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Opinion

What's Going on in the Trenches of the Cervical Cancer Battle?

Thais Heinke[1]* and Tatiana Megale Lima[2]

[1]Associate Professor, Department of Pathology, Brazil

[2]Doctor in Sciences, Department of Gynecology, Brazil

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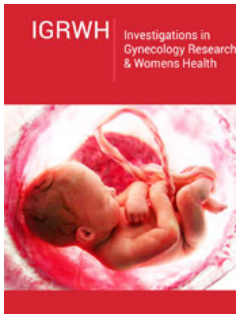

***Corresponding authors:** Thais Heinke, Department of Pathology, Federal University of São Paulo, Sao Paulo, Brazil

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Abstract

Cervical cancer remains a significant global public health issue, particularly in Low- and Middle-Income Countries (LMICs), where its burden is disproportionately high. Although there has been increasing attention from the global scientific community, governmental actions have not aligned with the ambitious targets set by the World Health Organization (WHO) for the eradication of cervical cancer by 2030. International collaborations are essential to address disparities in access to HPV vaccination and screening programs, both crucial components for scaling up prevention efforts in underserved regions. Since 2020, following the WHO's launch of a strategy focused exclusively on the elimination of cervical cancer, new considerations have emerged, including relevant changes on screening guidelines. These developments reflect divergent perceptions and the need for updated strategies to make the 2030 targets achievable. A brief summary of the Evidence-to-decision framework that is explained on WHO's guidelines for HPV mRNA testing in cervical cancer prevention is outlined.

Keywords: HPV; Cervical cancer; Screening

Introduction

Cervical cancer continues to pose a significant health challenge globally. According to recent estimates from the International Agency for Research on Cancer (IARC), approximately 660,000 new cases of cervical cancer were diagnosed worldwide in 2022, with around 350,000 deaths resulting from the disease [1]. The burden remains highest in Low- and Middle-Income Countries (LMIC), accounting for nearly 90% of both new cases and deaths, particularly in sub-Saharan Africa, South America, and Southeast Asia. This disparity is largely attributed to limited access to screening and preventive measures like HPV vaccination [2].

In response to the growing burden of cervical cancer, the World Health Organization (WHO) initiated a global call to action aiming for its elimination. The objective is to reduce cervical cancer incidence to four new cases per 100,000 women, a threshold that signifies elimination as a public health problem.

In May 2018, Dr. Tedros Adhanom Ghebreyesus, WHO Director-General, launched this initiative, culminating in the development of a comprehensive Global Strategy. Unanimously endorsed by the Seventy-third World Health Assembly in August 2020, the strategy was officially introduced on November 17, 2020, with the aim of achieving elimination targets by 2030 [3].

A cornerstone of this effort was the revision and simplification of WHO's screening and treatment guidelines. This updated guidance emphasizes equitable and accelerated progress toward three ambitious goals: 90% HPV vaccination coverage among eligible girls, 70% screening coverage with high-performance tests, and 90% appropriate treatment for women with positive screening results or cervical lesions.

The reduction in cervical cancer mortality through screening programs is influenced by several key factors. Among the most significant are the epidemiology of HPV infections,

particularly the prevalence and distribution of high-risk HPV strains in a given population. The design and implementation of the screening program are also crucial, including the age range for screening, frequency of intervals, and the overall coverage achieved. In this context, sensitivity of screening tests emerges as a critical factor, especially when considering the balance between sensitivity and specificity in detection. While specificity is essential for accurate triage, sensitivity plays a more significant role in identifying true positive cases, thereby reducing missed diagnoses.

Discussion

Cytology, or the Pap smear, has long been a cornerstone of cervical cancer screening. However, its role in primary screening has limitations due to its lower sensitivity compared to molecular tests. As such, co-testing, which combines molecular HPV testing with cytology, has gained traction in recent years. This dual approach leverages the high sensitivity of HPV testing with the specificity of cytology, enabling the identification of cases that may have been missed by either test alone. Studies have shown that this combination can improve screening outcomes and reduce the risk of false negatives [4-6].

Despite these advances, cervical cancer screening remains challenging, especially in Low- and Middle-Income Countries (LMICs), where access to screening and treatment programs is limited. The introduction of alternative screening methods, such as Visual Inspection with Acetic Acid (VIA) or molecular tests like HPV DNA testing, has provided options for resource-constrained settings. However, disparities persist in the effectiveness and coverage of these programs across different regions.

In 2020, the World Health Organization (WHO) launched its global strategy to eliminate cervical cancer as a public health issue by 2030. One of the key pillars of this strategy is improving access to primary cervical cancer screening. The first set of recommendations under this strategy emphasized the importance of expanding and improving screening methods worldwide. This includes the shift towards primary HPV testing, which offers superior sensitivity and long-term negative predictive value compared to cytology. However, challenges remain in achieving comprehensive coverage and ensuring timely follow-up and treatment for women with abnormal results, particularly in resource-limited settings. As the global strategy unfolds, it will require robust policy frameworks, widespread education, and equitable healthcare access to reduce the burden of cervical cancer globally [3].

Recognizing this challenge, the World Health Organization (WHO) revised its guidelines to establish a more inclusive, equitable, and effective approach to cervical cancer screening. The updated guidelines reflect advancements in technology and address global inequities, aiming to accelerate progress toward eliminating cervical cancer as a public health problem [7,8].

Historically, cervical cancer screening relied heavily on cytology, commonly known as the Papanicolaou (Pap) smear test. This method has substantially reduced cervical cancer mortality in high-income countries, achieving up to a fivefold decline in incidence over the past 50 years. However, its reliance on well-resourced healthcare systems, trained personnel, and robust infrastructure has limited its success in LMICs [9] Consequently, WHO's updated guidelines introduced alternative screening strategies to enhance global applicability and effectiveness [7].

Primary Human Papillomavirus (HPV) DNA testing has emerged as the preferred screening method due to its superior sensitivity and long-term negative predictive value. This molecular approach is particularly recommended for women aged 25-29, as it excels in detecting high-risk HPV types and identifying precursor lesions. The interval for primary HPV testing is set at five years, based on evidence demonstrating the low risk of developing cervical cancer after a negative result. While cytology and co-testing remain acceptable alternatives, HPV testing is prioritized for its efficacy and practicality across diverse settings.

In the first round, the recommendation considered that in resource-limited settings where HPV testing is unavailable, Visual Inspection with Acetic Acid (VIA) provides a cost-effective alternative. Though less accurate than HPV testing or cytology, VIA is accessible and can be used to triage HPV-positive cases, ensuring timely diagnosis and treatment in some cases. Unfortunately, it didn't perform as good as expected. In 2021, when the second edition was released with by the Guidelines Review Committee, published with a key focus on optimizing primary screening methods [7].

A significant highlight of this update was the elevation of HPV mRNA testing as a primary tool, alongside other existing screening tests. This review emphasized the robust scientific evidence supporting HPV mRNA testing as an effective alternative to traditional HPV DNA testing for detecting cervical pre-cancerous lesions.

HPV mRNA testing works by detecting the E6/E7 oncoproteins, which are produced during HPV infection and directly involved in the oncogenic transformation process. These proteins are strongly linked to the development of cervical cancer, making their detection in mRNA tests potentially more specific than HPV DNA testing. The presence of these oncoproteins is considered a more precise indicator of the potential for cancer development, thus making mRNA testing an important tool in cancer prevention. Moreover, by detecting high-risk HPV types, mRNA tests offer a more focused approach to identifying women at greatest risk of developing cervical pre-cancer [10].

This shift in focus toward HPV mRNA testing reflects the growing recognition of its specificity and potential to improve the accuracy of screening efforts globally, particularly in detecting lesions that may be closer to progressing into full-blown cancer [3,7].

Since the first guideline the content highlight advancements in screening technologies. Molecular innovations, such as mRNA testing, oncoprotein detection, and DNA methylation analyses, have

enhanced diagnostic precision, offering promising alternatives for future implementation. Similarly, cytological advancements, including p16/Ki-67 dual staining and machine learning-based automated platforms and tele cytology have improved test sensitivity and interpretation, addressing some of the traditional method's limitations. However, cytology alone, as a primary screening method, remains less effective than molecular tests, particularly in addressing global challenges of sensitivity and objectivity [11-13].

The guideline emphasizes equity and adaptability, aiming to bridge gaps in access and implementation. WHO's approach prioritizes underserved populations, focusing on scalable solutions that align with its 2030 elimination targets, that remain the same.

By integrating innovative technologies with a global equity perspective, the WHO guidelines represent a significant step toward eliminating cervical cancer through the adoption of the high-performance test it stated to be needed from the beginning. After the second edition, many other publications contributed to a better understanding of some peculiarly challenging aspects of this issue.

However, sustained efforts, comprehensive policy frameworks, and global collaboration remain essential to translate these guidelines into meaningful outcomes worldwide.

Disparities in Low- and Middle-Income Countries

LMICs face significant challenges in implementing cervical cancer prevention strategies due to financial constraints, limited healthcare infrastructure, and cultural barriers. These disparities contribute to higher cervical cancer incidence and mortality rates. Addressing these challenges requires targeted interventions, better resource allocation, and culturally sensitive solutions.

At the most basic level, the success of a cancer screening program depends on high rates of regular participation by the target population and the accuracy of the screening tests. However, several other factors are integral to achieving successful outcomes, such as addressing individual risk factors for cervical cancer, ensuring quality assurance, eliminating access barriers, promoting communication between patients and clinicians, managing abnormal findings, implementing updated guidelines, and adopting new technologies.

It is not feasible to believe that simply having updated, expert-driven guidelines will eliminate the substantial burden that cervical cancer still represents in much of the world. Cooperation and effective initiatives are required to ensure the quality of the tests-whatever method can be applied-adequate patient follow-up, especially for those with abnormal results, and treatment for patients requiring therapeutic intervention.

Furthermore, vaccination has not yet had the widespread impact we hoped for globally. Its adoption and availability have proven to be challenging, and disappointing results in terms of population coverage persist in many parts of the world.

International partnerships are critical to addressing disparities in cervical cancer prevention. Collaborations between governments, non-governmental organizations, and global alliances can help scale up vaccination and screening program and also to promote a more equitable access to new technologies that can impact directly on the result of a screening program.

Advancements in artificial intelligence, particularly in liquid-based cytology and what can follow after its implementation, have shown promising results in improving test accuracy, workflow efficiency, and remote access to case management.

These technologies represent a revolutionary step forward, particularly in settings with limited infrastructure. However, the challenge remains to integrate these innovations into systems that lack access to the necessary tools and expertise. In summary, while substantial progress has been made in cervical cancer prevention, significant gaps remain, especially in LMICs.

Collaborative efforts, investment in healthcare infrastructure, and the adoption of innovative technologies are key to reducing cervical cancer incidence and mortality globally. The path forward requires both scientific and human commitment to achieve the WHO's 2030 goals, acknowledging that the success of this global battle depends on the collective action of all stakeholders.

Final Considerations

In 2020, 194 countries made a vow to eliminate - for the first time - a cancer. This led to the Global strategy to eliminate cervical cancer as a public health problem, initiative that remains a challenge.

After this second edition, several documents and new perspectives have emerged-notably, but not exclusively, in official WHO guidelines. Currently, the WHO is launching new guidance on Target Product Profiles (TPPs) for HPV screening tests [14]. This technical document outlines the preferred standards for new HPV tests, emphasizing their ability to function effectively even in remote areas of low- and middle-income countries, where the disease burden is highest. It also includes the need to make possible for women to collect their samples and highlight the value of having an HPV testing performed in settings closer to where women receive medical attention.

This new publication, hopefully, can drive innovation in the market, focusing on high-performing, low-cost, and accessible solutions that can be transformative worldwide and will impact mainly low resource settings. Since the launch of the Global Initiative, numerous adaptations and changes have been introduced and those adjustments did promote a good outcome.

Yet, the core efforts seem insufficient to finally succeed and overcome the incomprehensible paradox cervical cancer represents. How can we grasp that a neoplasm, which takes many years to develop, has had its carcinogenesis and causal agent known for decades, and presents precursor lesions that, when appropriately and timely treated, prevent the cancer from even emerging in the affected patient still kill so many women?

These characteristics features give to cervical cancer screening a unique place, since its purpose is not early diagnosis but rather the prevention of cancer itself. and still, this very tumor claims the lives of women daily, as we fail to channel our collective efforts and resources more wisely as a society.

The fight against cervical cancer, like all of humanity's great struggles, is marked not only by technical challenges but also by profound human issues. The greatest obstacle lies in ensuring that the potential of all, especially vulnerable communities, is united for a common goal. Global health, as a battleground, requires collaboration without borders, where diverse cultures, policies, and contexts converge to promote the life and well-being of every individual.

The reflection we can draw from the battle against cervical cancer is that the possibilities for progress are inextricably linked to union and collective effort, whether among countries, communities, or individuals. This reflects the belief that, despite the difficulties imposed by limited health structures and resource disparities, humanity can and must collaborate for a common good: the eradication of cervical cancer. We are one species, with one race: the human race, and our potential for transformation lies in this unity. In this context, it seems worth sharing a quote from Ernest Hemingway, taken from his famous novel For Whom the Bell Tolls, published in 1940, which helps us reflect on the importance of human relationships even in the most adverse circumstances:

"Who will be in the trenches beside you? - And does it matter? - More than the war itself."

This phrase, said by the character within the context of the Spanish Civil War, reflects the importance of human connections during moments of adversity. Hemingway teaches us that, although the chaos of war -or the fight against cervical cancer-surrounds us, the true value lies in the people beside us, those who share the same mission, not in the battle itself [15].

The answer to the title of the book lies in its epigraph, where, in the sermon by the 17th-century poet and cleric John Donne, the following passage appears:

"No man is an island, entire of itself; every man is a piece of the continent, a part of the main. If a clod be washed away by the sea, Europe is the less, as well as if a promontory were, as well as if a manor of thy friend's or of thine own were: any man's death diminishes me, because I am involved in mankind, and therefore never send to know for whom the bell tolls; it tolls for thee."

The final phrase symbolizes the interconnectedness of humanity. Hemingway uses this epigraph to reinforce the central theme of his novel: human solidarity and the collective impact of our actions, even in times of war and suffering. As human beings, our worth lies in the relationships we build, in the solidarity we show, and in the collective effort to overcome difficulties. Therefore, when looking to the side, we have more worthy and honorable soldiers than villains or cowards. Thus, we continue with an unwavering mission: none of our hands can afford to falter. The battle continues, not only for what is scientifically necessary but also for a higher purpose of humanity and collaboration, where everyone has a vital role to play.

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