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Review Article

Perspectives on Cervical Cancer: Insights into Screening Methodology and Challenges

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Abstract

Cervical cancer is a significant public health concern worldwide. Current screening approaches include Pap smears, human papillomavirus testing, visual inspections, and emerging molecular techniques, aimed at enhancing precision and accessibility. The landscape also includes the increasing prominence of self-sampling and telemedicine, which broaden the reach of screening services. Human papillomavirus vaccination programs targeting young girls have the potential to significantly reduce long-term risk. These evolving strategies are supported by global initiatives such as the World Health Organization's Cervical Cancer Elimination Initiative, aiming to increase screening efforts and reduce the global impact of cervical cancer. The key findings of this study suggested that current methodologies for the detection and prevention of cervical cancer are a little beneficial and there is a pressing need to use advanced technologies such as highly sophisticated equipment integrated with artificial intelligence. In addition, the detection of cervical cancer screening provides insights into evolving methodologies, promising prospects, and nuanced challenges that must be addressed to prevent this condition in females worldwide. Looking forward, future cervical cancer screening involves further refinements in molecular testing, expanded vaccine coverage, and the integration of telehealth solutions, promising increased accessibility and improved early detection to overcome insightful challenges.

Introduction

Cervical cancer remains a significant global health challenge, with its pervasive impact extending across geographical boundaries and socioeconomic strata. The lower segment of the uterus, referred to as the cervix uteri, is anatomically divided into two distinct compartments: the endocervix and the ectocervix. The ectocervix is lined with delicate, flat squamous cells, contrasting with the inner endocervix, which is characterized by columnar glandular cells. Of particular significance is the transformation zone, situated at the junction of these two regions, which is highly susceptible to pre-cancerous lesions triggered by human papillomavirus (HPV) infection. These initial infections typically manifest as low-grade squamous intraepithelial lesions or cervical intraepithelial neoplasia grade 1 (CIN1). Notably, a substantial proportion of these early-stage infections exhibit spontaneous resolution, with up to 90% of cases resolving within a two-year timeframe. However, despite this potential for natural resolution, the burden of cervical cancer remains profound. A sobering projection from the Cervical Cancer Action in 2012 warned of a significant increase in mortality rates, estimating that by 2030, cervical cancer could cause more than 474,000 deaths annually.[1–4] Furthermore, more than 95% of these fatalities are anticipated to occur in low- and middle-income countries (LMICs), with rates in sub-Saharan Africa expected to double.[5,6] This underscores the urgent need for comprehensive strategies to address cervical cancer prevention, detection, and treatment, particularly in underserved regions.

Statistics from 2008 indicated that an estimated 500,000 women were diagnosed with cervical cancer, resulting in 274,000 attributed deaths. These figures closely align with maternal mortality statistics reported by the World Health Organization (WHO) in 2010. Alarmingly, this devastating burden disproportionately affects women in low-income countries, with a staggering 88% of cervical cancer deaths occurring in these regions.[7,8] Furthermore, in November 2020, the WHO embarked on a momentous global endeavor: the elimination of cervical cancer as a pervasive public health concern throughout the 21st century. Consequently, harmonizing and standardizing these procedures to ensure equitable access to screening services is paramount to the success of

Keywords: Cancer; Cervical cancer; Health concern; Non-communicable disease; Priority setting; Women's health.

Abbreviations: CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynaecology and Obstetrics; HLA, human leukocyte antigen; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; LBC, liquid-based cytology; LMICs, low- and middle-income countries; TLR, toll-like receptors; VIA, visual inspection with acetic acid; VILI, visual inspection with lugol's iodine; WHO, World Health Organization.

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the WHO's initiative to eliminate cervical cancer worldwide.[9–13] Through collaborative efforts, information sharing, and the implementation of best practices, it becomes possible to work collectively toward a future where cervical cancer is no longer a pervasive public health issue.[12]

This review focuses on the complex ways cervical cancer screening works. It looks at the different methods used worldwide to find precancerous cells and early cancers. It also discusses the big challenges that make it hard for everyone to get screened and for screening programs to work well everywhere globally to detect precancerous lesions and early-stage malignancies, as well as the formidable challenges that continue to impede universal access and effectiveness of screening programs.

Cervical cancer: a global burden

Bridging the gap between knowledge and practical implementation is crucial, requiring concerted efforts to ensure that evidence-based strategies are readily accessible to all individuals, ultimately reducing the global burden of cervical cancer, particularly in the most underserved regions. The connection between oncogenic HPV infection and cervical cancer has been a pivotal discovery in women's health. Dr. Harald zur Hausen, a distinguished German virologist and physician, was the visionary who, in the 1970s, first proposed the pivotal role of HPV in the development of cervical cancer.[14] By 1984, his groundbreaking work led to the specific isolation of HPV types 16 and 18, two HPV variants that are responsible for approximately 70% of cervical cancer cases.[15] Globally, the burden of cervical cancer remains substantial, with more than half a million new cases diagnosed each year, and a striking 90% of these cases occurring in the least developed economies. From this perspective, the United States reported a cervical cancer incidence rate of 8.1 cases per 100,000 women in 2012, whereas LMICs collectively experienced a substantially higher rate of 15.7 cases per 100,000 women.[16] The importance of cervical cancer screening programs cannot be overstated, as they play a pivotal role in identifying pre-cancerous lesions that can be effectively managed through low-cost outpatient procedures. Furthermore, early detection of invasive cancers offers the potential for successful treatment and improved outcomes. However, the translation of these evidence-based recommendations into effective and widespread cervical cancer screening programs remains a challenge. As a result, resource-limited settings continue to struggle with persistently high rates of cervical cancer incidence and mortality. Currently, HPV stands as the most frequently diagnosed sexually transmitted infection, with a staggering estimated prevalence of 43% among females aged 14–59 years in the United States.[17] Factors such as limited access to healthcare, lack of awareness, and inadequate screening programs contribute to disparities in its prevalence. Moreover, the social and economic repercussions of cervical cancer extend far beyond its medical aspects, disrupting families, communities, and economies, exacerbating existing inequalities, and underscoring the urgency of addressing this global burden comprehensively. This review will delve into the statistics and data defining cervical cancer as a global health issue, highlighting its profound impact on women's health and society at large, and emphasizing the need for a united, global response to mitigate its devastating effects.

Global impact of cervical cancer on women's health

Cervical cancer screening encompasses a diverse array of evidence-based techniques meticulously developed and tested to suit a wide range of contexts. In high-resource settings, the Pap smear, a cytologic screening method, is frequently employed. Cervical cell samples were collected, and subsequent examination for signs of dysplasia and pre-cancerous lesions was performed. Although effective, this approach can be resource-intensive due to the need for specialized specimen preservation and the involvement of cyto-pathologists with advanced technical expertise.[6–8,14] To complement such cytologic methods, visual inspection techniques have been introduced. These methods offer a valuable balance of sensitivity and specificity, allowing for the identification of later-stage pre-cancerous lesions. When detected, these pre-cancers can be treated using approaches such as cryotherapy freezing or the loop electrosurgical excision procedure, which are commonly implemented in low-resource settings alongside visual inspection screening services. Additionally, there is the option of HPV testing, renowned for its exceptional sensitivity in detecting high-grade lesions. HPV testing can be conducted using samples obtained by clinicians or even through self-sampling techniques. In some cases, it can serve as a primary screening tool and be employed in conjunction with cytology or visual inspection for triage, depending on the available infrastructure.

The 2011 WHO Prioritized Research Agenda for the Prevention and Control of Non-communicable Diseases recognizes the effectiveness of cancer screening services in high-income countries and HPV screening in reducing cervical cancer deaths in resource-limited settings, such as rural India. However, reports on the successful implementation and sustained operation of cervical cancer screening programs in LMICs are limited. This underscores the need for research to investigate context-specific barriers and facilitators and inform the adaptation of evidence-based interventions to ensure successful program implementation and sustainability across diverse settings. Furthermore, a 2015 scoping study on breast and cervical cancer in LMICs revealed that while the literature primarily focuses on prevention and detection, it lacks attention to implementation considerations. It also highlighted that recommendations often appear detached from the study context, particularly those concerning governance, systems development, workforce capacity, and community-centered approaches. Nevertheless, due to the availability of these diverse and context-appropriate screening modalities, global cervical cancer screening coverage remains disheartenedly low. Several reports revealed a global coverage rate of less than 40%, and in the least developed countries, the coverage decreases to a mere approximately 20%.[15–18] This underlines the critical need to bridge the gap between the existence of effective screening methods and their practical implementation, particularly in the most underserved regions, to effectively combat the global burden of cervical cancer.

Remarkably, young women exhibit a remarkable ability to clear HPV infections. In the first year of infection, clearance rates can reach as high as 70%, and within two to five years, clearance rates can increase from 70% to 100%. These statistics are intriguing, especially when considering the negligible incidence of cervical cancer in the same age group, which stands at a mere 0.1 per 100,000.[19] Furthermore, even high-grade CIN 2 in adolescents regresses 60% of the time within the first three years, indicating a substantial likelihood of self-resolution and other relevant infectious diseases.[20–24] These advancements in understanding HPV dynamics and the distinct risks associated with various strains are propelling the field toward more precise and tailored screening strategies for the prevention of cervical cancer.[6,17] Cervical cancer poses a significant and disproportionate burden on underserved

populations with limited access to quality healthcare services. In these resource-constrained settings, there is a pressing need to enhance our understanding of sustainable strategies for the effective implementation of cervical cancer screening services. Addressing this issue is essential for reducing the inequalities in healthcare access and improving the overall health outcomes of these vulnerable communities.

Screening methodologies

As we advance in the field of cervical cancer screening, it becomes increasingly apparent that HPV testing plays a pivotal role as a primary screening method. This is underscored by its high sensitivity in detecting high-grade cervical lesions, offering a powerful tool for the early identification of potential risks. The strategic approach is to employ HPV testing as the initial step in screening, followed by triage using additional diagnostic methods such as cytology, HPV genotyping, or other genetic profiling. This multi-step screening process holds promise for enhancing the efficiency of cervical cancer prevention. By detecting HPV infections early and then carefully assessing the associated risks, healthcare providers can more precisely target their interventions.[12–14,18] The invasive phase of cervical cancer involves a critical juncture in its progression and is often associated with a less favorable prognosis. During this stage, cancer cells exhibit an alarming capacity for spreading via direct extension into nearby structures, including the parametrium, vagina, uterus, and adjacent organs. It's important to distinguish this invasive phase from the precancerous phase, which is classified under CIN staging. In regard to precisely characterizing invasive cervical cancer, the gold standard for staging is the system outlined by the International Federation of Gynecology and Obstetrics (FIGO). The FIGO guidelines categorize invasive cervical cancer into four distinct stages, denoted as I, II, III, and IV.[19,25] These stages are pivotal in clinical practice because they provide essential information about the extent of the disease, which, in turn, informs treatment decisions and helps predict patient outcomes.

This not only minimizes unnecessary procedures but also ensures that those at the greatest risk receive the most appropriate and timely care. This represents a significant step forward in the quest to prevent invasive cervical disease and reduce the global burden of cervical cancer. Several screening methodologies are available and discussed herein, each with its advantages and considerations.

Pap smear (papanicolaou test)

The traditional Pap smear, also known as the Papanicolaou smear or Pap test, is a well-established cervical cancer screening method. Its fundamental principle lies in detecting abnormal cellular changes in the cervix, with a primary focus on identifying precancerous or cancerous cells. The procedure involves collecting a sample of cervical cells, typically achieved by using a specialized spatula or brush to scrape cells from the surface of the cervix. These collected cells are then spread onto a glass slide or placed in a liquid preservative solution, after which the sample is sent to a laboratory for examination. In the laboratory, a trained cytotechnologist or pathologist examines the cells under a microscope to identify any abnormalities in their appearance.

Effectiveness

The traditional Pap smear has played a pivotal role in reducing the incidence of cervical cancer and related mortality. Its effectiveness lies in its ability to detect early changes in cervical cells, thereby enabling timely intervention to prevent progression to invasive cancer.

Limitations:

- *Sensitivity:* The Pap smear exhibits moderate sensitivity, implying it may overlook some instances of precancerous or cancerous cells, leading to false-negative outcomes. It is notably less sensitive in identifying CIN 2/3, representing more advanced precancerous lesions;
- *Specificity:* There is a potential for false-positive outcomes, indicating the presence of abnormal cells when none are present. This circumstance can prompt unnecessary follow-up tests and cause anxiety for the patient;
- *Interoperator Variability:* The accuracy of Pap smears can fluctuate based on the proficiency and experience of the healthcare provider who collects the sample and the laboratory staff who interprets the results;
- *Missed Infections:* The Pap smear does not assess the presence of HPV, a primary cause of cervical cancer. HPV testing has become crucial in cervical cancer screening because it can identify high-risk HPV (hrHPV) strains that increase the risk of cervical cancer development.

Therefore, while the traditional Pap smear has played a pivotal role in cervical cancer prevention, it is accompanied by limitations related to sensitivity, specificity, and the necessity for frequent screening. Advances in cervical cancer screening methodologies, such as integrating Pap smears with HPV testing or transitioning to primary HPV testing, aim to mitigate these limitations and bolster the overall efficacy of screening programs.

HPV DNA testing

Concept and procedure

HPV testing is a molecular diagnostic technique used to identify the presence of hrHPV DNA in cervical cells. hrHPV strains, particularly types 16 and 18, are known to be the primary cause of cervical cancer. The procedure involves collecting a cervical cell sample during a pelvic exam, much like a Pap smear. The sample is typically placed in a liquid-based solution and then sent to a laboratory for analysis. In the laboratory, the DNA in cervical cells is examined to determine whether any hrHPV strains are present. This test can be performed as a standalone test or in combination with a Pap smear (co-testing). The pathogenesis of cervical cancer. It starts with epithelial cells located in the transformation zone of the cervix, which develop lesions as a result of persistent infection with hrHPV.[5] In some instances, these lesions naturally resolve. However, in other cases, when viral integration occurs, these cells transform, progressing from CIN1, CIN2, and CIN3. During this process, the viral proteins E6 and E7 are released, interfering with critical cellular functions. They inhibit apoptosis mediated by TP53, disrupt cell cycle checkpoints controlled by p21, impede T-cell responses *via* toll-like receptors, and hinder macrophage activation through cytokines. These actions collectively result in an inadequate immune response, unchecked viral replication, uncontrolled cell proliferation, genome instability, and the development of either cancer in situ or invasive cervical cancer.[5,25]

HPV vaccination programs have had a significant impact on cervical cancer prevention by reducing the incidence of hrHPV infections. By preventing initial HPV infection, these vaccines help decrease the risk of developing cervical cancer. However, successful implementation depends on factors such as vaccine availability, public acceptance, and equitable distribution. Challenges in implementing HPV vaccination programs include vaccine supply issues, vaccine hesitancy, and reaching remote populations. Successes include the development of affordable vaccines, increasing vaccine

coverage, and education campaigns that promote the importance of vaccination. To maximize the impact of vaccination, efforts must be made to overcome these challenges and ensure broad access to the vaccine.

Effectiveness

HPV testing has become a valuable tool in cervical cancer screening, offering several advantages:

- *Early detection:* HPV testing is highly effective in identifying hrHPV infections, including those that may lead to cervical cancer. HPV infections can be detected even before cellular changes occur, enabling early intervention;
- *High sensitivity:* HPV testing has greater sensitivity than Pap smear, particularly in detecting advanced precancerous lesions (CIN 2/3);
- *Risk stratification:* The results can help stratify women into low-, intermediate-, or high-risk categories, allowing for more tailored follow-up and management.

Limitations:

- *Lack of specificity:* HPV testing is highly sensitive but less specific than Pap smears. Transient or low-risk HPV infections that are often clear on their own may be detected, leading to unnecessary follow-up tests and patient anxiety;
- *Co-infections:* HPV testing cannot differentiate between multiple HPV types in the same sample, making it challenging to determine which type contributes to the greater risk;
- *Age considerations:* HPV is common among young individuals and often clears without causing harm. Therefore, guidelines recommend different screening strategies for different age groups;
- *Resource intensive:* Incorporating HPV testing into screening programs may require additional resources and infrastructure.

Thus, HPV testing is a highly effective tool in cervical cancer screening, particularly for the early detection of hrHPV infections. However, it is less specific than the Pap smear and requires careful interpretation. Combining HPV testing with other screening methods and considering the age and risk profile of the individual can help optimize its effectiveness while minimizing its limitations.

Visual inspection with acetic acid (VIA) and lugol's iodine (VILI)

Concept and procedure

VIA and VILI are both low-cost, visual methods used for cervical cancer screening, particularly in resource-constrained settings.

VIA

This technique involves the application of a dilute acetic acid solution (commonly known as vinegar) to the cervix. Healthy cervical tissue remains unaffected, but any precancerous or cancerous lesions turn white (acetowhite) and become more visible. This method is performed during a pelvic exam using a speculum and a cotton swab soaked in acetic acid.

VILI

In this method, a solution of Lugol's iodine (potassium iodide and iodine) is applied to the cervix. Healthy tissue absorbs iodine, appearing brown, while precancerous or cancerous lesions do not take up iodine, remaining yellow. VILI, like VIA, is conducted during a pelvic exam using a speculum and iodine-soaked swabs.

Effectiveness

VIA and VILI are valuable screening methods, particularly in areas where more advanced technologies are less accessible.

- *Low cost and simplicity:* VIA and VILI are cost-effective and relatively easy to perform, making them suitable for low-resource settings and as one-time screen-and-treat approaches;
- *Immediate results:* Results are available instantly, allowing for immediate treatment if abnormalities are detected;
- *Reasonable sensitivity:* These methods have reasonable sensitivity, although not as high as that of Pap smears or HPV testing. They can identify visible cervical abnormalities.

Limitations:

- *Limited diagnostic precision:* These methods do not provide a definitive diagnosis; rather, they identify areas of concern that require further evaluation, which can be a limitation in terms of specificity;
- *Limited to visible lesions:* These lesions may miss abnormalities that are not visually evident, leading to a risk of false negatives.

Therefore, VIA and VILI are valuable cervical cancer screening methods, especially in areas with limited access to more advanced screening tools. They are cost-effective, provide immediate results, and can contribute to cervical cancer prevention. However, their limitations include subjectivity, lack of diagnostic precision, and reliance on visible lesions, making them most effective when integrated into a broader cervical cancer screening and treatment program.

Innovative and emerging technologies

Liquid-based cytology (LBC)

LBC is an advancement over traditional Pap smears. Rather than smearing collected cells onto a glass slide, the sample is immersed in a liquid preservative solution. This method offers several advantages, including improved sample quality, reduced rates of unsatisfactory samples, and the capacity to perform additional tests, such as HPV testing, on the same sample. LBC is particularly valuable in addressing some of the limitations associated with conventional Pap smears;

Molecular testing method

Molecular tests, such as HPV DNA testing, have gained prominence in cervical cancer screening. HPV DNA testing identifies the presence of hrHPV strains, which are strongly associated with cervical cancer. This approach is highly sensitive and can detect HPV infections even before cellular changes occur. It is often utilized as a primary screening tool, either alone or in combination with Pap smears. The development of more specific and cost-effective HPV tests has expanded their utility;

Digital cervicography method

Digital cervicography is a screening technique used to assess the cervix for abnormalities related to cervical cancer. During the procedure, a digital camera equipped with a specialized lens captures close-up photographs of the cervix. These images provide detailed visual documentation of the cervix, enabling healthcare providers to examine the surface for any suspicious lesions, growths, or discolorations. Digital cervicography serves as a tool for monitoring changes in the cervix over time and can be particularly useful in tracking the progression of precancerous lesions or monitoring the effectiveness of treatment interventions. Additionally, these images can be utilized for patient education and counseling, facilitating discussions about findings and treatment options in a more tangible and comprehensible manner. While digital cervicography offers benefits such as visual documentation and patient education,

its widespread implementation may be limited by factors such as the availability of equipment, infrastructure requirements, and the need for specialized training in image interpretation. Nonetheless, it remains a valuable adjunct to traditional screening methods such as Pap smear and HPV testing, particularly in settings where resources for more advanced screening techniques may be limited;

Colposcopy

This is a medical procedure used to closely examine the cervix, vagina, and vulva for signs of abnormalities or precancerous changes. Abnormal results from other screening tests, such as Pap smear and HPV DNA test, or visual inspection methods such as VIA or VILI, are typically obtained. The procedure includes:

- *Preparation:* Before the procedure, the patient will be asked to empty their bladder. They will then lie down on an examination table, similar to a pelvic exam;
- *Speculum Insertion:* A speculum, a metal or plastic instrument, is gently inserted into the vagina to hold the walls apart. This allows the healthcare provider to see the cervix clearly;
- *Application of Solutions:* The healthcare provider may apply a solution of acetic acid (vinegar) to the cervix. This solution helps to highlight any abnormal areas by causing them to turn white. In some cases, Lugol's iodine solution may also be used, which stains normal tissue brown, making abnormal areas stand out;
- *Colposcopic Examination:* The colposcope, a specialized magnifying instrument with a light source, is then positioned near the opening of the vagina. The healthcare provider examines the cervix through the colposcope, which provides a magnified view of the cervical tissues;
- *Evaluation and Biopsy:* If any abnormal areas are detected during the colposcopy, the healthcare provider may choose to perform a biopsy. During a biopsy, a small tissue sample is removed from the suspicious area for further examination under a microscope. This helps to confirm the presence of precancerous or cancerous cells;
- Colposcopy is generally a safe procedure with minimal risks. It's an important tool in the diagnosis and management of cervical abnormalities, enabling healthcare providers to accurately identify and monitor changes in cervical tissue. The results of the colposcopy and any biopsies taken help guide further treatment decisions, such as close observation, additional testing, or treatment to remove abnormal tissue.

Hence, the choice of screening methodology depends on various factors, including a woman's age, risk factors, and available healthcare resources. A comparison of various screening methodologies for cervical cancer screening is provided in Table 1.[4,8,26] The combination of different methods, as well as the integration of HPV vaccination programs, contributes to a comprehensive approach to cervical cancer prevention and early detection. Regular screenings, starting at an appropriate age, are crucial for effectively reducing the incidence and mortality associated with cervical cancer.

In low-resource settings, where healthcare infrastructure may be limited and access to advanced medical technologies is often constrained, integrating various screening methods for cervical cancer presents a unique set of challenges and opportunities. Despite these challenges, there is growing recognition of the importance of implementing effective screening programs to reduce the burden of cervical cancer in these regions. The potential integration of various screening methods within healthcare systems can offer a comprehensive approach to cervical cancer screening, tailored to the specific needs and resources of each setting. One of the primary considerations in integrating screening methods in low-resource settings is the feasibility of implementation. Although effective, traditional methods such as Pap smear, may face logistical challenges due to the need for well-equipped laboratories, trained personnel, and infrastructure for sample collection and processing. However, alternative methods such as VIA or VILI offer simpler and more cost-effective options that can be performed by trained non-specialists in low-resource settings. These methods require minimal equipment and can provide immediate results, making them suitable for resource-constrained environments where access to laboratory facilities is limited. Furthermore, the integration of point-of-care HPV DNA testing holds promise for enhancing cervical cancer screening programs in low-resource settings. Despite the initial investment required for equipment and training, point-of-care HPV tests offer several advantages, including high sensitivity and specificity, rapid turnaround time, and the potential for on-site diagnosis. By incorporating HPV testing into existing screening programs, healthcare providers can identify high-risk individuals who may benefit from further evaluation and follow-up, thereby optimizing the allocation of limited resources and improving overall screening efficiency.

The successful integration of multiple screening methods hinges not only on technological considerations but also on addressing broader systemic challenges such as healthcare infrastructure, workforce capacity, and community engagement. Sustainable screening programs require investment in training and capacity-building initiatives to empower healthcare workers with the skills and knowledge necessary to perform screening and follow-up procedures effectively. Additionally, efforts to strengthen healthcare infrastructure, including the establishment of quality assurance mechanisms and supply chain management systems, are essential to ensure the availability and reliability of screening services over time. Moreover, community engagement and education play a crucial role in promoting awareness of cervical cancer prevention and encouraging women to participate in screening programs. Culturally sensitive approaches that address barriers to screening, such as stigma, fear, and misconceptions, are essential for increasing uptake and adherence to screening recommendations. Leveraging existing community networks, such as community health workers and peer educators, can facilitate the dissemination of information and the promotion of screening services at the grassroots level, thereby enhancing the reach and impact of cervical cancer prevention efforts. Additionally, the integration of primary screening modalities, colposcopy, and biopsy services is vital for the accurate diagnosis and management of cervical abnormalities detected through screening. While colposcopy may pose challenges in terms of equipment availability and specialized training, task-shifting strategies that train mid-level providers or nurses to perform colposcopy can help expand access to diagnostic services in low-resource settings. Furthermore, establishing referral pathways and partnerships with higher-level facilities for confirmatory testing and treatment ensures that women with abnormal screening results receive timely and appropriate care, thereby reducing the risk of disease progression. Therefore, the integration of different screening methods within healthcare systems offers a pragmatic approach to cervical cancer prevention in low-resource settings, where multi-modal screening may be more challenging. By leveraging a combination of traditional and innovative screening modalities, tailored to the local context and resource constraints, healthcare systems can maximize the impact of cervical can-

Table 1. Comparison of different screening methodologies for cervical cancer[4,8,26]

Screening Methods	Description	Advantages	Disadvantages
Pap smear	Collects cells from the cervix to detect abnormalities or precancerous changes. Effective in detecting precancerous cells	Low-cost. Widely available	Requires a follow-up test for HPV if abnormalities are found. Relatively high false-negative rate.
HPV DNA Test	Detects the presence of high-risk strains of human papillomavirus (HPV) which are linked to cervical cancer.	Highly sensitive in detecting HPV infections. Can detect high-risk HPV even before cellular changes occur.	Higher cost compared to Pap smear. Limited availability in some regions.
Visual Inspection with Acetic Acid (VIA)	Visual examination of the cervix after applying acetic acid which highlights abnormal areas.	Low-cost. Can be performed by trained non-specialists. Subjective interpretation	Limited sensitivity and specificity compared to cytology or HPV testing.
Visual Inspection with Lugol's Iodine (VILI)	Similar to VIA but uses Lugol's iodine solution which stains normal tissue, making abnormal areas more visible.	Low-cost. Easy to perform. Subjective interpretation.	Less sensitive than cytology or HPV testing.
Liquid-based cytology	Similar to Pap smear but cells are preserved in a liquid medium rather than being smeared on a slide.	Less chance of inadequate sampling. Can be tested for HPV concurrently.	Higher cost compared to conventional Pap smear. False positives due to contaminating factors.
Molecular Testing Method	Molecular tests, such as HPV DNA testing, have gained prominence in cervical cancer screening. It is often used as a primary screening tool, either alone or in combination with Pap smears.	HPV DNA testing identifies the presence of high-risk HPV strains, which are strongly associated with cervical cancer.	Higher cost compared to conventional Pap smear.
Digital Cervicography Method	Digital cervicography is a screening technique used to assess the cervix for abnormalities related to cervical cancer. During the procedure, a digital camera equipped with a specialized lens is used to capture close-up photographs of the cervix. These images provide detailed visual documentation of the cervix, allowing healthcare providers to examine the surface for any suspicious lesions, growths, or discolorations.	Digital cervicography serves as a tool for monitoring changes in the cervix over time, which can be particularly useful in tracking the progression of precancerous lesions or monitoring the effectiveness of treatment interventions.	Advanced screening techniques on sophisticated instruments are required.
Colposcopy	Visual examination of the cervix using a magnifying instrument (colposcope) after applying acetic acid.	Provides detailed examination of abnormal areas. Can guide biopsy if necessary.	Requires specialized equipment and trained personnel. Higher cost compared to other screening methods.

cer screening programs and ultimately reduce the burden of this preventable disease on women and communities worldwide. Additionally, sustained investment, collaboration, and commitment from policymakers, healthcare providers, and communities are essential to overcome barriers and achieve equitable access to quality cervical cancer screening and care for all women, regardless of their socioeconomic status or geographic location.

Potential impact on global cervical cancer screening

Emerging technologies for cervical cancer screening, such as LBC and molecular tests, hold considerable promise for improving global screening efforts in several ways:

- *Increased Sensitivity and Accuracy:* These innovative methods offer improved sensitivity and accuracy in detecting cervical abnormalities, including early precancerous lesions. This approach results in more reliable identification of high-risk cases and better patient outcomes;
- *Reduction in False Negatives and Positives:* By decreasing the likelihood of false negatives and positives, these technologies enhance the efficiency of screening programs. Fewer false negatives indicate early intervention, and fewer false positives lead to less unnecessary follow-up testing;
- *Streamlined Screening Protocols:* Emerging technologies, particularly molecular tests, enable streamlined screening protocols. Primary HPV testing, for instance, is a robust approach to cervical cancer screening that can replace or complement other methods, simplifying the screening process;
- *Resource Efficiency:* LBC and molecular tests can improve resource allocation by reducing the need for frequent screenings, allowing for longer intervals between tests without compromising accuracy. This can be especially beneficial in low-resource settings;
- *Global Accessibility:* As these technologies become more accessible and affordable, they can be deployed in a wider range

of settings, helping to reach underserved populations more effectively. This is crucial for reducing cervical cancer disparities;
- *Integration into Comprehensive Programs:* The integration of emerging technologies into comprehensive cervical cancer screening programs, alongside preventive measures such as HPV vaccination and public health education, can contribute to substantial reductions in cervical cancer incidence and mortality globally.

Nevertheless, emerging technologies in cervical cancer screening, including LBC and molecular tests, have the potential to revolutionize the approach to global cervical cancer prevention. They offer improved sensitivity, reduced false results, and greater efficiency, making them key components in the fight against cervical cancer, particularly in resource-constrained regions. As these technologies become more accessible and integrated into healthcare systems, they have the potential to significantly reduce the global burden of this preventable disease.

Challenges

Accessibility and infrastructure

Disparities in access to cervical cancer screening services are becoming increasingly evident worldwide. Low-resource and underserved regions often contend with inadequate healthcare infrastructure, insufficient screening facilities, and a shortage of trained healthcare professionals. These disparities lead to limited access to screening for a significant portion of the global population, contributing to an unequal cervical cancer burden. Several infrastructure-related challenges are encountered in low-resource settings, including a lack of screening facilities, diagnostic laboratories, and well-trained healthcare providers. Remote and rural areas, in particular, struggle to provide access to regular screening services, leading to delays in diagnosis and treatment. Insufficient resources for quality assurance and data management further complicate efforts to establish effective screening programs.

Cultural barriers

Cultural beliefs and societal norms often present significant barriers to cervical cancer screening. Stigma, misconceptions, and fear surrounding gynecological examinations may deter women from participating in screenings. Some cultures impose restrictions on discussions of women's health, making it challenging to promote awareness and access to screening services.

Education and lack of awareness

Education and awareness campaigns are crucial for overcoming cultural barriers. Public health initiatives and community-based programs can provide information about the importance of cervical cancer screening, dispel myths, and reduce stigma. Accessible and culturally sensitive information can empower women to make informed decisions about their health, ultimately increasing screening participation.

Financial crisis

Cervical cancer screening and treatment can impose a significant financial burden on individuals and healthcare systems. The costs associated with screening tests, follow-up diagnostics, and treatments are often unaffordable for low-income individuals. The cumulative expense can deter women from pursuing screening and treatment, particularly in regions with limited access to healthcare coverage. Various initiatives aim to make screening more affordable and accessible, including subsidizing the cost of screenings, increasing health insurance coverage, and supporting low-cost or free screening programs in underserved areas. International organizations and governments also collaborate to reduce the cost of HPV vaccines and make them available to populations in need.

Impact of socioeconomic factors on screening effectiveness

Socioeconomic factors like income level, education, and access to healthcare can greatly influence the effectiveness of various screening methods. Lower-income individuals may face barriers such as lack of awareness, transportation issues, or inability to afford screening tests. These disparities must be considered in implementing screening programs to ensure equitable access and effectiveness across all socioeconomic groups.

Role of male HPV vaccination

While cervical cancer primarily affects females, the role of male HPV vaccination is crucial in preventing transmission of the virus and reducing the overall disease burden. Discussion on the importance of vaccinating males can complement the focus on female screening, highlighting the broader impact of HPV vaccination as a preventive strategy for both genders.

Integration of digital health technologies and telemedicine

Digital health technologies and telemedicine present promising opportunities to improve screening accessibility and follow-up care, particularly in remote or underserved areas. These tools can facilitate remote consultations, self-sampling kits, and electronic medical records, overcoming geographical barriers and enhancing patient engagement. However, challenges such as digital literacy and infrastructure limitations must be addressed to maximize the potential benefits of these technologies.

Evaluation of potential bias

It is essential to evaluate and acknowledge any potential bias in the presentation of research findings and recommendations. Bias can arise from various sources, including funding sources, author affiliations, or personal beliefs. Maintaining a neutral and evidence-based stance throughout the review is crucial to ensure transparency and credibility. By critically assessing the quality and relevance of evidence, the review can provide a balanced perspective on cervical cancer screening strategies and their potential impact on diverse populations.

Future directions

Cervical cancer specialists and public health advocates should obtain valuable insights from such analyses to advance cervical cancer prevention and treatment globally. It is imperative for these stakeholders to understand that shaping policy agendas involves more than simply presenting evidence of health burden or distribution. Ongoing research and developments in cervical cancer screening have focused on advanced technologies such as next-generation sequencing and point-of-care tests to enhance accuracy and accessibility. Personalized screening approaches based on individual risk profiles and tighter integration with HPV vaccination programs are also under exploration. These breakthroughs have the potential to improve the early detection of cervical abnormalities, reduce disparities in screening access, and optimize resource allocation while strengthening global collaborations to combat cervical cancer on a larger scale. To effectively advocate for their causes, public health proponents should consider themselves par-

ticipants in a social movement and engage in persuasive dialogue to influence what has gained prominence in the global health and development arena, acknowledging that global agendas may not inherently mirror epidemiological realities.

States that uphold current school vaccination requirements despite opposition are poised to see significant enhancements in vaccination rates. In the broader political landscape, implementing outreach programs to administer vaccines in schools, regardless of mandate status, could propel the United States toward achieving vaccination rates aligned with Healthy People 2020 objectives.[26] Moreover, clinicians have a pivotal role in elevating HPV vaccination rates over the next five years. With increasing emphasis on quality metrics and cost reduction in healthcare delivery, clinicians are incentivized to ensure high vaccination rates among their patient populations. Strategies such as implementing reminder/recall systems, standing orders/nursing protocols, and point-of-care reminders have demonstrated efficacy in improving vaccination rates at the practice level. By embracing these population health interventions, clinicians can make substantial strides in HPV vaccination rates within their patient cohorts.

Persistent infection with high-risk strains of HPV can lead to the development of cervical dysplasia and CIN.[27] If left untreated, these precancerous lesions can progress to invasive cervical cancer. Cervical dysplasia refers to abnormal changes in the cells of the cervix, while CIN represents the growth of abnormal cells on the surface of the cervix. Over time, these abnormal cells can infiltrate deeper layers of cervical tissue, ultimately leading to the formation of invasive cancerous tumors. Therefore, timely detection and management of HPV infections and precancerous lesions are crucial for preventing the development and progression of cervical cancer.[27] Regular screening through methods such as Pap smear or HPV testing can aid in the early identification of abnormal changes, allowing for prompt intervention and reducing the risk of cervical cancer. Additionally, vaccination against HPV offers primary prevention against infection with hrHPV strains, further mitigating the risk of cervical cancer development.

To date, limited knowledge surrounding cervical cancer susceptibility variants and genes has imposed constraints on the advancement of precision medicine strategies in this domain. Consequently, large-scale cohort studies focused on cervical cancer through genome-wide association studies and comprehensive meta-analyses are urgently needed. Such endeavors are geared toward the identification of additional susceptibility loci, which is vital for a more comprehensive understanding of the genetic underpinnings of this disease. In this context, national biobanking initiatives have emerged as invaluable resources for genomic research, facilitating the acquisition and curation of large-scale genetic datasets. These resources serve as crucial components in the endeavor to unearth novel risk factors associated with the ailment. Through sustained and collaborative endeavors, we envision the potential for early detection of disease-associated risk factors, ultimately integrated into proactive cancer surveillance strategies, heralding a promising era for cervical cancer prevention and management. This approach aligns with the ongoing developments in cervical cancer screening, where advances in technology and personalization are redefining the landscape of prevention and early detection on a global scale.

Conclusions

Considerable evidence underscores the significant role of genetics in influencing susceptibility to cervical cancer, complementing well-established risk factors such as lifestyle and HPV infection. While genetic research in cervical cancer remains relatively sparse, a recurrent theme has emerged—the human leukocyte antigen (HLA) region within our DNA exhibits consistent associations with the disease across diverse population groups. Notably, this HLA region is intricately linked to various autoimmune and immune-related conditions, suggesting a crucial role for the immune system in cervical cancer. This intriguing connection paves the way for personalized preventive strategies that leverage our understanding of how HLA interactions with other molecular components can offer clinical advantages, potentially reshaping the landscape of cervical cancer prevention.

In 2020, at the global level, the WHO launched the Global Cervical Cancer Elimination Initiative, aiming to reduce cervical cancer incidence worldwide and bridge international disparities. The initiative sets a 90–70–90 target for 2030, aiming to vaccinate 90% of girls by age 15, screen 70% of women twice by age 45, and treat 90% of women with cervical precancer or cancer. Surveillance and monitoring are emphasized to identify and address gaps in cervical cancer care, moving toward a future of prevention and treatment equity. Cervical cancer screening has evolved with a focus on precision and accessibility. Current methodologies include Pap smears, HPV testing, visual inspections, and emerging molecular tests, enabling more accurate detection of cervical abnormalities. Self-sampling and telemedicine have improved access to screening, especially in underserved areas. HPV vaccination programs for young girls aim to reduce long-term risk. The future of cervical cancer screening involves further advancements in molecular testing, enhanced vaccine coverage, and the integration of telehealth and digital health solutions for wider accessibility and improved early detection. Additionally, global initiatives such as the WHO's Cervical Cancer Elimination Initiative are working toward expanding screening and reducing the global burden of cervical cancer, but further exploration is required to achieve milestones for a safer world.

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Conflict of interest

None.

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