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Cervical cancer screening: the shift from Pap smear to HPV-based strategies

AUTHORS

1. **Angelika Złotnik**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0004-5142-6199
2. **Agata Zabierowska**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0002-1149-0108
3. **Agnieszka Walus**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0000-5903-633X
4. **Małgorzata Filak**
   Independent Public Health Care Facility, Municipal Hospitals Complex in Chorzów, 11 Strzelców Bytomskich Street, 41-500 Chorzów
   ORCID: https://orcid.org/0009-0009-9099-5083
5. **Agnieszka Suszek**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0002-4640-8143
6. **Monika Suszek**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0000-4794-4410
7. **Julia Surowaniec**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0008-5469-7727
8. Natalia Wieczorek – Durdzińska
   Regional Blood Donation and Transfusion Center in Racibórz, Henryka Sienkiewicza 3A, 47-400 Racibórz
   ORCID: https://orcid.org/0009-0005-6115-1640

9. Anna Puchowska
Katowickie Centrum Onkologii, Raciborska 26, 40-074 Katowice, Poland
ORCID: https://orcid.org/0009-0008-1575-0644
10. Bartłomiej Gałuszka
Independent Public Health Care Facility, Municipal Hospitals Complex in Chorzów, 11 Strzelców Bytomskich Street, 41-500 Chorzów
ORCID: https://orcid.org/0009-0006-1426-6709

Corresponding author:
Angelika Złotnik

Abstract

Introduction

Cervical cancer remains one of the most preventable malignancies in the world, and while effective screening and prophylactic human papillomavirus (HPV) vaccines have significantly reduced disease risk, it continues to cause substantial morbidity and mortality. For years, cervical cancer screening has relied on cervical cytology—Pap smear test which examines cells from the cervix to detect abnormalities before they progress to cancer. However, given the well-established etiological link between HPV infection and cervical cancer, testing for HPV has emerged as a superior alternative to the Pap smear.

Purpose

The aim of this paper was to examine the recent transition from Pap smear to HPV-testing as the primary cervical cancer screening method, review the supporting evidence, highlight key benefits and challenges, and discuss future directions toward the global goal of cervical cancer elimination.

Materials and methods

A comprehensive literature review was conducted using PubMed and Google Scholar to identify relevant studies published from 1995 to 2025 on the topics of cervical cancer, Pap smear and its history, and HPV-based screening. Articles were selected based on relevance, study quality, and recency.

Discussion

The transition from cytology-based screening to HPV testing marks a significant advancement in cervical cancer prevention. Evidence consistently shows that HPV testing offers superior sensitivity

for identifying individuals at risk, allowing for earlier detection and extended screening intervals. This shift has been reflected in updated guidelines worldwide, with many countries now recommending HPV-based screening as the primary method.

Key words: cervical cancer, prevention, screening, human papillomavirus, HPV, cervical cytology, pap smear, dual-stain

Introduction

Cervical cancer is ranking as the fourth most common cancer among women. In 2022, an estimated 660,000 new cases were reported worldwide, resulting in approximately 350,000 deaths. The age-standardized incidence rate was 14,12 per 100,000 women, while the age-standardized mortality rate stood at 7,08 per 100,000 women. The disease is most prevalent in low- and middle-income countries, where access to human papillomavirus (HPV) vaccination and screening is limited, contributing to higher mortality rates (1). In Poland, between 2013 and 2021, approximately 32,000 cases of cervical cancer were reported. Although the incidence rate has been declining at an average annual rate of -3.3%, mortality remains significantly high with over 14,000 deaths recorded in the same timeframe—twice the European average. Alarmingly, only 55,1% of women diagnosed with cervical cancer in Poland survive five years post-diagnosis, indicating the ongoing need for expanding prevention, improving early detection, and advancing treatment options (2).

Although cervical cancer remains a serious global challenge the situation has improved dramatically since widespread screening was made available—the incidence rate in the early 20th century is estimated to be around 30 cases per 100,000 women (3). The introduction of the Papanicolaou (Pap) smear in the mid-20 century revolutionized cervical cancer prevention and early detection, leading to a reduction of over 50% in both incidence and mortality by the mid-1970s (4). The primary goal is to detect precancerous cervical intraepithelial neoplasia (CIN) before progression, as well as early invasive cancer. To this day, widespread implementation of screening programs—alongside public health education and follow-up services—remain a cornerstone of national guidelines. Although widely adopted and effective, the Pap smear has notable limitations, including low sensitivity, the need for repeated testing, and the importance of experienced specialists (5,6). The identification of HPV as the crucial cause of cervical cancer has paved a way for more accurate, molecular-based methods, replacing Pap smear as the preferred primary screening method in many countries. HPV testing allows earlier detection of high-risk infections, reducing the frequency of testing while

maintaining effectiveness, and offers potential innovations like self-sampling improving accessibility and broader reach among population (7,8).

Pap Smear: basis and limitations

The Pap smear is a cytology-based cervical cancer screening method that has been implemented for the early detection of CIN. During this procedure, exfoliated epithelial cells are obtained from the transformation zone of the cervix using a cytobrush or spatula and subsequently prepared either on a glass slide or suspended in a liquid medium (liquid-based cytology). Samples are then microscopically examined by trained specialists to identify cellular abnormalities indicative of premalignant or malignant transformation (6).

Cytology-based screening schedules vary across countries, reflecting differences in healthcare infrastructure, population risk profiles, and national guidelines. The World Health Organization (WHO), the American College of Obstetricians and Gynecologists (ACOG), and the American Cancer Society (ACS) recommend screening with cytology every three years if HPV testing is not available, starting at the ages of 21 to 30. When using HPV-based testing alone or co-testing (both HPV and cytology), the screening interval can be extended to 5-10 years (9). Australia historically followed a two-year cytology schedule beginning at age 18-20 before transitioning to primary HPV screening in 2017 (8). The Polish Society of Gynecologists and Obstetricians recommends cytology-based screening every 1 to 3 years and HPV testing or co-testing every 3 to 5 years if the initial results are negative (10). In low- and middle-income countries, screening practices are frequently shaped by resource availability and are often opportunistic rather than part of formal, organized programs—meaning that individuals are responsible for seeking out screening themselves. Screening recommendations in these settings vary considerably, with intervals ranging from every three to five years to a once in a lifetime screening, depending on national capacity (11). While the Pap smear is a well-tolerated and quick procedure and has significantly contributed to the reduction of cervical cancer incidence and mortality, it is not without limitations. Its sensitivity for detecting high-grade lesions (defined as CIN2/CIN3) is estimated to be in the range of 50-55% (9). This can lead to false-negative results, requiring repeated or additional testing. Moreover, cytology is highly dependent on the quality of sample collection, slide preparation, and cytological interpretation due to subjective nature, making it vulnerable to human error and variability between providers and laboratories, especially in low-resource settings (12). Finally, because the Pap smear does not test for the

underlying causal agent, HPV, it lacks the ability to identify women at risk before cellular abnormalities develop (9).

Human Papillomavirus: the causal nexus to cervical cancer

Over 200 different types of HPV have been identified, with types 16 and 18 being the most oncogenic and accounting for a majority of cervical cancers—71% worldwide (1). Other oncogenic—high-risk HPV (HR-HPV) subtypes include 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. Low-risk HPV (LR-HPV) subtypes responsible for cutaneous and anogenital warts are 6, 11, 40, 42, 43, and 44 among many others (9).

HPV infection typically follows a predictable course, beginning with transmission through sexual contact, often occurring during adolescence or early adulthood (1). It is estimated that around 80% of sexually active people will be exposed to at least one HPV subtype during their lifetime. The virus infects the basal epithelial cells of the cervix and in the majority of cases, the immune system eliminates the virus without clinical consequences. However, in a subset of individuals, HR-HPV infection persists, leading to an increased risk of developing CIN, which may progress to invasive cervical cancer if undetected or left untreated (13).

The integration of viral DNA into the host genome disrupts the normal regulation of the cell cycle through the actions of viral oncoproteins E6 and E7. The E6 protein facilitates the degradation of the tumor suppressor p53, which plays a crucial role in recognizing DNA damage, inducing cell cycle arrest, and triggering apoptosis (the process of programmed cell death). The loss of functional p53 permits the survival and proliferation of genetically compromised cells, thereby increasing the likelihood of oncogenic transformation. Simultaneously, the E7 protein binds to and inactivates the retinoblastoma protein (pRb), another crucial tumor suppressor that typically prevents excessive cell growth by regulating progression from the G1 (growing) to the S (replication) phase of the cell cycle. The G1/S checkpoint prevents cells with DNA damage from progressing into S-phase, suppressing the initiation of DNA replication. The functional impairment of pRb results in the atypical release of transcription factors, leading to genomic instability, uncontrolled cellular replication, and accumulation of mutations. Over time, these pathological disruptions facilitate the progression of normal cervical epithelial cells into precancerous dysplastic lesions (13–15).

The identification of HPV as the causative agent of cervical cancer, pioneered by Harald zur Hausen, revolutionized oncological research and prevention strategies. His discovery of HR-HPV types—particularly HPV-16 and HPV-18—as primary drivers of cervical carcinogenesis earned him the 2008

Nobel Prize in Physiology or Medicine. This finding laid the foundation for two major public health advances: the development of prophylactic HPV vaccines and the advent of molecular HPV-based screening, which surpasses cytology-based screening by directly detecting viral genetic material (DNA or RNA) (16).

HPV testing: principles and practice

A variety of HPV testing methods are available to ensure early detection and risk assessment of HPV-related cervical disease. During the procedure, a healthcare provider uses a swab or brush to collect cervical epithelial cells, similar to the Pap test. These samples are subsequently analyzed via molecular techniques such as polymerase chain reaction (PCR) to directly identify the presence of the virus by primarily analyzing HPV DNA or RNA in cervical specimens—unlike traditional cytology, which relies on the observation of morphological changes in cervical cells. DNA-based assays determine the presence of high-risk HPV genotypes, however the mere presence of HPV DNA does not necessarily indicate active oncogenic processes, as latent infections often exhibit minimal cellular dysregulation and may persist without immediate malignant transformation or even undergo spontaneous resolution (5). In contrast, RNA-based tests—such as those targeting E6/E7 mRNA transcripts—may provide enhanced specificity by identifying viral oncogene expression, which is more closely associated with oncogenic activity and progressive cellular transformation (17). This distinction facilitates the differentiation between transient infections and those with a higher likelihood of progressing to neoplasia. Additionally, certain molecular assays evaluate viral load, quantifying the concentration of HPV genetic material within a sample. Higher viral loads have been associated with an increased risk of developing CIN2 and CIN3 and, ultimately, invasive cervical carcinoma (18).

Beyond standalone HPV testing, advanced triage tools such as dual-staining methods have emerged to improve risk stratification. Immunocytochemical assays like p16/Ki-67 dual-staining offer an additional layer of diagnostic precision by identifying cellular biomarkers indicative of transformation. The p16 marker functions as a critical indicator of disrupted cell cycle regulation, signifying aberrant activation of the HPV-mediated oncogenic pathway—it’s overexpression is linked to the loss of pRb function. Meanwhile, Ki-67 serves as a marker of cellular proliferation, reflecting increased mitotic activity and heightened replicative stress within affected epithelial cells. When expressed simultaneously, these biomarkers provide valuable insight into the biological behavior of HPV-infected cells. Patients exhibiting dual biomarker positivity may require closer

medical surveillance or further diagnostic evaluation, such as colposcopy and histopathological assessment, to confirm the presence of CIN. Integrating biomarker-based testing into cervical screening protocols enhances the predictive value of HPV testing, mitigating unnecessary interventions for individuals with self-limiting infections while ensuring timely identification of those at elevated risk for malignancy (19,20).

Rationale and benefits of the global shift to HPV-based screening

Multiple landmark studies have provided crucial data supporting the transition from cytology-based screening to primary HPV testing. The US-based ATHENA trial was among the first large-scale randomized studies to compare HPV testing with Pap cytology in a cohort of over 47,000 women, demonstrating that primary HPV testing significantly enhanced the detection of CIN2 and CIN3, particularly among women over 25 (21). Similarly, the Canadian HPV-FOCAL trial reinforced the higher sensitivity of HPV testing, revealing that women who tested negative for high-risk HPV had a markedly lower risk of developing cervical lesions over time, supporting extending screening intervals without compromising patient safety (22). The New Mexico HPV Pap Registry provided substantial evidence that HPV-based screening programs enhance earlier detection and improve overall effectiveness in preventing cervical cancer across diverse populations (23). Arbyn et al. pooled data from multiple international trials and confirmed that HPV testing offers significantly better protection against invasive cervical cancer than cytology, particularly in subsequent screening rounds (24). Ronco et al. further showed that HPV-based screening results in earlier identification of precancerous lesions and a sustained reduction in cervical cancer incidence (25). Collectively, these studies laid the scientific foundation for updating national and international guidelines, firmly positioning HPV testing as the preferred method for cervical cancer screening.

Recent developments between 2023 and 2025 have further advanced the global adoption of HPV-based cervical cancer screening and introduced innovative approaches to improve accessibility and accuracy. In 2024, the U.S. Preventive Services Task Force (USPSTF) released draft guidelines endorsing primary HPV testing as the preferred method for cervical cancer screening for women aged 30 to 65 years, citing its superior sensitivity and capacity to safely extend screening intervals to five years (26). In 2025, Belgium announced its nationwide transition to primary HPV screening, becoming one of the first European countries to implement HPV testing as the sole primary screening method in its national program for women over 30 years old (27). According to the guidelines issued in 2024 by the Polish Society of Gynecologists and Obstetricians, if the initial results of hrHPV are

negative, HPV testing or co-testing is advised at extended intervals of 3 to 5 years for women aged 25-64 (10). Complementing these efforts, the WHO updated its cervical cancer screening guidelines in 2024 to incorporate dual-stain cytology as a recommended triage tool for HPV-positive women, improving risk stratification and reducing unnecessary referrals for colposcopy (11).

This transition as a triage tool, involves both upfront and long-term cost considerations. Healthcare systems may incur substantial costs related to upgrading laboratory infrastructure, procuring advanced diagnostic platforms, training healthcare professionals, and revising screening guidelines and information systems. Additionally, investment in public education campaigns is essential to foster awareness and acceptance of the new screening program. However, despite these initial investments, primary HPV testing with dual-stain triage has been shown to be more cost-effective over time. Increased sensitivity of HPV testing allows for screening intervals to be safely extended, while the incorporation of p16/Ki-67 testing reduces unnecessary colposcopies and overtreatment. Multiple economic evaluations across different countries support the financial advantages of HPV-based screening strategies that incorporate dual-stain cytology for triage (28–30). A 10-year budget analysis in Germany and a 6-year study in Belgium both found that dual-stain testing resulted in lower annual healthcare costs than conventional cytology. In Belgium, replacing cytology with dual-stain triage in a five-year screening framework was projected to save approximately €15 million. Likewise, modeling studies in Thailand identified HPV screening combined with dual-stain triage as the most cost-effective approach, particularly in resource-limited settings (20).

While clinician-collected samples, obtained during a pelvic examination, still remain the gold standard for HPV screening, self-collected samples are increasingly recognized for their comparable accuracy and improved accessibility, particularly in resource-limited settings and hard-to-reach populations. Self-sampling allows individuals to obtain cervical specimens autonomously, enhancing participation in HPV screening programs and addressing barriers related to clinical access, stigma, or discomfort. In 2024, the U.S. Food and Drug Administration (FDA) approved the use of self-collected samples for HPV testing, a major step forward in addressing disparities by empowering individuals who encounter geographic, socioeconomic, or cultural obstacles to participate in screening without the need for in-clinic procedures (31). Additionally, the Daye Diagnostic Tampon study demonstrated comparable accuracy of self-collected samples to those collected by clinicians in detecting high-risk HPV, offering a convenient, highly acceptable to users, home-based alternative for cervical screening (32).

Together, these recent advancements reflect a growing consensus on the values of HPV-based screening and highlight the ongoing efforts to make cervical cancer prevention more effective, affordable, equitable, and patient-centered worldwide.

Challenges and considerations

While HPV-based screening offers clear advantages in cervical cancer prevention, its widespread implementation also presents several challenges and important considerations that must be addressed to ensure its success. One of the primary concerns is the lower specificity of HPV testing compared to cytology, particularly in younger women where transient infections are common. This reduced specificity can lead to an increased number of positive test results, which may trigger more referrals for colposcopy and raise the risk of overtreatment for lesions that might otherwise regress spontaneously. Unnecessary procedures not only drive up healthcare expenditures but also pose potential risks to women's well-being including psychological distress, physical discomfort, and clinical complications such as cervical stenosis or an elevated risk of preterm birth in subsequent pregnancies. To minimize these harms, effective triage methods, such as p16/Ki-67 dual-stain cytology or HPV genotyping, play a vital role in accurately identifying which HPV infections are likely to progress to high-grade lesions and which are benign and self-limiting. In alignment with these risk-based approaches, the USPSTF currently recommends cervical cancer screening every three years with cytology alone for women aged 21 to 29, reserving primary HPV testing for women aged 30 and older (6,9,26). Similarly, Belgium's national screening program begins primary HPV testing at age 30 (27). This reflects a growing international consensus to tailor screening strategies based on age-related risk profiles and the natural history of HPV infection.

Another key consideration is the psychological impact of receiving a positive HPV test result. Unlike cytology, which identifies abnormal cellular changes, HPV testing detects a sexually transmitted infection (STI), which can carry social stigma and cause significant anxiety for many women. Addressing this requires thoughtful communication strategies, clear educational materials, and supportive counseling to help women understand the meaning of their results and the relatively low immediate risk of cancer associated with an HPV-positive result (33).

Cost and resource barriers also pose challenges, especially in low- and middle-income countries where health budgets are limited, and laboratory infrastructure may be underdeveloped. The initial investment required for HPV testing platform, medical staff training, and quality assurance systems can be substantial. Ensuring equitable access to testing, follow-up, and treatment remains a priority

to avoid widening disparities in cervical cancer outcomes. Integration with existing healthcare infrastructure is another crucial factor. Successful implementation requires laboratory capacity to process HPV tests reliably and promptly, as well as comprehensive training for healthcare providers in sample collection, triage protocols, and patient communication. Transitioning from cytology-based systems to HPV-based screening may also necessitate updates to national guidelines, electronic medical records, and reporting systems (9,28,34). In recognition of these complexities the International Federation of Gynecology and Obstetrics (FIGO) advocates for a tailored approach to cervical cancer screening, encouraging countries and regions to adapt their strategies based on local context, considering factors such as healthcare access, systemic barriers, and available resources to best serve their populations (34).

Finally, as HPV vaccination programs mature and the prevalence of hrHPV types declines, screening strategies will need to be adapted for vaccinated cohorts. This could include adjusting the age at which screening begins, extending screening intervals even further, or refining triage protocols to maintain cost-effectiveness and minimize unnecessary interventions. Balancing these challenges while leveraging the strengths of HPV-based screening is essential for maximizing its public health impact (6,8).

Future directions

The future of cervical cancer screening is poised to be transformed by several promising innovations and strategic shifts that aim to enhance effectiveness, accessibility, and equity. One of the most exciting developments is the expansion of self-sampling and home-based HPV testing kits. This can empower individuals to take part in screening on their own terms, reducing barriers related to stigma, geography, or limited healthcare access.

In parallel, advances in artificial intelligence (AI) and laboratory automation are redefining how cytology and HPV testing are performed. AI-powered image analysis enhances diagnostic accuracy and efficiency in cytology review, while automated molecular platforms streamline HPV testing and triage processes, enabling high-throughput testing with consistent quality control (35).

Looking ahead, the adoption of personalized screening strategies will likely play a central role in optimizing care. By tailoring screening intervals, starting ages, and triage methods to individual risk factors, such as vaccination status, age, and medical history, precision screening can improve health outcomes while minimizing unnecessary procedures and associated costs.

These innovations align with the WHO's 2030 targets for cervical cancer elimination, which call for 90% of girls to be fully vaccinated against HPV, 70% of women to be screened with a high-performance test by ages 35 and 45, and 90% of those diagnosed to receive timely treatment (36). With the convergence of cutting-edge technologies, person-centered care, and strong global policy momentum, we are closer than ever to making the elimination of cervical cancer a reality.

Conclusion

The shift from cytology-based screening to primary HPV testing marks a transformative step forward in cervical cancer prevention. With its superior sensitivity, extended screening intervals, and adaptability to self-sampling and vaccinated populations, HPV-based screening offers a more effective and sustainable approach to early detection and prevention. However, this shift requires thoughtful implementation, balancing benefits with potential challenges such as lower specificity, increased colposcopy rates, and the psychological impact of an HPV-positive result. Public education and provider training will be essential to ensure informed participation, reduce stigma, and build trust in the new system. As technologies such as self-collection kits, dual-stain triage, and AI-driven diagnostics evolve, and as personalized screening strategies become more refined, we are better equipped than ever to reach those who have historically been under-screened. When combined with widespread HPV vaccination, HPV-based screening forms a powerful foundation for achieving the WHO's goal of eliminating cervical cancer as a public health problem by 2030. The challenge now lies in turning commitment into coordinated action, ensuring that every girl is vaccinated, every woman is screened, and every patient receives timely and effective care. These are no longer distant aspirations but global opportunities, with the tools, data, and a drive to make it happen, but it is essential that we accelerate and intensify our efforts to achieve this goal worldwide.

Disclosure

Author's Contribution:

Conceptualization: Anna Puchowska, Monika Suszek

Methodology: Julia Surowaniec, Agnieszka Walus

Software: Bartłomiej Gałuszka, Julia Surowaniec

Check: Agnieszka Suszek

Formal analysis: Natalia Wieczorek-Durdzińska, Monika Suszek

Investigation: Bartłomiej Gałuszka

Resources: Małgorzata Filak , Agnieszka Suszek

Data curation: Agata Zabierowska

Writing – rough preparation: Agata Zabierowska

Writing – review and editing: Angelika Złotnik

Visualization: Julia Surowaniec

Supervision: Agata Zabierowska, Angelika Złotnik

Project administration: Agata Zabierowska, Angelika Złotnik

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