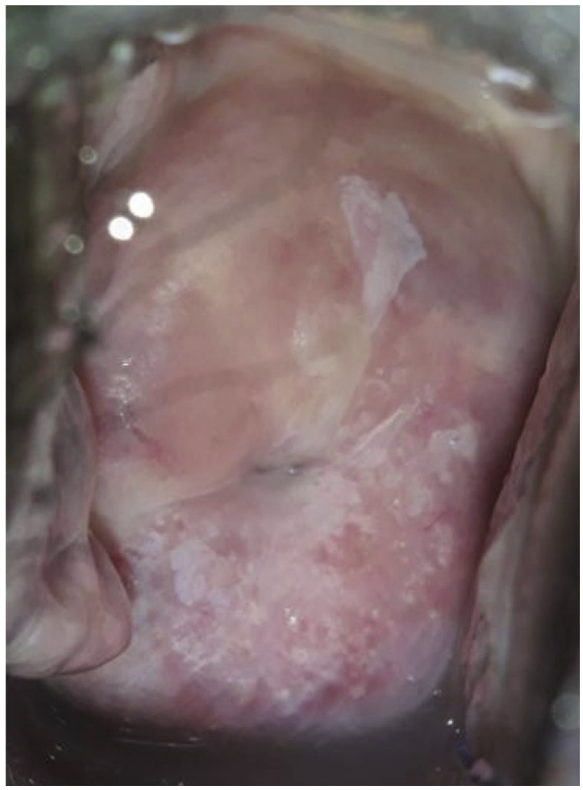

Figure 4. Digital cervicograph obtained with the Enhanced Visual Assessment (EVA) System showing CIN3. Figure 4 is available in color online at www.smr.jsexmed.org.

cryoprobe being used, or into the endocervical canal, the patient is not eligible for cryotherapy, and LEEP is recommended. CKC is not recommended in this see-and-treat strategy. Regarding screening, HPV testing is preferred over VIA and cytology-based methods.[44]

Currently, gas-based cryotherapy is the only ablative treatment endorsed by the WHO for the treatment of CIN2-positive patients in low-resource settings. Unfortunately, this can be limiting not only due to the cost of compressed gas, but the logistics related to its procurement and transport. Accordingly, screen-and-treat regimens involving thermoablation have begun to emerge.[61,62] New devices, such as the WISAP Cold Coagulator device (WISAP Medical Technology, Brunnthal, Germany) are simple to use, are handheld, and can be operated by an external battery. Moreover, in a recent meta-analysis, Dolman et al[63] found that thermoablation carries an estimated cure rate of 96% for CIN1 and 95% for CIN2-positive.[63] Cure rates for cryotherapy are similar to LEEP and range from 77–93%.[64] With its improved cure rates and less cumbersome nature, thermoablation serves as a promising treatment option for low- or middle-income countries.

Newer research has also focused on the development of therapeutic HPV vaccines to help treat the considerable population suffering from high-risk HPV infection and its associated disease. This is warranted because prophylactic HPV vaccines do not provide any therapeutic benefit for existing infections or lesions. The primary target antigens for the majority of developing therapeutic vaccines are the viral proteins E6 and E7. As mentioned previously, E6 and E7 are necessary for the malignant conversion of host cells as they drive oncogenesis. E6 and E7 are also constitutively expressed in both premalignant and invasive lesions but are absent on healthy cells, and are, therefore, ideal targets for therapies.[65] So far, one of the more promising therapies lies in a therapeutic DNA-vectored HPV vaccine called VGX-3100, which aims to treat HPV genotypes 16 and 18. In a phase IIb study, 167 women with histologically confirmed HPV-16/18-positive CIN2/3 were randomized 3:1 to receive VGX-3100 or placebo, administered at 0, 4, and 12 weeks. Pathology-confirmed regression occurred in 49.5% of vaccine recipients compared with 30.6% of placebo recipients.[66] Currently, a phase III trial (REVEAL) is ongoing with an expected completion date in 2020 (NCT03185013). Similarly, a peptide-vectored vaccine using HPV 16 E6 peptides called PepCan is currently being studied in a phase II trial (NCT02481414). In a single-arm, dose-escalation, phase I clinical trial involving its use, a regression rate of 83% at a dose of 50 μg was observed in women with biopsy-proven CIN2/3. Additionally, vaccine-induced immune responses to E6 were detected in 65% of recipients.[65]

A Vision of the Future

Screening a woman just one time in her life after the age of 35 decreases her risk of dying from cervical cancer by 70%. Her risk of dying from cervical cancer drops by more than 85% if she is

screened every 5 years. However, more than 1.5 billion women worldwide have never been screened for cervical cancer. As discussed above, the traditional cytology-based screening is not a viable option to screen these 1.5 billion women. However, the new technologies discussed above offer a way to accomplish this daunting goal. It is not hard to imagine a future where screening programs utilize rapid, low-cost, high-volume, self-swab HPV testing of thousands of women per day. The approximate 15% of women could then have DC by nurses, midwives, or trained local healthcare workers. The images would be interpreted by artificial intelligence software and lower grade lesions could immediately be treated by these same providers with thermocoagulation. Highly skilled providers could then focus their time treating the CIN2-positive lesions. Concurrently, HPV vaccines could be provided to younger members of the community.

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STATEMENT OF AUTHORSHIP

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REFERENCES

1. World Health Organization. Cancer, Key Statics. Available at: https://www.who.int/cancer/resources/keyfacts/en/.
2. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. **J Pathol 1999;189:12-19**.
3. National Cancer Institute. HPV and cancer 2019. Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-fact-sheet#q1.
4. Committee on Practice Bulletins—Gynecology. Practice bulletin no. 168: Cervical cancer screening and prevention. **Obstet Gynecol 2016;128:e111-e130**.
5. Rerucha C, Caro R, Wheeler V. Cervical cancer screening. **Am Fam Physician 2018;97:441-447**.
6. Centers for Disease Control and Prevention. 2015 Sexually transmitted diseases treatment guidelines: Human papillomavirus (HPV) infection. Available at: cdc.gov.
7. Martin-Hirsch PL, Wood NJ. Cervical cancer. **BMJ Clin Evid 2011;2011. pii:0818**.
8. Rodríguez AC, Schiffman M, Herrero R, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. **J Natl Cancer Inst 2008;100:513-517**.
9. Plummer M, Schiffman M, Castle PE, et al. A 2-year prospective study of human papillomavirus persistence among women with a cytological diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. **J Infect Dis 2007;195:1582-1589**.
10. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Human Papillomaviruses. Lyon, France: International Agency for Research on Cancer; 2007. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 90.) Available at: https://www.ncbi.nlm.nih.gov/books/NBK321760/.
11. Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. 2012 ASCCP Consensus Guidelines Conference [published erratum appears in *J Low Genit Tract Dis* 2013;17:367]. **J Low Genit Tract Dis 2013;17:S1-S27**.
12. Santesso N, Mustafa R, Schünemann H, et al. World Health Organization Guidelines for treatment of cervical intraepithelial neoplasia 2—3 and screen-and-treat strategies to prevent cervical cancer. **Int J Gynecol Obstet 2016;132:252-258**.
13. Stanley M. Pathology and epidemiology of HPV infection in females. **Gynecol Oncol 2010;117(2 Suppl):S5—10**.
14. Southern SA, Herrington CS. Molecular events in uterine cervical cancer. **Sex Transm Infect 1998;74:101-109**.
15. Hoffman BL, Williams JW. Ch. 29: Preinvasive Lesions of the Lower Genital Tract. Williams Gynecology. 2nd ed. New York: McGraw-Hill Medical; 2012. p. 730-768.
16. Yim EK, Park JS. The Role of HPV E6 and E7 oncoproteins in HPV-associated cervical carcinogenesis. **Cancer Res Treat 2005;37:319-324**.
17. Gargano J, Meites E, Watson M, Unger E, Markowitz L. Centers for Disease Control and Prevention. Manual for the Surveillance of Vaccine-Preventable Diseases. Ch. 5: Human Papillomavirus (HPV). Available at: cdc.gov.

18. National Cancer Institute. Human Papillomavirus (HPV) Vaccines. Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet.
19. Centers for Disease Control and Prevention. Vaccination Schedules & Recommendations. Available at: https://www.cdc.gov/hpv/hcp/schedules-recommendations.html.
20. U.S. Food and Drug Association New Release. FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. October 2018. Available at: fda.gov.
21. Bruni L, Diaz M, Barrionuevo-Rosas L, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: A pooled analysis. **Lancet 2016;4:E453–463.**
22. Buck CB, Thompson CD, Roberts JN, et al. Carrageenan is a potent inhibitor of papillomavirus infection. **PLoS Pathog 2006;2:e69.**
23. Tan SY, Tatsumura Y. George Papanicolaou (1883–1962): Discoverer of the Pap smear. **Singapore Med J 2015; 56:586-587.**
24. Soost HJ, Lange HJ, Lehmacher W, et al. The validation of cervical cytology. Sensitivity, specificity and predictive values. **Acta Cytol 1991;35:8-14.**
25. Shingleton HM, Patrick RL, Johnston WW, et al. The current status of the Papanicolaou smear. **CA Cancer J Clin 1995; 45:305-320.**
26. Safaeian M, Solomon D, Castle PE. Cervical cancer prevention–cervical screening: Science in evolution. **Obstet Gynecol Clin North Am 2007;34:739-760.**
27. Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. **Am J Epidemiol 1995;141:680-689.**
28. Nanda K, McCrory DC, Myers ER, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: A systematic review. **Ann Intern Med 2000;132:810-819.**
29. Bradford L, Goodman A. Cervical cancer screening and prevention in low-resource settings. **Clin Obstet Gynecol 2013; 56:76-87.**
30. LabCE. FDA-Approved HPV Tests. Available at: https://www.labce.com/spg761630_fda_approved_hpv_tests.aspx.
31. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: End of study results from the ATHENA study using HPV as the first-line screening test. **Gynecol Oncol 2015;136:189-197.**
32. U.S. Food and Drug Administration. Cobas® HPV Test - P100020/S008. Silver Spring (MD): FDA; 2014.
33. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance. **Obstet Gynecol 2015;125:330-337.**
34. Rizzo AE, Feldman S. Update on primary HPV screening for cervical cancer prevention. **Curr Probl Cancer 2018; 42:507-520.**
35. Wright TC Jr, Denny L, Kuhn L, et al. HPV DNA testing of self-collected vaginal samples compared with cytologic screening to detect cervical cancer (comment). **JAMA 2000;283:81-86.**
36. Ogilvie GS, Patrick DM, Schulzer M, et al. Diagnostic accuracy of self collected vaginal specimens for human papillomavirus compared to clinician collected human papillomavirus specimens: A meta-analysis. **Sex Transm Infect 2005;81:207-212.**
37. Parkin DM, Nambooze S, Wabwire-Mangen F, et al. Changing cancer incidence in Kampala, Uganda, 1991-2006. **Int J Cancer 2010;126:1187-1195.**
38. Dzuba IG, Diaz EY, Allen B, et al. The acceptability of self-collected samples for HPV testing vs. the Pap test as alternatives in cervical cancer screening. **J Womens Health Gend Based Med 2002;11:265-275.**
39. Tisci S, Shen YH, Fife D, et al. Patient acceptance of self-sampling for human papillomavirus in rural China. **J Low Genit Tract Dis 2003;7:107-116.**
40. Smith K, Harrington K, Wingood G, et al. Self-obtained vaginal swabs for diagnosis of treatable sexually transmitted diseases in adolescent girls. **Arch Pediatr Adolesc Med 2001;155:676-679.**
41. Sauvaget C, Fayette JM, Muwonge R, et al. Accuracy of visual inspection with acetic acid for cervical cancer screening. **Int J Gynecol Obstet 2011;113:14-24.**
42. Jeronimo J, Bansil P, Lim J, et al. A multicountry evaluation of careHPV testing, visual inspection with acetic acid, and Papanicolaou testing for the detection of cervical cancer. **Int J Gynecol Cancer 2014;24:576-585.**
43. Goldstein A, Goldstein L, Lipson R, et al. A rapid, high-volume, see-and-treat screening program using HPV self-sampling, rapid DNA hybrid, and digital colposcopy. **J Low Genit Tract Dis 2019;23(2S):S5.**
44. WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva, Austria: World Health Organization; 2013.
45. Herfs M, Yamamoto Y, Laury A, et al. A discrete population of squamocolumnar junction cells implicated in the pathogenesis of cervical cancer. **Proc Natl Acad Sci USA 2012;109:10516-10521.**
46. Marina OC, Sanders CK, Mourant JR. Effects of acetic acid on light scattering from cells. **J Biomed Opt 2012;17. 085002-1.**
47. Nessa A, Hussain MA, Rahman JN, et al. Screening for cervical neoplasia in Bangladesh using visual inspection with acetic acid. **Int J Gynecol Obstet 2010;111:115-118.**
48. Ngoma T, Muwonge R, Mwaiselage J, et al. Evaluation of cervical visual inspection screening in Dar es Salaam, Tanzania. **Int J Gynecol Obstet 2010;109:100-104.**
49. Muwonge R, Manuel MG, Filipe AP, et al. Visual screening for early detection of cervical neoplasia in Angola. **Int J Gynecol Obstet 2010;111:68-72.**
50. Gaffikin L, Lauterbach M, Blumenthal PD. Performance of visual inspection with acetic acid for cervical cancer screening: A qualitative summary of evidence to date. **Obstet Gynecol Surv 2003;58:543-550.**
51. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. **N Engl J Med 2009;360:1385-1394.**

52. Davis-Dao CA, Cremer M, Felix J, et al. Effect of cervicitis on visual inspection with acetic acid. **J Low Genit Tract Dis 2008;12:282-286.**

53. Sun ZC, Cui Y, Yang L, et al. Study on the prevalence of reproductive tract infections and influencing factors on women in rural areas of the Middle and Western regions in China. **Chin J Epidemiol 2010;31:961-964.**

54. Paçarada M, Lulaj S, Kongjeli G, et al. Factors associated with pathologic colposcopic and cytologic changes in 500 clinically asymptomatic women. **Int J Gynecol Obstet 2010;108:7-11.**

55. Liu AH, Gold MA, Schiffman M, et al. Comparison of colposcopic impression based on live colposcopy and evaluation of static digital images. **J Low Genit Tract Dis 2016;20:154-161.**

56. Thay S, Goldstein A, Goldstein LS, et al. Prospective cohort study examining cervical cancer screening methods in HIV-positive and HIV-negative Cambodian Women: A comparison of human papilloma virus testing, visualization with acetic acid and digital colposcopy. **BMJ Open 2019;9:e026887.**

57. MobileODT. Colposcopy streamlined. Available at: https://www.mobileodt.com/products/eva-colpo/. Accessed April 14, 2019.

58. Hermens M, Ebisch RM, Galaal K, et al. Alternative colposcopy techniques: A systematic review and meta-analysis. **Obstet Gynecol 2016;128:795-803.**

59. Spitzer M. The Era of "Digital Colposcopy" will be here soon. **J Low Genit Tract Dis 2015;19:273-274.**

60. Hu L, Bell D, Antani S, et al. An observational study of deep learning and automated evaluation of cervical images for cancer screening. **J Natl Cancer Inst 2019;111:923-932.**

61. Cremer ML, Conzuelo-Rodriguez G, Cherniak W, et al. Ablative therapies for cervical intraepithelial neoplasia in low-resource settings: Findings and key questions. **J Glob Oncol 2018;4:1-10.**

62. Viviano M, Kenfack B, Catarino R, et al. Feasibility of thermocoagulation in a screen-and-treat approach for the treatment of cervical precancerous lesions in sub-Saharan Africa. **BMC Womens Health 2017;17:2.**

63. Dolman L, Sauvaget C, Muwonge R, et al. Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: A systematic review. **BJOG 2014;121:929-942.**

64. Martin-Hirsch PP, Paraskevaidis E, Bryant A, et al. Surgery for cervical intraepithelial neoplasia. **Cochrane Database Syst Rev 2013;12:CD001318.**

65. Hancock G, Hellner K, Dorrell L. Therapeutic HPV vaccines. **Best Pract Res Clin Obstet Gynaecol 2018;47:59-72.**

66. Trimble CL, Morrow MP, Kraynyak KA, et al. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: A randomised, double-blind, placebo-controlled phase 2b trial. **Lancet 2015;386:2078.e88.**