



NAVIGATING THE LANDSCAPE OF HUMAN PAPILLOMAVIRUS-RELATED ANAL CANCER SCREENING: A REVIEW FOR MEN WHO HAVE SEX WITH MEN



Przegląd badań przesiewowych w kierunku raka odbytu związanego z wirusem brodawczaka ludzkiego: analiza dla mężczyzn mających kontakty seksualne z mężczyznami

Dominik Trojanowski¹, Magdalena Iwan¹, Błażej Szymczuk¹, Ksawery Adamiec¹, Jakub Milczarek¹, Małgorzata Rodak², Magdalena Kajzar², Joanna Smorońska-Rypel², Kamila Nitka³, Natalia Piątkowska⁴

1. Faculty of Medical Sciences, Medical University of Silesia in Katowice, Poland

2. Department of Internal Medicine, Bonifraters Medical Center Ltd., Poland

3. Department of Internal Medicine, Medical Center in Łańcut Ltd., Poland

4. Department of Internal Medicine, Provincial Hospital in Poznań, Poland

Dominik Trojanowski –  0009-0003-0758-9567

Magdalena Iwan –  0009-0000-0385-0877

Błażej Szymczuk –  0009-0000-0515-5413


Ksawery Adamiec –  0009-0006-0867-9291

Jakub Milczarek –  0000-0002-4099-0999

Małgorzata Rodak –  0000-0002-5517-1558

Magdalena Kajzar –  0009-0005-4616-7636

Joanna Smorońska-Rypel –  0009-0008-3364-209X

Kamila Nitka –  0009-0007-3399-571X

Natalia Piątkowska –  0009-0001-7508-6043

Abstract

Introduction: Human papillomavirus (HPV) infection presents a significant global health concern, particularly due to its association with anal cancer, disproportionately affecting men who have sex with men (MSM). There is an urgent need for tailored screening strategies for this demographic. This review provides an overview of HPV-related anal cancer screening methods in MSM, highlighting their strengths, limitations, and future research directions. **State of knowledge:** Epidemiological studies have elucidated the prevalence of HPV-associated anal squamous intraepithelial lesions among MSM, underscoring the necessity for targeted screening. Various methods, including anal cytology, high-risk HPV (hrHPV) testing, and high-resolution anoscopy, have been proposed and evaluated. Despite challenges, tailored screening protocols have been developed to accommodate high-risk populations. **Conclusions:** Targeted screening strategies, especially for MSM living with HIV, are pivotal in mitigating the burden of HPV-related anal cancer. Expanding access to high-resolution anoscopy and addressing knowledge gaps are imperative. Further research into effective screening methods, including HPV-related biomarkers, is essential to enhance early detection and improve outcomes for at-risk MSM populations. This synthesis of evidence provides valuable insights for healthcare providers, policymakers, and stakeholders engaged in anal cancer prevention and control efforts.

Streszczenie

Wprowadzenie i cel: Zakażenie wirusem brodawczaka ludzkiego (HPV) stanowi istotny problem zdrowia publicznego na całym świecie, szczególnie ze względu na jego związek z rakiem odbytu, który częściej dotyka mężczyzn mających kontakty seksualne z mężczyznami (MSM). Istnieje pilna potrzeba opracowania dostosowanych strategii badań przesiewowych dla tej grupy. Niniejszy artykuł oferuje przegląd metod badań przesiewowych w kierunku raka odbytu związanego z HPV w populacji MSM, omawiając ich mocne strony, ograniczenia oraz kierunki przyszłych badań. **Stan wiedzy:** Badania epidemiologiczne wykazały zwiększoną częstość występowania związanych z HPV zmian śród-nabłonkowych odbytu wśród MSM, co podkreśla potrzebę prowadzenia ukierunkowanych badań przesiewowych. Przedstawiono i oceniono różne metody, w tym cytologię odbytu, testy na występowanie wysokiego ryzyka HPV oraz anoskopię wysokiej rozdzielczości. Pomimo wyzwań opracowano specjalne protokoły badań przesiewowych, które uwzględniają populacje wysokiego ryzyka. **Podsumowanie:** Ukierunkowane strategie badań przesiewowych, zwłaszcza dla MSM żyjących z HIV, są kluczowe w redukcji obciążenia rakiem odbytu związanym z HPV. Konieczne jest poprawienie dostępu do anoskopii wysokiej rozdzielczości oraz uzupełnienie luk w wiedzy. Dalsze badania nad skutecznymi metodami przesiewowymi, takimi jak biomarkery związane z HPV, są niezbędne dla lepszego wczesnego wykrywania i poprawy wyników zdrowotnych w populacjach MSM. Niniejszy przegląd literatury dostarcza cennych informacji dla pracowników służby zdrowia, decydentów oraz interesariuszy zaangażowanych w działania na rzecz profilaktyki i kontrolowania raka odbytu.

Keywords: HPV; cancer screening; MSM; anal cancer**Słowa kluczowe:** HPV; badania przesiewowe; MSM; rak odbytu**DOI** 10.53301/lw/192274**Received:** 03.07.2024**Accepted:** 13.08.2024**Corresponding author:**Dominik Trojanowski
Faculty of Medical Sciences, Medical University
of Silesia in Katowice,
15 Poniatowskiego Str., 40-055 Katowice
e-mail: dttrojanowski@gmail.com

The human papillomavirus (HPV) infection represents a significant public health concern on a global scale, particularly due to its association with anal cancer, a malignancy that affects men who have sex with men (MSM) in a disproportionate manner [1]. While there has been an increase in the incidence of anal cancer globally, the disease has a greater impact on MSM than on the general population [2, 3].

Epidemiological studies have elucidated the prevalence and distribution of HPV-associated anal squamous intraepithelial lesions (ASIL) among MSM, highlighting the need for targeted screening and prevention efforts [4, 5].

In response to the increasing prevalence of HPV-related anal cancer, a number of screening methods have been proposed and evaluated for their efficacy in detecting precancerous lesions and early-stage disease. These include anal cytology, high-risk human papillomavirus (hrHPV) testing, cytology and hrHPV co-testing, high-resolution anoscopy (HRA), and digital anal rectal examination (DARE) [6–8]. However, the implementation of these screening modalities presents challenges and limitations, including resource constraints, healthcare provider training, and patient acceptability [9, 10].

The objective of this review is to provide a comprehensive overview of the current state of knowledge regarding HPV-related anal cancer screening methods in MSM. By synthesizing evidence from epidemiological studies, meta-analyses, and clinical guidelines, we aim to delineate the strengths and limitations of existing screening strategies, identify areas for improvement, and outline future research directions. Ultimately, the objective is to inform healthcare practitioners, policymakers, and stakeholders involved in anal cancer prevention and control efforts, with the overarching goal of reducing the burden of this preventable disease among MSM populations.

Description of the state of knowledge

Epidemiology of HPV-related anal cancer in MSM

Despite its relative rarity, anal cancer incidence is projected to increase significantly, with an estimated surge to 78,000 cases by 2040. MSM represent a demographic at heightened risk for this malignancy, particularly those with Human Immunodeficiency Virus (HIV) infection, who exhibit the highest incidence rates [11]. Notable disparities are evident in the prevalence of anal high-grade squamous intraepithelial lesions (HSIL+) among MSM. HIV-positive individuals demonstrate a pooled prevalence of 22.4%, compared to 11.3%

in HIV-negative counterparts. Moreover, there is considerable heterogeneity across studies, contributing to variability in prevalence estimates. Among HIV-negative MSM, the prevalence of anal HPV16 is 13.7%, with a corresponding prevalence of hrHPV at 41.2%. Conversely, HIV-positive MSM exhibit higher rates, with an anal HPV16 prevalence of 28.5% and an hrHPV prevalence of 74.3%. The detection of HSIL+ exhibits considerable variation, with rates ranging from 7.5% to 54.5% in HIV-positive MSM. After adjusting for heterogeneity between studies, HIV status emerges as a significant predictor of HSIL+, HPV16-positive HSIL+, and HSIL+ specifically in HPV16-positive MSM. Notably, the prevalence of HSIL+ among HPV16-positive individuals increases with age. In light of these findings, HIV-positive MSM represent a priority population for targeted anal cancer screening, particularly in the context of initiatives aimed at addressing HPV16-positive HSIL+ [3].

Screening populations

Several population groups have been identified as being at an increased risk of developing anal cancer. These include individuals with a weakened immune system, such as those living with HIV, MSM, and women with genital HPV-associated diseases, even after successful treatment [6]. Screening protocols for anal cancer are designed to target these elevated-risk groups, with recommendations varying based on specific risk factors. For MSM living with HIV, screening is recommended from the age of 35 years onwards. Conversely, for individuals with HIV who do not identify as MSM, as well as for MSM without HIV, the recommended age to initiate screening is 45 years [12].

It is essential to guarantee the availability of sufficient human resources for the provision of screening services, as denoted by the capacity to perform an HRA evaluation within a six-month period following an abnormal screening test in the eligible population. Conversely, a scarcity of such resources will inevitably result in a prolonged wait times for HRA. These screening strategies are designed for populations with access to HRA [12]. Where HRA availability is lacking, screening may be restricted to DARE for the detection of anal cancer [13, 14].

Screening methods

The low prevalence of anal cancer in the general population represents a significant challenge to the implementation of routine screening protocols. Nevertheless, evidence indicates that targeted screening of selected populations may prove to be a more effective strategy.

It is thought that early identification of anal intraepithelial neoplasia will contribute significantly to a reduction in the incidence of invasive anal cancer. A variety of screening methods have been proposed, including DARE, anal cytology, HPV co-testing, and HRA [7]. These strategies are based on findings from systematic reviews and meta-analyses, primarily conducted among individuals living with HIV (PWH). Research has demonstrated that anal cytology, HPV16 genotyping, and hrHPV-cytology co-testing are effective approaches for screening for anal cancer, demonstrating satisfactory performance indicators [15].

Anal cytology

Anal cytology has emerged as a pivotal element in anal cancer screening initiatives, particularly in developed countries where recent endeavors have been concentrated [16]. Early detection and subsequent treatment of high-grade anal intraepithelial neoplasia (HGAIN) are of paramount importance in reducing the incidence of anal cancer. Anal cytology is a valuable tool for the detection of HGAIN, with evidence indicating that annual screening for HIV-positive MSM and biennial screening for HIV-negative MSM is a cost-effective approach. In cases of abnormal cytology findings, referral for HRA and biopsy is indicated [17]. Anal cytology is an acceptable method for screening for anal cancer. Individuals presenting with atypical squamous cells of undetermined significance (ASC-US) or worse cytology results should be immediately referred for HRA [12]. Those with negative cytology findings should undergo repeat screening after 12 months, while unsatisfactory cytology results necessitate a repeat examination [18].

Guidelines targeting specific populations, such as solid-organ transplant recipients and HIV-positive individuals, emphasize the importance of anal cytology screening. For HIV-positive MSM, recommendations stress the need for regular cytology follow-up. This should be conducted on an annual basis for those with normal results, while in cases of squamous cytological abnormalities, prompt referral for anoscopy/HRA is advised.

It is noteworthy that, while anal cytology has traditionally been performed using methods such as the anal Pap smear, its ability to accurately predict histological dysplasia is being questioned. Despite its utility, anal cytology has several limitations, including subjectivity, restricted sensitivity, and the need for frequent repetition, similar to cervical cytology. In high-risk populations, such as HIV-positive MSM, the accuracy of anal cytology remains a topic of debate, with evidence suggesting poor correlation with histological findings. Consequently, there is growing interest in exploring HPV-related biomarkers to enhance the effectiveness of anal cancer screening [19, 20].

hrHPV testing

HPV 16, one of the hrHPV genotypes, is identified as the predominant genotype in both anal HSIL and squamous cell carcinoma within the general population. Nevertheless, there is a paucity of research examining the distribution of other hrHPV genotypes in the anus of PWH [21].

The use of hrHPV testing in anal cancer screening has emerged as a promising approach, comparable to its role

in cervical sample analysis. It has been demonstrated that tests for the presence of HPV DNA exhibit high sensitivity (92.4%, 95% CI 84.2%–96.5%), although they are associated with a notably low level of specificity (41.7%, 95% CI 33.9%–44.9%). This indicates the potential value of these tests in screening procedures, particularly when followed by a subsequent test with higher specificity [22].

In anal cancer screening, hrHPV testing as a standalone approach is deemed an acceptable option. In the event of a positive result for hrHPV, an immediate referral for HRA is indicated. Conversely, individuals testing negative for hrHPV should undergo repeat screening within 12–24 months. Triage of hrHPV-positive individuals using cytology can help reduce the number of immediate referrals for HRA, and is therefore considered an acceptable strategy. Furthermore, if the screening test includes HPV genotyping, immediate referral HRA is recommended for individuals testing positive for HPV16, irrespective of cytological findings [12].

The evaluation of hrHPV genotypes, including HPV16, serves two purposes in anal cancer screening. Firstly, it assists in the initial detection of infection. Secondly, it facilitates the monitoring of infection clearance or persistence over time. This information is crucial for guiding treatment decisions and ongoing disease monitoring efforts [23].

Cytology and hrHPV co-testing

The incorporation of cytological and hrHPV testing into screening algorithms has significantly improved sensitivity for the identification of anal precancerous lesions and cancer within high-risk populations [24]. Co-testing enhances the specificity of atypical cytology diagnoses, thereby aiding in the identification of individuals requiring further intervention [25]. Immediate referral for HRA is recommended in the following scenarios: individuals with ASC-US or worse cytology alongside a positive hrHPV test result; those with atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion (ASC-H) or a HSIL cytology result irrespective of hrHPV status; and individuals testing positive for HPV16, regardless of cytological findings. It is recommended that individuals with ASC-US cytology testing negative for hrHPV undergo repeat screening within 12 months. Similarly, individuals with negative for intraepithelial lesions or malignancy (NILM) cytology testing negative for hrHPV should be screened again within 12–24 months. The management of NILM cytology with a positive hrHPV result or low-grade squamous intraepithelial lesion cytology with a negative hrHPV result is at the discretion of the healthcare provider, who may elect to refer the patient for HRA or schedule repeat screening in 12 months. In settings where HRA capacity is limited, immediate referral for HRA is recommended for individuals with ASC-H or HSIL cytology, regardless of hrHPV result, as well as those testing positive for HPV16, irrespective of cytological findings [12].

Digital anorectal examination

It is recommended that MSM undergo a DARE every 1–3 years [8]. DARE should be conducted at all screening visits following the collection of samples for cytology and/

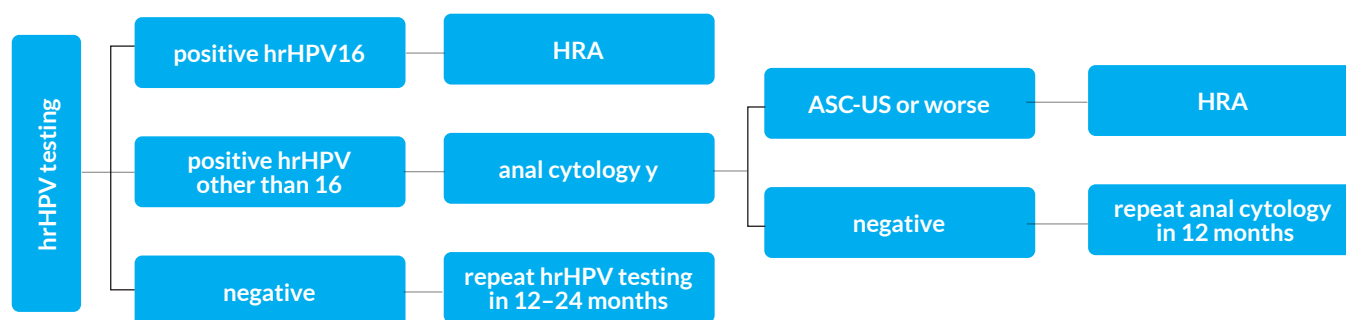


Figure 1. Anal cancer screening algorithm

or hrHPV testing. It serves as a means of screening for early-stage anal cancers that may be detectable through palpation. In cases where HRA referral is unavailable, routine DARE is recommended for populations identified for anal cancer screening [12].

High-resolution anoscopy

HRA plays a pivotal role in the identification of precancerous lesions by providing comprehensive visualization of the anal canal and rectum. This allows for the detection of abnormal tissue changes that are indicative of HPV-related anal cancer [26]. HRA is a vital diagnostic tool for detecting ASIL, particularly among individuals at elevated risk of anal cancer, such as MSM and those with HIV. The histopathological results from HRA-guided biopsies are considered the gold standard for confirming the presence of ASIL [27]. Individuals presenting with condyloma typically undergo resection, though HRA remains imperative for localizing and treating microscopic disease [28].

Challenges and limitations in screening practices

Notwithstanding the potential of screening strategies, a number of challenges and limitations remain. The paucity of cases of anal cancer in the general population presents logistical challenges to the implementation of routine screening programs. Furthermore, barriers to accessing HRA, coupled with a lack of awareness and the social stigma surrounding the issue, impede the participation of sexual minority men in screening and treatment procedures. To address these challenges, a multifaceted approach is required, encompassing improvements in access to screening services, the resolution of knowledge disparities, and the mitigation of stigma and discrimination.

Although anal cytology is considered an acceptable screening method, its limitations in terms of subjectivity and sensitivity highlight the need for additional screening modalities.

Many PWH, especially those at high risk of developing anal cancer, encounter difficulties in accessing HRA, whether on-site or through referral at their HIV care facility [29]. A significant issue highlighted in recent studies is the impact of patients' knowledge gaps regarding HPV-related health conditions on their screening practices. Lack of awareness is often linked to a sense of invulnerability, which in turn leads to delays in seeking medical care. Furthermore, the use of language associated with

cervical cancer screening and treatment when discussing anal cancer care presents unique challenges to sexual minority men. This population is already sensitive to societal confusion surrounding sexual orientation and gender identity, which further complicates their engagement with screening and treatment [30].

Conclusions

The increasing global incidence of anal cancer, particularly among MSM, underscores the urgent need for effective preventive measures and screening strategies. The correlation between HPV16 and anal HSIL+ in HIV-positive MSM reinforces the necessity for targeted initiatives to reduce the prevalence of anal cancer in this demographic.

It is imperative that screening protocols are implemented for high-risk populations to facilitate early detection and prevention efforts. Screening at defined ages, based on risk profiles, facilitates the optimal allocation of resources and ensures the timely implementation of interventions. Nevertheless, it is of the utmost importance to address the obstacles preventing marginalized MSM populations from accessing screening services, in order to guarantee equitable healthcare access and outcomes.

A variety of screening techniques, including anal cytology, hrHPV testing, and HRA, present promising avenues for anal cancer screening in MSM. The potential of hrHPV testing, either alone or in combination with cytology, is emphasized, as is the importance of HPV16 genotyping in guiding treatment decisions and monitoring infection, as outlined in Figure 1. Continued research into more effective screening methods, including the exploration of HPV-related biomarkers, is needed to further enhance early detection and reduce the burden of anal cancer in MSM populations. Improving access to HRA and addressing knowledge gaps surrounding HPV-related health conditions are crucial steps toward enhancing early detection and prevention efforts. Additionally, initiatives to promote awareness, reduce stigma, and improve healthcare access for sexual minority men are essential for achieving equitable health outcomes in this population.

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