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Adapting Cervical Dysplasia Screening, Treatment and Prevention Approaches to Low Resource Settings

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Authors' contributions

This work was carried out in collaboration between all authors. Authors EKV, KK and DJS collaborated on the conception, research, writing and editing of this article. Author KK prepared the figures. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Cervical cancer is a common disorder worldwide. Screening and treatment paradigms in highly developed countries have dramatically decreased disease prevalence and the implementation of preventive vaccination against high risk human papillomavirus (HPV) subtypes should decrease prevalence even further. Promising advances are also being made toward the development of a therapeutic vaccine for cervical neoplasia. Under-resourced countries suffer from an inability to implement many of the approaches to prevention and diagnosis that have proved successful in countries with adequate resources. Several protocols are presently being developed that are low cost and require minimal training and infrastructure that may allow low-resource areas to begin to improve the early diagnosis of low and moderate grade cervical neoplasia. These protocols should support efforts at early treatment to prevent progression to cancer. Simultaneous expansion of prophylactic and possibly therapeutic vaccine availability is essential in the worldwide fight against this prevalent but largely preventable disease.

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1. INTRODUCTION

Cervical cancer is the third most common female cancer in both incidence and mortality worldwide. Every year, it affects 530,000 women, with 275,000 cases resulting in death. Over 80 percent of these deaths occur in underdeveloped countries [1,2].

The correlation between cervical cancer and human papillomavirus (HPV) was established in the 1970s. Since that time, a much better understanding of the disease process has been established [3]. Studies have shown that it can take up to 10 years from initial HPV infection to the development of cervical intraepithelial neoplasia (CIN) III (an immediate cervical cancer precursor) and up to 30 years for CIN III to develop into cancer. Interventions can be made during this prolonged "incubation" period in order to prevent progression to invasive cancer [4,5].

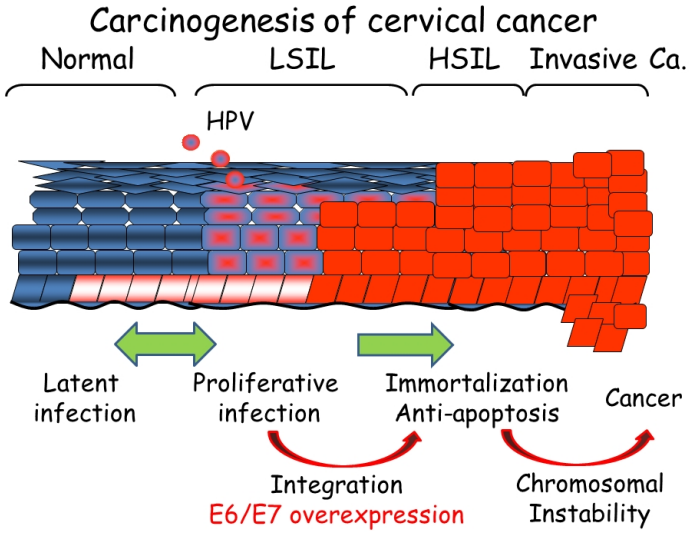


Fig. 1. Mechanism of HPV-related carcinogenesis

Persistent HPV infection is identified as the most important risk factor for cervical dysplasia and neoplasia and generally involves persistent virus proliferation, as verified by the detection of virus DNA in exfoliated cervical cells. Depicted here is a cartoon of cervical neoplasia progression from initial infection of the basal layer of normal squamous epithelium (bottom, depicted in white with pink borders). Chronic virus proliferation induces the active proliferation/differentiation of infected epithelial cells (blue cells with pink centers), and some infected cells incidentally immortalize (red cells), which is the first step of carcinogenesis. Integration of the viral genome into the host genome is the most important event in immortalization since HPV viral oncogenes E6 and E7 will be expressed continuously and ubiquitously after integration. E6 exerts an anti-apoptotic effect by inactivating and p53 and telomerase. Ultimately, the immortalized cells accumulate chromosomal instability and acquire the behaviors of cancer. The proportion of the squamous epithelial cells that have been infected and then immortalized corresponds with the severity of the neoplastic process.

To better understand the disease progression requires an adequate understanding of HPV and its typical lifespan in infected cervical tissue. HPV is a double stranded DNA virus that infects squamous epithelium. The initial viral infection is transient in approximately 90% of women, most often becoming non-detectable within one to two years [6,7]. When infection

ispersistent; however, it can lead to abnormal cellular development on the surface of the cervix [8]. This process begins with early neoplastic changes, categorized as CIN I (Fig. 1). Consistent with the transient character of most infections, CIN I is thought to be a self-limiting lesion. Still, a small percentage of initial HPV infections (10%) will persist. In many persistent infections, a set of subtype-specific HPV viral proteins enable cells to grow uncontrollably, resulting in the cancer precursor lesions known as CIN II and CIN III. If left untreated, these cellular abnormalities can cross through the basement membrane and become cancer [4,7,9,10].

Abnormal cervical lesions can be detected through screening with cervical cytology. Such screening allows for early detection of abnormalities and provides an opportunity for interventions aimed at preventing cervical cancer. In 1947, George Papanicolaou changed the landscape of cervical cancer diagnosis and treatment paradigms with studies showing that changes in cervical cytology could predict present and future disease. Utilization of what is commonly known as the Pap smear rapidly became the standard of care and significant changes in the test have been made over the intervening years. With improved understanding of the cervical neoplasia disease process, cervical cytology screening models with increased sensitivity and specificity have been developed in an effort to standardize collection and interpretation to prevent overtreatment of less severe disease states. Prior to the introduction of colposcopy in the 1970s, all high grade pap smears were treated with anexcisionalcone biopsy as both a diagnostic and therapeutic procedure. In 1988, the Bethesda system was developed as a more uniform way of reporting cellular atypia. HPV genotyping was introduced in 1988. The utility of this technique in triaging early cellular changes has driven its rapid incorporation into, and has rapidly become an important part of, most cervical cancer screening protocols in well-resourced countries [3,6,9].

2. THE CHALLENGE FOR RESOURCE-POOR COUNTRIES

Despite great advances in screening and prevention, cervical cancer remains the second leading cause of cancer related deaths in underdeveloped countries. Such countries typically lack the infrastructure to support cancer screening programs similar to those with demonstrated success in more developed countries. In the absence of effective screening protocols, HPV-related cervical disease often remains undetected until quite advanced stages. Those same countries that lack resources for screening almost certainly lack the necessary medical support to manage advanced stage cervical cancer. An excellent example of this concept is the Caribbean country, Haiti. Haiti has the highest incidence of cervical cancer in the Western Hemisphere but an overwhelming paucity of medical oncologists [11]. This provider shortage combines with an almost complete lack of facilities that are able to provide typical treatment approaches for advanced cervical cancers, namely radiation therapy in the presence or absence of chemotherapeutic sensitizers. Most, if not all under-resourced countries face similar problems. This significant unmet demand further encourages the development of cost- and time-effective screening programs as a means to eradicate cervical cancer related deaths. For the foreseeable future, provider and facility availability and costs in these areas will continue to hinder the implementation of standard cervical cancer screening and treatment protocols that are routine in well-resourced countries. In response to this unfortunate reality, alternative approaches have been proposed. These include the implementation of low cost and reproducible screening tests and increasing the availability and utilization of screening, diagnosis and treatment modalities that can be offered at a single site, and sometimes combined and accomplished in a single visit [12,13]. Several large organizations have attempted to implement screening programs in fairly desolate areas, albeit with variable success. A variety of methodologies

incorporating screening techniques such as cervical cytology (the traditional Pap smear), visual inspection with acetic acid (VIA), and HPV testing have been proposed. Some organizations have included community education regarding HPV and cervical cancer screening, along with HPV vaccination programs as a means for primary prevention. Studies have shown that women who are educated in their own communities regarding cervical cancer and the role of screening in its prevention are more likely to seek out preventive services [14,15]. Furthermore, community education can help to decrease the negative connotations associated with HPV and cervical cancer (i.e. many people in underdeveloped areas, including health care professionals, associate HPV infection with poor hygiene or prostitution) [8].

Attempts to mirror the cytology-based cervical cancer screening programs used in developed countries have proven to be generally unsuccessful in less-resourced settings. The requirements for 1) well-trained pathologists, 2) high quality laboratories with stringent quality control monitoring and 3) ready availability of appropriate preservatives for specimen transport are difficult to attain in resource-poor areas [14,15]. Even in areas capable of supporting the necessary components, patient access and follow up can be problematic. Processing requirements for standard cytology samples make it impossible for patients to wait for their results and many patients may live hours away from the nearest medical facility. These obstacles dramatically decrease the likelihood that a given patient will seek medical screening and follow-up at the recommended time intervals--if at all [16]. Further complicating cervical cancer screening regimens is the fact that acquisition and interpretation of cervical cytology using PAP testing remains subject to significant operator-dependent error--even in well-established programs [8,10].

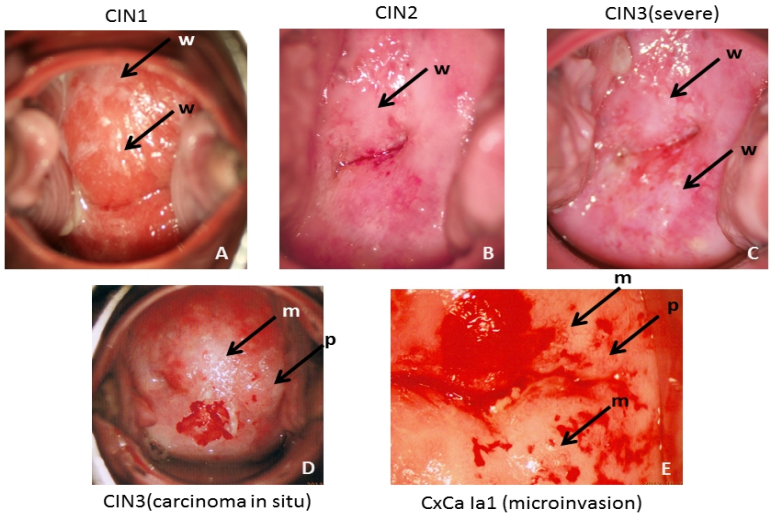
3. CERVICAL CANCER SCREENING AND PREVENTION PROGRAMS FOR UNDER-RESOURCED LOCATIONS

In 1938, Walter Schiller discovered that certain cellular abnormalities that were highly correlated with cervical dysplasia could be observed visually after the application of Lugol's iodine to the cervix—normal, glycogen-containing cervical epithelial cells take up the stain and appeared mahogany brown while those with cellular abnormalities and reduced glycogen exclude the dye and appear light yellow when compared to the surrounding tissues [17].While the test was ultimately shown to be fairly non-specific, this discovery spearheaded the development of modern day colposcopy. In well-resourced settings, practitioners typically use the high magnification afforded by the colposcope in conjunction with staining of the ectocervix and transformation zone with either acetic acid or Lugol's iodine to further evaluate abnormal results obtained through cervical cytology and HPV testing. Topical application of dilute acetic acid to the cervix is believed to reversibly agglutinate intracellular proteins. Neoplastic cells, which have a higher protein density than non-neoplastic counterparts, will appear white to the naked eye, therefore the presence of acetowhite areas close to the squamocolumnar junction (the area most commonly infected by the HPV virus) is considered a positive finding (Fig. 2). Acetowhite changes are not specific to cervical cancer or cervical cancer precursors. Other conditions, such as immature squamous metaplasia and inflamed or regenerating cervical epithelium can also induce acetowhite changes [12,16,18] and represent a source of false positive results when using acetic acid in conjunction with cervical visualization as a screening tool for cervical neoplasia. Still, the sensitivity, low cost and ease of the procedure have led many under-resourced areas to apply the basic principles of colposcopy towards the development of screening processes that can be done when a colposcope is not available. This procedure, called visual

inspection with acetic acid (VIA), may be an excellent central component in primary cervical cancer screening protocols in less-developed settings.

3.1 Visual Inspection with Acetic Acid (VIA)

The use of VIA provides immediate results and allows the trained practitioner to manage detectable lesions appropriately at the time of diagnosis, either through an excisional procedure or cryotherapy (destroying affected tissues through freezing). This screening approach has several specific advantages when implemented in lower resourced areas. It requires minimal training and can be performed by midlevel providers. It is inexpensive and requires almost no specialized equipment [12,13,16]. VIA screening has been endorsed by the Alliance for Cervical Cancer Prevention (ACCP) as a viable substitute when standard cytology, viral testing and colposcopy are not readily available [18]. The sensitivity of VIA in detecting high grade precursor lesions and invasive cancers ranges from 67 to 79 percent; the reported specificities range between 49 and 86 percent [3,12]. The value of visual inspection using acetic acid (VIA) and/or Lugol's iodine (VILI) has been evaluated in low-resource settings. In just the past year, this approach has been reported to be effective in studies from Egypt (486 subjects) [19], South Africa (1202 HIV-infected participants) [20] and China (10,269 women) [21]. One 2013 study from Nigeria [22], however, stands in disagreement with the others, reporting that VIA results were quite variable among different providers. The ready availability of appropriate provider training may be an important drawback to this approach, although several online resources are being developed that may help to ameliorate this difficulty.



Photos from the personal collection of Dr. K. Kawana

Fig. 2. Cervical colposcopic pictures showing CIN1 to cancer

*The color of HPV-infected cervical epithelium becomes visibly whiter (acetowhite; **w**) than the surrounding epithelium after topical exposure to dilute acetic acid. If the white color of the lesion changes back to the more normal dark pink color of unaffected epithelium within one minute and the edge of the lesion appears somewhat indistinct, the lesion is consider to be minor (arrows in A) and commensurate with CIN1. When the edge of the white lesions is sharp or the white lesion appears thickened, it is considered a major lesion (arrows in B, C and D) or CIN2-3. Sometimes the acetowhite lesions are characterized as having a mosaic appearance (**m**) or punctation (**p**)which suggest vascular or glandular involvement.*

3.2 The See and Treat Approach

As a means to avoid loss of patients to follow up, many lower-resourced countries have combined VIA with either an immediate excisional procedure or cryotherapy in a paradigm also known as “see and treat”. Many studies have shown this to be an effective means of managing abnormal cervical lesions, including recent reports from Indonesia [23], Thailand [24] and Uganda [25]. Although this method has proven to be effective in under-resourced settings, it does have some important drawbacks. The most glaring is its inherent bias toward overtreatment, as not all visually-detected abnormalities will signify those lesions that mandate treatment (high grade lesions) [3,12]. While this is a valid concern, many authorities feel that the potential decrease in the number of women lost to follow up using see and treat approaches significantly eclipses this flaw.

3.3 A Possible Role for HPV Testing in Low-Resource Settings

Over 130 different HPV genotypes have been identified, but only approximately 40 are associated with diseases of the human genitalia. Of these, many cause benign genital warts (e.g., types 6 and 11), while a different subset (including types 16, 18, 31 and 45) are linked to genital neoplasia. The latter subgroup of HPV viruses is referred to as high-risk subtypes. Techniques that quickly identify the presence of high-risk subtypes in clinical specimens have evolved rapidly over the past few decades so that modern HPV testing is now highly reproducible. Most modern HPV genotyping approaches require minimal laboratory equipment. HPV testing is more easily monitored than cervical cytology, it is more sensitive than a pap smear, and its cost is significantly lower [26,27,28]. The specificity of detecting abnormal cervical lesions using HPV genotyping increases with patient age, as it is known that persistence of the virus is associated with progression to pre-cancerous lesions [18]. The recent development of a rapid HPV test that can be self-collected has proven to be quite successful in large population screening programs. Several studies have shown that women are more likely to participate in cancer screening involving self-collected specimens when compared to more conventional practitioner-collected specimens. The self-collection approach decreases costs and avoids the need for repeated patient follow-up visits to their health care providers [11,27,28,29,30,31]. Drawbacks of the self-collection techniques include the potential for poor follow-up adherence and for reduced test sensitivity when compared to provider-collected specimens. The latter may result from inadequate collection, inappropriate storage and/or specimen contamination.

4. THE PROMISE OF VACCINATION

4.1 Prophylactic Vaccines

Unlike other lethal viruses, such as HIV, the HPV genome does not appear to mutate rapidly, making the development of the HPV vaccine a significantly more feasible task. At least 9 different high risk HPV subtypes have been shown to cause cervical cancer; the most frequently detected being types 16 and 18. In fact, HPV types 16 and 18 cause nearly 70% of cervical cancers worldwide [7,32]. This has led those involved in developing the preventive HPV vaccines to target at least these two viral subtypes (Table 1). Since the virusitself is oncogenic (cancer-producing), the use of live virus and even heat-inactivated virus as a source for vaccine antigen is generally considered a suboptimal approach.

Table 1. Epitope and subtype coverage of the existing preventive vaccines

Company	Product	Epitope site	Targeted HPV subtypes
Merck	Gardasil®	HPV L1 proteins	6, 11, 16, 18
Glaxo Smith Kline	Cervarix®	HPV L1 proteins	16, 18

For this reason, the existing vaccines have utilized virus-like particles (VLPs) whose surface contains antigens that mimic those of particular high-risk HPV subtypes (typically 16 and 18) to stimulate a protective host immune response to virus. The first of the vaccines developed using this strategy entered the commercial market in 2006. While there remains great optimism that this vaccine will significantly reduce the incidence of cervical cancer and its precursors, it will take several years to detect a protective effect [4,6].

While many organizations have been hard at work attempting to initiate vaccination programs in developing countries, the currently available vaccines do provide some technical hurdles. The vaccines require cold storage, which may not be feasible in particularly desolate areas and in tropical climates. Young girls may also have difficulty receiving the three separate injections over a 6 month time interval that are required to complete the vaccination regimen, as many patients live far away from the closest medical facility. Scientists have been working on developing "next generation HPV vaccines" that would be single dose and capable of withstanding harsh environments. This goal, however, remains in the too distant future and it is predicted that the costs to attain it will be significantly more than those associated with the existing vaccines [8].

4.2 Therapeutic Vaccines

Despite the great promise of prophylactic HPV vaccination programs, implementation can be difficult even in well-resourced countries. Universal coverage difficulties are likely to be even more problematic in less-resourced settings. Further, intention to treat analyses have demonstrated that the existing prophylactic vaccine preparations have fairly poor cross-over protection for HPV subtypes not included in the inoculates; intention to treat investigations show a 19-30% efficacy for non-covered subtypes [33,34].

In response to these shortcomings, there has been a push over the last decade to develop therapeutic vaccines for HPV-related neoplasia. Therapeutic vaccines should promote the reversal of HPV-related precancerous lesions prior to their ultimate progression to cancer. Several vaccine candidates have moved into clinical trials and nearly all take a similar approach that involves subcutaneous or intramuscular injection of HPV E6 and /or E7 antigens via a variety of delivery systems. The goal of these injections is the induction of cell-mediated immunity against HPV E6/E7. Some investigators have hypothesized that the generation of systemic cytotoxic T lymphocyte (CTL) immunity against cervical antigens may be less effective than antigen delivery approaches that optimize generation of protective cell-mediated immunity that more specifically targets the female reproductive tract [35]. To this end, one group of investigators administered HPV E2 antigens to the uterine cavity in an effort to generate CTL against HPV in the vulva in an effort to treat vulvar intraepithelial neoplasia [36]. Others have taken the very promising approach of orally immunizing with the E7 antigen of HPV in an effort to generate HPV-specific CTLs in the cervix [37]. Early results from phase I/II trials using the latter approach have demonstrated rapid and substantial lesion regression in treated patients (K. Kawana, unpublished observations).

5. SUMMARY

Great strides have been made toward the eradication of cervical cancer worldwide, but there is still a long way to go. As we move forward in evaluating the outcomes of the several available screening and treatment regimens aimed at preventing cervical cancer, consistency and reproducibility will be central attributes of any successful approach. Although mimicking the models used in the developed world has shown limited utility in more rural settings, improvements in quality of care and access to well-trained physicians, modern health care facilities and up-to-date equipment will likely follow the growth of urban centers in less developed countries. For those areas that continue to have limited access due to distance and resources, the implementation of those approaches that use minimal resources but maintain acceptable outcomes should be encouraged. This would include VIA alone and high risk HPV testing with follow-up VIA for positive tests. Full involvement of the local community in the implementation of affordable cervical neoplasia screening programs helps to optimize utilization and efficacy. Widespread HPV vaccination and education regarding HPV and its transmission will maximize program success [12,15,16].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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