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2734 17 Avenue SW,
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+15878858911
editorial-office@sciformat.ca

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HUMAN PAPILLOMAVIRUS (HPV) INFECTION IN CARCINOGENESIS AND THE ROLE OF PROPHYLACTIC VACCINATION: A NARRATIVE REVIEW

Kinga Bukala (Corresponding Author, Email: kinga.bukala@gmail.com)

Medical University of Lodz, Al. Kościuszki 4, 90-419 Łódź, Poland

ORCID ID: 0009-0003-9587-4826

Anton Osnytskyy

Medical University of Lodz, Al. Kościuszki 4, 90-419 Łódź, Poland

ORCID ID: 0009-0001-9456-8224

Kamil Rutkowski

Medical University of Lodz, Al. Kościuszki 4, 90-419 Łódź, Poland

ORCID ID: 0009-0003-0667-6685

Magdalena Ślifierska

Medical University of Lodz, Al. Kościuszki 4, 90-419 Łódź, Poland

ORCID ID: 0009-0004-7797-7757

Daria Furman

Medical University of Lodz, Al. Kościuszki 4, 90-419 Łódź, Poland

ORCID ID: 0009-0007-3166-9937

Karina Udrycka

Medical University of Lodz, Al. Kościuszki 4, 90-419 Łódź, Poland

ORCID ID: 0009-0003-8577-4100

Szymon Klimaszewski

Private dental practice, Poland

ORCID ID: 0009-0001-3505-2797

ABSTRACT

Human papillomavirus (HPV) is among the most prevalent sexually transmitted pathogens worldwide and an established cause of both benign proliferative lesions and malignant neoplasms. This narrative review examines the role of HPV infection in carcinogenesis at the principal anatomical sites involved and evaluates the contribution of prophylactic vaccination to disease control. A structured search of PubMed/MEDLINE, Scopus, and Web of Science was conducted for English-language publications available up to August 2026, supplemented by current guidance from international health authorities. The evidence confirms a causal role for high-risk genotypes, principally HPV-16 and HPV-18, in oropharyngeal squamous cell carcinoma and in cancers of the cervix, vulva, vagina, penis, and anus, mediated by the E6 and E7 oncoproteins through inactivation of the p53 and retinoblastoma pathways. The strength of this association is markedly site-dependent: it is well established in the oropharynx, cervix, and anus, but remains equivocal in the oral cavity and larynx. In oropharyngeal carcinoma, HPV status is an independent prognostic factor and is incorporated into current staging. Vaccination substantially reduces infection, precancerous lesions, and cervical cancer incidence, with the greatest benefit among individuals immunized before sexual debut. Vaccination and organized screening are complementary rather than alternative strategies, and suboptimal uptake—as observed in Poland—remains the principal barrier to realizing the full preventive potential of available vaccines.

KEYWORDS

Human Papillomavirus, Carcinogenesis, Oropharyngeal Cancer, Cervical Cancer, HPV Vaccination, Cancer Prevention

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1. Introduction

Human papillomavirus (HPV) is one of the most common infectious agents in humans. Infection may be asymptomatic, but depending on the viral genotype and the site of infection it may lead to the development of benign lesions and malignant neoplasms. Of particular importance are the high-oncogenic-risk genotypes, primarily HPV-16 and HPV-18; their presence is associated with the development of malignant neoplasms, including cervical cancer and cancers of the anogenital region, head, and neck. Low-risk genotypes such as HPV-6 and HPV-11 are responsible mainly for the development of benign lesions, including condylomata acuminata and recurrent respiratory papillomatosis (Jensen et al., 2024; Wolf et al., 2024).

The clinical significance of HPV infection stems not only from its prevalence, but above all from the fact that the infection may persist and that the virus may participate in the process of carcinogenesis. A key role in this process is played by the viral oncoproteins E6 and E7, which disrupt the function of the most important mechanisms controlling cell proliferation through their effect on, among others, the p53 and retinoblastoma (Rb) proteins. This process leads to disruption of cell cycle control and promotes gradual neoplastic transformation (Kreimer et al., 2005; zur Hausen, 2002).

HPV is significant in the pathogenesis of oropharyngeal cancer, where infection with HPV-16 currently constitutes an important etiological factor. In recent decades, an increasing proportion of HPV-positive cases of this cancer has been observed, particularly in highly developed countries. At the same time, the association of HPV with individual cancers is not uniform: in the case of oral cavity and laryngeal cancer, the significance of infection is smaller or remains a matter of debate (Ang et al., 2010; Bishop et al., 2015).

A further major clinical problem is posed by cancers associated with HPV infection within the anogenital and genitourinary tract. These include, among others, cancers of the cervix, vulva, vagina, penis, and anus. Cervical cancer is of particular importance, being in the vast majority of cases associated with persistent infection with high-oncogenic-risk HPV types. The infection may lead to the development of precancerous lesions, which can be detected early (de Martel et al., 2017; Olesen et al., 2019).

Understanding the relationship between HPV infection and the development of cancer is of considerable importance not only for diagnosis and treatment, but also for prevention. HPV vaccination constitutes a fundamental element of primary prevention and makes it possible to reduce the risk of infection with the virus

types responsible for the development of precancerous lesions, neoplasms, and genital warts. The effectiveness of vaccination programs has been confirmed both in clinical trials and in population-based observations (Drolet et al., 2019; Falcaro et al., 2021; Huh et al., 2017; World Health Organization, 2009).

Despite this accumulated evidence, three problems continue to limit the translation of knowledge about HPV into clinical and public health practice. First, the strength of the causal association between HPV and cancer varies substantially between anatomical sites, and the boundary between causal involvement and incidental detection of viral DNA has not been established with equal confidence at every site. Second, the diagnostic algorithms used to establish HPV status-in particular immunohistochemical assessment of p16 expression-perform unevenly across sites, which has direct consequences for staging and treatment decisions. Third, although prophylactic vaccines of demonstrated efficacy have been available for almost two decades, population-level uptake remains highly variable, and in several countries, including Poland, coverage has remained well below the level required to achieve the anticipated reduction in disease burden.

The aim of this review is therefore to present, in an integrated manner, the significance of human papillomavirus infection in the development of benign lesions and malignant neoplasms, with particular emphasis on cancers of the head and neck and of the anogenital and genitourinary tract. The molecular mechanisms of HPV-dependent carcinogenesis, current diagnostic approaches, the significance of HPV status for prognosis, and the role of prophylactic vaccination in preventing HPV-related infections and neoplasms are addressed in turn, with specific attention to the implementation of universal vaccination in Poland.

2. Methodology

This article is a narrative review. PubMed/MEDLINE, Scopus, and Web of Science were searched for publications available up to August 2026, combining terms for the pathogen (*human papillomavirus*, *HPV-16*, *HPV-18*, *E6*, *E7*, *p16INK4a*), the clinical entities under review, and prophylactic vaccination; the reference lists of retrieved articles and the websites of the World Health Organization and the National Health Fund (Narodowy Fundusz Zdrowia) were screened in addition. Publications were eligible if they addressed HPV in relation to benign lesions, precancerous lesions, neoplasms, or vaccination, with preference given to systematic reviews, meta-analyses, randomized controlled trials, large registry studies, and current guidelines. The resulting evidence base comprised 71 publications spanning 1993 to 2026. Findings were synthesized narratively by anatomical site. Estimates are reported as published by their original authors, and where sources diverged the range is given rather than a pooled value, since the HPV detection technique differs between studies. No protocol was registered and no formal risk-of-bias assessment was undertaken; the implications are addressed in Section 4.2.

3. Results

3.1. HPV-Associated Lesions of the Head and Neck

3.1.1. Classification and General Epidemiology

HPV in the head and neck region gives rise to both benign and malignant lesions. The character of the lesion depends on the viral genotype. Low-risk genotypes, primarily HPV-6 and HPV-11, are responsible for the development of benign lesions. These include recurrent respiratory papillomatosis, squamous cell papillomas of the oral cavity and oropharynx, oral condylomata acuminata, and focal epithelial hyperplasia. Less frequently, HPV-13 and HPV-32 constitute the underlying etiology (Gillison et al., 2000; Gillison & Shah, 2001; zur Hausen, 2002). High-risk genotypes, in particular HPV-16, are the main etiological factor in oropharyngeal squamous cell carcinoma (OPSCC). They are also involved in the malignant transformation of inverted papilloma of the nasal cavity and paranasal sinuses. High-risk HPV additionally accounts for a proportion of cases of oral cavity, laryngeal, and nasopharyngeal carcinoma (Gillison et al., 2000; Gillison & Shah, 2001; zur Hausen, 2002).

The prevalence of HPV infection in head and neck cancers depends on the anatomical location of the tumor. HPV shows the greatest etiological significance in OPSCC, whereas its contribution to oral cavity cancers is considerably smaller. In the meta-analysis by Fonsêca et al. (2024), comprising 65 studies, HPV was detected in 42% of OPSCC cases (95% CI [36, 49]) and in 10% of oral cavity cancer cases (95% CI [7, 13]). The predominant genotype in both locations was HPV-16, which accounted for 89% of infections in OPSCC and 69% of infections in oral cavity cancer (Table 1).

Table 1. Frequency of HPV Detection According to the Anatomical Location of Head and Neck Cancer

Tumor location	HPV detection rate (%)	95% CI	Predominant HPV genotype
Oropharyngeal squamous cell carcinoma (OPSCC)	42	[36, 49]	HPV-16 (89%)
Oral cavity squamous cell carcinoma (OSCC)	10	[7, 13]	HPV-16 (69%)

Note. CI = confidence interval. Data from Fonsêca et al. (2024), a systematic review and meta-analysis comprising 65 studies.

In highly developed countries, particularly in the United States and Western Europe, an increasing proportion of HPV-positive oropharyngeal cancers is being observed. Over the past three decades, the proportion of HPV-related OPSCC cases has risen to approximately 60–70% of all newly diagnosed cases. This phenomenon is associated with a rising incidence of HPV-dependent oropharyngeal cancers alongside a simultaneous decline in the number of cases related to classical risk factors such as tobacco smoking (Chaturvedi et al., 2011; Mehanna et al., 2013).

3.1.2. Benign Lesions Associated with HPV

Recurrent respiratory papillomatosis. Recurrent respiratory papillomatosis (RRP) is a rare, chronic proliferative disease of the respiratory epithelium and the most common benign laryngeal neoplasm in children. The disease occurs both in the pediatric population as the juvenile-onset form (JoRRP) and in adults as the adult-onset form (AoRRP). Lesion development is attributable almost exclusively to HPV infection, primarily with the low-oncogenic-risk types HPV-6 and HPV-11. Infection of the child most often occurs in the perinatal period, during vaginal delivery through contact with an infected birth canal. The pediatric form usually manifests in early childhood, most often before the age of 5, and its course is characterized by a tendency to recur and the need for long-term clinical monitoring (Welschmeyer & Berke, 2021).

The disease manifests as progressive dysphonia and biphasic stridor. In advanced cases it may lead to airway obstruction. The lesions tend to recur despite repeated surgical excision. In rare cases they may spread distally to the trachea and lung parenchyma. In such situations there is an increased risk of malignant transformation to squamous cell carcinoma, particularly in patients with a severe disease course (Sechi et al., 2024; Welschmeyer & Berke, 2021). Malignant transformation of laryngeal papillomas is a rare but well-documented complication of RRP, particularly in patients with a severe, treatment-resistant course and involvement of the lower airways (Sechi et al., 2024).

The mainstay of therapy remains surgical removal of the lesions using, among others, a microdebrider and CO₂ laser. Recurrent respiratory papillomatosis is also a disease whose incidence has decreased in populations covered by HPV vaccination programs. A systematic review including data from countries conducting vaccination demonstrated a significant reduction in the incidence of the juvenile-onset form of RRP following the implementation of immunization programs (Jacobsen et al., 2025; Welschmeyer & Berke, 2021).

Squamous cell papilloma of the oral cavity and oropharynx. Squamous cell papilloma is the most common benign epithelial lesion of the oral cavity and oropharynx. It is associated with infection by low-risk genotypes, most often HPV-6 and HPV-11 (Leslie et al., 2025). The lesions usually present as small, exophytic, cauliflower-like or verrucous growths. They are located on the soft palate, uvula, tongue, or labial mucosa. The course is benign, and the risk of malignant transformation is practically absent. Local surgical excision is the treatment of choice (Leslie et al., 2025).

Oral condylomata acuminata. Condylomata acuminata may also be located within the oral cavity and oropharynx. They result from orogenital contact. As in the anogenital location, in more than 90% of cases they are associated with HPV-6 or HPV-11 infection (Leslie et al., 2025). The lesions present as soft, pedunculated or cauliflower-like growths, sometimes multiple. They involve the mucosa of the lips, tongue, or palate. The lesion is benign. Given the route of transmission, assessment for coexisting genital infection is indicated (Leslie et al., 2025).

Focal epithelial hyperplasia (Heck's disease). Focal epithelial hyperplasia, known as Heck's disease, is a rare, benign lesion of the oral mucosa. It is specifically associated with infection by the HPV-13 and HPV-32 genotypes (Conde-Ferráez & González-Losa, 2024; Ramos-Gregorio et al., 2025). The disease primarily affects children and adolescents, and a particularly high prevalence has been described in indigenous populations of the Americas (Conde-Ferráez & González-Losa, 2024; Ramos-Gregorio et al., 2025). The clinical picture comprises multiple, soft, painless papules or nodules. The color of the lesions is similar to that

of the surrounding mucosa. They are located mainly on the lips, buccal mucosa, and tongue, forming a characteristic cobblestone pattern. The lesions usually resolve spontaneously. No risk of malignant transformation has been documented, and treatment is indicated only for esthetic or functional reasons (Conde-Ferrández & González-Losa, 2024; Ramos-Gregorio et al., 2025).

Papillomas of the nasal cavity and paranasal sinuses. Papillomas of the nasal cavity and paranasal sinuses are divided into three histological subtypes: inverted papilloma, fungiform (exophytic) papilloma, and oncocytic papilloma (Ferrel et al., 2022; Zhao et al., 2016). The fungiform variant is consistently associated with the low-risk genotypes HPV-6 and HPV-11 and practically never undergoes malignant transformation. The oncocytic variant shows only a weak association with HPV infection (Ferrel et al., 2022; Zhao et al., 2016). Inverted papilloma is characterized by a tendency to recur and a documented risk of malignant transformation; it is therefore discussed in Section 3.1.4, devoted to malignant neoplasms of this region.

3.1.3. Molecular Basis of HPV-Dependent Carcinogenesis

The mechanism of HPV-dependent carcinogenesis is based on the expression of two early viral oncoproteins, E6 and E7. The E6 oncoprotein binds to the cellular ubiquitin ligase E6-associated protein (E6-AP), which leads to proteasomal degradation of the p53 tumor suppressor protein (Gillison et al., 2000; Gillison & Shah, 2001). The result is abolition of p53-dependent cell cycle control and of apoptosis in response to DNA damage. The E7 oncoprotein, in turn, binds to the hypophosphorylated, active form of the retinoblastoma protein (Rb). It thereby releases E2F transcription factors and forces uncontrolled entry of the cell into the S phase of the cell cycle. Simultaneous inactivation of the p53 and Rb pathways constitutes the central molecular event of HPV-dependent carcinogenesis (Gillison et al., 2000; Gillison & Shah, 2001; zur Hausen, 2002).

This distinguishes HPV-dependent carcinogenesis from the classical tobacco-related pathway, in which the *TP53* gene is usually inactivated through mutation rather than virally induced degradation (Gillison et al., 2000; Gillison & Shah, 2001; zur Hausen, 2002). A consequence of Rb inactivation by the E7 oncoprotein is compensatory overexpression of the p16INK4a protein, which is used as a surrogate immunohistochemical marker of transcriptionally active HPV infection (Ang et al., 2010; Bishop et al., 2015).

3.1.4. Malignant Neoplasms Associated with HPV

Oropharyngeal squamous cell carcinoma. Oropharyngeal cancer involves the palatine tonsils, base of the tongue, soft palate, and posterior pharyngeal wall. This is the location in which the causal role of high-risk HPV is best documented (Chaturvedi et al., 2011; Mehanna et al., 2013). The majority of cases are attributable almost exclusively to HPV-16. In the United States and Western Europe, HPV currently accounts for approximately 60–70% of newly diagnosed OPSCC cases, a proportion that has increased substantially over the past three decades despite a decline in tobacco exposure (Chaturvedi et al., 2011; Mehanna et al., 2013).

HPV-positive OPSCC constitutes a distinct biological and clinical entity. It arises from the crypt epithelium of the palatine and lingual tonsils and is characterized by non-keratinizing, basaloid histological architecture (Gillison et al., 2008; Mehanna et al., 2013). It affects a demographically distinct population: younger patients, more often male, without a significant history of tobacco or alcohol use, although a greater number of sexual partners is reported in the history (Gillison et al., 2008; Mehanna et al., 2013). In HPV-positive tumors, the *TP53* gene usually remains unmutated, and the p53 protein is degraded through the action of the E6 oncoprotein (Bishop et al., 2015; Gillison et al., 2008). In HPV-negative tumors, classically associated with tobacco smoking and alcohol abuse, *TP53* mutations predominate. This results in strong, diffuse p16 overexpression in HPV-positive tumors, in contrast to negative or focal expression in HPV-negative tumors (Bishop et al., 2015; Gillison et al., 2008). These differences translate directly into clinical course and prognosis, discussed in Section 3.1.6.

Oral cavity cancer. In the oral cavity, high-risk HPV DNA is detected in only a minority of squamous cell carcinoma cases. The pooled prevalence according to the meta-analysis by Kreimer et al. (2005) is 23.5%. The independent causal role of infection remains equivocal, and it is unclear whether the infection is causal or merely coincidental. The situation therefore differs from the well-documented causal association in the oropharynx (Kreimer et al., 2005). Population-based studies using Surveillance, Epidemiology, and End Results (SEER) registries have demonstrated differences between potentially HPV-related and HPV-unrelated oral cavity cancers, concerning both age at diagnosis—a mean of 61.0 versus 63.8 years—and survival (Chaturvedi et al., 2008). The role of HPV in oral verrucous carcinoma is considered separately below.

Laryngeal cancer. In the larynx, the pooled HPV detection rate is approximately 24.0% (Kreimer et al., 2005). However, p16 expression correlates poorly with actual HPV infection at this site. p16

immunohistochemistry is therefore not considered a reliable surrogate marker in the larynx, in contrast to the oropharynx (Bishop et al., 2015). A separate clinical entity associated with low-risk genotypes is recurrent laryngeal papillomatosis, described in Section 3.1.2, which in rare cases may undergo malignant transformation (Sechi et al., 2024; Welschmeyer & Berke, 2021).

Paranasal sinus cancer and malignant transformation of inverted papilloma. Inverted papilloma is a benign but locally aggressive epithelial neoplasm of the paranasal sinuses, characterized by a marked tendency to recur and associated with a documented risk of malignant transformation to squamous cell carcinoma of the paranasal sinuses. Systematic reviews and meta-analyses have demonstrated a statistically significant association between HPV infection and malignant transformation of inverted papilloma, particularly for high-risk genotypes. The meta-analysis by Zhao et al. (2016) demonstrated a pooled odds ratio of 2.16 (95% CI [1.46, 3.21]). The meta-analysis by Ferreli et al. (2022) confirmed a significant association between HPV infection and malignant transformation, and the meta-analysis by McCormick et al. (2022), based on polymerase chain reaction (PCR) detection of HPV, additionally confirmed an increased risk of malignant transformation associated with high-oncogenic-risk HPV genotypes. Tobacco smoking and high-risk HPV infection have been identified as independent risk factors for malignant transformation of inverted papilloma (Ferreli et al., 2022), which points to a multifactorial mechanism of carcinogenesis at this site.

Verrucous carcinoma. Verrucous carcinoma, also known as Ackerman tumor, is a rare, highly differentiated variant of squamous cell carcinoma characterized by exophytic growth, a slow course, and low metastatic potential. It may occur in the oral cavity and larynx (Lechien & Hans, 2023; Tamboon et al., 2022). Oral verrucous carcinoma shows an association with irritant factors, including exposure to smokeless tobacco. The role of HPV in its pathogenesis remains equivocal: available studies indicate the possible presence of the virus in a proportion of cases, but its causal significance has not been confirmed (Tamboon et al., 2022). The systematic review by Lechien and Hans (2023) on laryngeal verrucous carcinoma demonstrated that HPV status was rarely assessed and that current evidence does not confirm an unequivocal association between HPV infection and the development of this neoplasm. Laryngeal verrucous carcinoma is characterized by a different epidemiology compared with classical laryngeal cancer, with a predominance in men and more frequent occurrence in older age groups (Lechien & Hans, 2023).

HPV-associated nasopharyngeal carcinoma. Nasopharyngeal carcinoma is classically associated with Epstein-Barr virus (EBV) infection, particularly in endemic regions, which include South-East Asia and North Africa. In non-endemic populations, including North America and Europe, a distinct subgroup of EBV-negative nasopharyngeal carcinomas has been described (Huang et al., 2022). In these tumors, the presence of high-risk HPV, most often HPV-16, with accompanying p16 overexpression, has been demonstrated (Huang et al., 2022). HPV and EBV infection appear to be mutually exclusive phenomena at this site. The prognosis of patients with HPV-positive nasopharyngeal carcinoma is intermediate between that of classical EBV-positive carcinoma and non-viral carcinoma (Huang et al., 2022).

3.1.5. Determination of HPV Status: p16, Molecular Testing, and AJCC Staging

Current guidelines recommend determining HPV status in all newly diagnosed cases of OPSCC. This also applies to cervical lymph node metastases of unknown primary origin. Immunohistochemical assessment of p16 expression constitutes the basic screening test (Ang et al., 2010; Bishop et al., 2015). Positivity is defined as diffuse, strong nuclear and cytoplasmic staining in at least 70% of tumor cells. This test is characterized by high sensitivity in detecting transcriptionally active, high-risk HPV in the oropharynx (Ang et al., 2010; Bishop et al., 2015). The specificity of the test is, however, limited: a small proportion of p16-positive cases are in fact not associated with HPV infection, and this discordance is linked to an intermediate, less favorable prognosis compared with cases that are both p16-positive and HPV-positive (Bishop et al., 2015). In atypical cases, confirmation by HPV DNA or RNA in situ hybridization or by PCR is recommended.

The 8th edition of the American Joint Committee on Cancer (AJCC) staging classification, published in 2017, introduced a separate, simplified staging system for HPV-dependent, p16-positive OPSCC (Ang et al., 2010; Lydiatt et al., 2017). p16 overexpression was incorporated into this classification as the criterion defining HPV-dependent oropharyngeal cancer (Ang et al., 2010; Bishop et al., 2015). The previous, universal tumor-node-metastasis (TNM) system did not adequately reflect the substantially better prognosis of this group of patients (Lydiatt et al., 2017).

The T category has not undergone significant changes. The clinical N category, however, has been simplified to two grades: N1 comprises unilateral or bilateral metastases up to 6 cm, and N2 metastases larger than 6 cm, without taking into account the number of involved lymph nodes (Lydiatt et al., 2017). The system

for p16-negative OPSCC, by contrast, retains the classical division according to the number, size, and laterality of nodes and the presence of extranodal extension. A consequence of these changes is a shift of the stage groupings (I–IV) for HPV-dependent OPSCC toward lower values relative to the 7th edition of the classification (Lydiatt et al., 2017), which better reflects the more favorable prognosis of this group of patients.

3.1.6. Prognostic Significance of HPV Status

HPV-positive OPSCC is associated with a significantly better prognosis than HPV-negative squamous cell carcinoma of the head and neck at a comparable stage. In the study by Ang et al. (2010), which included patients treated within the RTOG 0129 trial, HPV status proved to be an independent prognostic factor for survival and a stronger factor than the classical staging criteria. Patients with HPV-dependent disease show a significantly better response to chemoradiotherapy and have higher overall and disease-specific survival rates (Bishop et al., 2015; Mehanna et al., 2013). This applies independently of traditional staging factors, including smoking history (Bishop et al., 2015; Mehanna et al., 2013).

The more favorable clinical course results to a significant extent from preserved, unmutated p53 function, in contrast to the frequently mutated *TP53* in HPV-negative head and neck squamous cell carcinoma. An enhanced host immune response is also of importance. The distinct biology of HPV-positive OPSCC is the subject of research into treatment de-escalation strategies, the aim of which is to reduce the late toxicity of therapy without compromising oncological control (Mehanna et al., 2013).

3.2. HPV-Associated Lesions of the Anogenital and Genitourinary Tract

3.2.1. Classification

HPV infection of the anogenital and genitourinary tract may contribute to the development of benign lesions, such as condylomata acuminata (genital warts). HPV-associated malignant neoplasms at these sites include cervical cancer, vulvar cancer, vaginal cancer, penile cancer, and anal cancer; an association with bladder cancer has also been reported, although the evidence remains considerably weaker (Gustafson et al., 2014; Sun et al., 2023). Figure 1 illustrates the proportion of cases of individual malignant neoplasms of the anogenital region attributable to HPV infection.

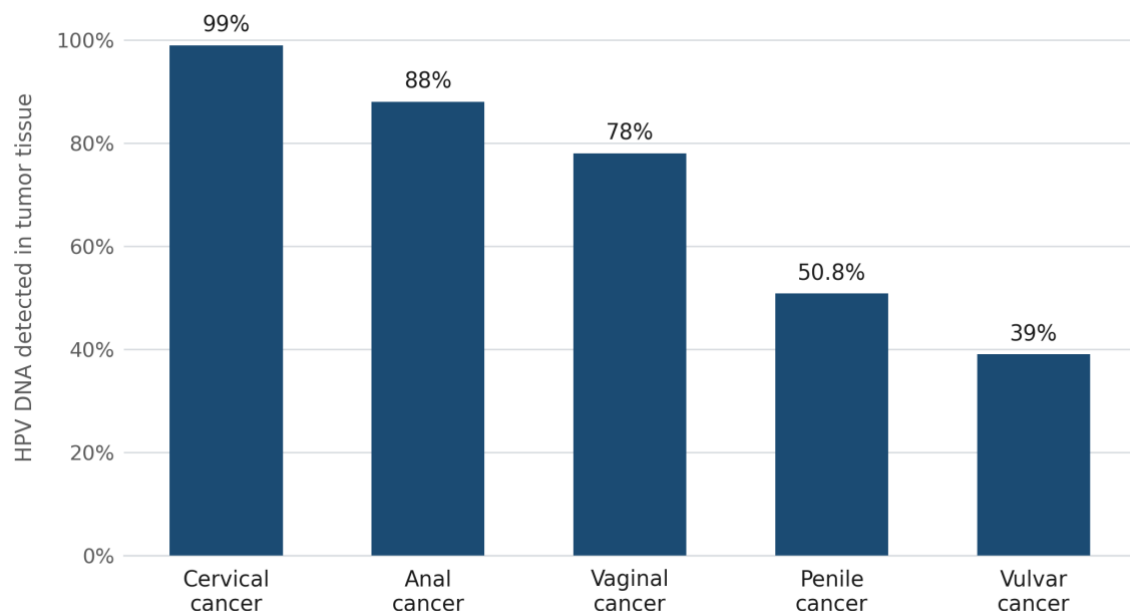


Fig. 1. Proportion of Cases of Selected Anogenital Malignant Neoplasms Attributable to Human Papillomavirus Infection, by Tumor Site

Note. Values represent the upper reported estimates of HPV DNA detection in tumor tissue at each site and are ordered by decreasing prevalence. Compiled from Bray et al. (2024), de Martel et al. (2017), Z. Li et al. (2023), Lu et al. (2020), and Olesen et al. (2019).

3.2.2. Condylomata Acuminata (Genital Warts)

Condylomata acuminata are epithelial lesions associated with HPV infection in approximately 90% of cases, predominantly caused by HPV types 6 and 11. They are classified as benign neoplastic lesions, with a very low risk of malignant transformation. These lesions most commonly occur on the penis, vulva, vagina, cervix, perianal region, and urethra. They present as flat, dome-shaped, cauliflower-like, or pedunculated lesions that may be flesh-colored, violaceous, or brown and may gradually increase in size. The lesions are typically painless; however, pruritus, burning, discomfort, irritation, and bleeding may occur. Treatment may involve either topical or surgical approaches, as presented in Table 2 (Erlandson et al., 2023; Leslie et al., 2025; Yanofsky et al., 2012).

Table 2. Treatment Modalities for Condylomata Acuminata

Topical treatment	Surgical and ablative treatment
Podophyllotoxin	Cryotherapy with liquid nitrogen
Imiquimod 5% or 3.75%	Electrocautery
Sinecatechins	Surgical excision
Trichloroacetic acid (TCA)	CO2 laser

Note. Adapted from Erlandson et al. (2023) and Yanofsky et al. (2012).

3.2.3. Buschke–Löwenstein Tumor

Buschke–Löwenstein tumor is a rare form of verrucous squamous cell carcinoma of the anogenital region, most commonly associated with HPV infection, particularly HPV types 6 and 11. The condition occurs more frequently in men, especially uncircumcised men, and is most commonly diagnosed in individuals under 50 years of age. Risk factors include immunosuppression, chronic tissue irritation, inadequate genital hygiene, tobacco smoking, diabetes mellitus, and low socioeconomic status. Although the tumor is rare, it is characterized by a high propensity for local recurrence and the potential for transformation into conventional squamous cell carcinoma.

Initially, the lesion presents as a small wart that gradually enlarges over many years, eventually forming an extensive, cauliflower-like mass. Ulceration, malodor, fistula formation, bleeding, pain, and secondary infections may accompany the lesion. The tumor exhibits locally infiltrative and destructive growth; however, distant metastases are very rare. Diagnosis is based on histopathological examination of tissue obtained by deep biopsy, supplemented by imaging studies, particularly magnetic resonance imaging, to assess the extent of local infiltration.

The mainstay of treatment is wide surgical excision with negative margins, with Mohs micrographic surgery considered the preferred surgical technique. In selected cases, adjuvant therapies may be employed, including imiquimod, 5-fluorouracil, interferon, cidofovir, or chemotherapy; however, their efficacy as standalone treatments is limited. Radiotherapy is used infrequently due to the risk of malignant transformation. Despite treatment, the recurrence rate remains high, and patients therefore require long-term follow-up (Azis & Djawad, 2022; Irshad & Puckett, 2023).

3.2.4. Cervical Cancer

Cervical cancer is the most common HPV-associated malignancy, the fourth most frequently diagnosed malignant neoplasm, and the fourth leading cause of cancer-related mortality among women worldwide, according to GLOBOCAN 2022. Studies have demonstrated that HPV DNA is detectable in approximately 90.6–99% of cases of invasive cervical cancer. Furthermore, approximately 66% of cases are associated with HPV types 16 and 18, while HPV types 31, 33, 45, 52, and 58 account for a further 14.7% of cases (Bray et al., 2024; Mwaka et al., 2016; Saraiya et al., 2015; Włoszek et al., 2025).

The development of cervical cancer is preceded by precancerous lesions referred to as cervical intraepithelial neoplasia (CIN) or, according to the Bethesda classification, squamous intraepithelial lesions (SIL). The development of these lesions is associated with the expression of the viral oncoproteins E6 and E7, as described in Section 3.1.3. Precancerous lesions are classified as low-grade squamous intraepithelial lesions (LSIL; CIN1) and high-grade squamous intraepithelial lesions (HSIL; CIN2 and CIN3). A comparison of these lesions is presented in Table 3 (Loopik et al., 2021; Ostör, 1993).

Table 3. Likelihood of Regression and Risk of Progression of Cervical Precancerous Lesions

Bethesda classification	CIN grade	Likelihood of regression	Risk of progression
LSIL	CIN1	57–60%	11% to CIN2; 2% to CIN3; 1% to invasive cancer
HSIL	CIN2	43–55%	19% to CIN3; 5% to invasive cancer
HSIL	CIN3	28–32%	2–12% to invasive cancer

Note. CIN = cervical intraepithelial neoplasia; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion. Compiled from Loopik et al. (2021) and Ostör (1993).

In its early stages, cervical cancer is often asymptomatic; prevention and regular screening are therefore of crucial importance. As the disease progresses, characteristic symptoms may develop, including abnormal vaginal bleeding (between menstrual periods, after sexual intercourse, or after menopause), increased or foul-smelling vaginal discharge, and persistent pain in the pelvic region, lower back, or lower extremities. In more advanced stages, symptoms may include weight loss, chronic fatigue, loss of appetite, vaginal discomfort, and lower-extremity edema. The occurrence of these symptoms requires prompt medical consultation and diagnostic evaluation (World Health Organization, 2026).

Screening constitutes the cornerstone of secondary prevention of cervical cancer, enabling the detection of precancerous lesions at the pre-invasive stage. In Poland, as of August 1, 2026, a new model of the population-based cervical cancer prevention program has been in effect, in which the primary screening test is the high-risk HPV DNA (HPV HR DNA) test performed in women aged 25–64 years. In the event of a positive HPV HR result, liquid-based cytology is performed on the same sample as a reflex test. In women with a negative HPV HR test result, the next screening examination is recommended after 5 years. The introduction of primary HPV testing is consistent with current international recommendations and aims to increase the sensitivity of screening and further reduce the incidence of and mortality associated with cervical cancer (Narodowy Fundusz Zdrowia, n.d.).

3.2.5. Vulvar Cancer

Vulvar cancer is a rare malignancy of the female reproductive system, accounting for approximately 5% of gynecological cancers. It has been shown to occur most frequently after menopause; however, an increase in incidence among younger women has recently been observed, most likely attributable to HPV infection. Studies have demonstrated that HPV DNA is detected in 39–40% of vulvar cancer cases (W. Li et al., 2024; Mix et al., 2022; Olesen et al., 2019).

Similarly to cervical cancer, HPV DNA integrates into the genetic material of the host cell, resulting in the synthesis of the E6 oncoprotein, which binds to E6-AP and thereby induces the degradation of p53. Reduced levels of p53 result in uncontrolled mitotic division and impaired DNA repair, thereby promoting the development of vulvar cancer. This mechanism is also relevant to radiotherapy, as studies have demonstrated that this treatment modality induces double-stranded DNA breaks, resulting in the preservation of p53 and potentially contributing to improved outcomes in affected women (W. Li et al., 2024; Mix et al., 2022).

Vulvar cancer may be asymptomatic in its early stages; however, most patients develop characteristic clinical symptoms. The most commonly reported symptoms include persistent vulvar pruritus and pain, as well as the presence of a palpable mass or ulceration within the vulva. Some patients may also experience abnormal bleeding and pathological vaginal discharge. Owing to the nonspecific nature of these symptoms, any suspicious vulvar lesion requires thorough clinical evaluation and histopathological verification by biopsy (Olawaiye et al., 2025).

3.2.6. Penile Cancer

Penile cancer is a rare malignancy of the male reproductive system, with a mean reported incidence of 0.8 per 100,000 men. Approximately 38.5–50.8% of penile cancers are associated with HPV, most commonly HPV-16, which accounts for 42–62.5% of HPV-positive penile cancer cases (Hernandez et al., 2014; Menon et al., 2023; Olesen et al., 2019).

Penile cancer most commonly presents as a persistent, non-healing lesion located on the glans penis or foreskin, which may manifest as a nodule, ulceration, or infiltrative lesion. Cutaneous lesions are often accompanied by bleeding, serous or purulent malodorous discharge, and localized pain or pruritus. As the disease progresses, enlargement of the inguinal lymph nodes may occur, indicating lymphatic spread of the malignancy. Owing to its initially nonspecific clinical presentation, diagnosis may be delayed, which adversely affects prognosis and treatment options (Engelskjær et al., 2024).

3.2.7. Vaginal Cancer

High-risk HPV infection is closely associated with vaginal cancer. The estimated global incidence ranges from 0.5 to 1 case per 100,000 women, with approximately 75–85% of cases being associated with HPV infection (Rasmussen et al., 2021; Wang et al., 2026). Rasmussen et al. (2021) demonstrated that HPV-associated vaginal cancer carries a more favorable prognosis than HPV-independent vaginal cancer, with 5-year survival rates of 57–68.8% versus 10.7–48%, respectively.

The most common symptoms include abnormal vaginal bleeding, particularly after menopause or following sexual intercourse, as well as pathological vaginal discharge. Some patients may experience urinary disturbances, including urinary retention, as well as other urinary tract symptoms. Involvement of the posterior vaginal wall may result in rectal symptoms, such as constipation or hematochezia. In more advanced stages of the disease, pelvic pain may also occur as a result of tumor extension into surrounding tissues (Baral et al., 2022).

3.2.8. Anal Cancer

The incidence of anal cancer is approximately 1–1.7 cases per 100,000 persons per year, with a substantially higher incidence among individuals living with HIV and among men who have sex with men. Approximately 88–100% of cases are associated with HPV infection, predominantly HPV-16, which is detected in 73% of cases. From an epidemiological perspective, it is noteworthy that HPV DNA has been detected in 91.5% of cases of anal intraepithelial neoplasia grade 1 (AIN1) and in 93.9% of cases of AIN2 and AIN3 (Clarke et al., 2022; Ebrahimi et al., 2024).

In the vast majority of cases, anal cancer presents with clinical symptoms already at the time of diagnosis. The most common symptoms include rectal bleeding, anal or perianal pain, and painful defecation. Some patients may also experience a sensation of a foreign body, a palpable mass, pruritus, and weight loss. In more advanced stages of the disease, constipation, altered bowel habits, and severe perianal pain may develop as a result of local tumor extension. The presence of these symptoms warrants further proctological and histopathological evaluation (Sauter et al., 2016).

3.3. Prophylactic HPV Vaccination

3.3.1. Efficacy and Population-Level Impact

Vaccination against HPV represents the most effective method of primary prevention of infection with oncogenic HPV types and of the associated malignancies and other diseases. Currently available prophylactic vaccines demonstrate high efficacy in preventing infection with the HPV types covered by the respective vaccine, as well as the development of precancerous lesions of the cervix, vulva, vagina, and anus, and of anogenital warts. The greatest benefit from vaccination is achieved by individuals vaccinated before the onset of sexual activity, which underscores the importance of administering vaccination at an early age in accordance with preventive health program recommendations. Nevertheless, significant benefits have also been demonstrated in older children, adolescents, and young adults (World Health Organization, 2009; Yoshikawa, 2008).

Available HPV vaccines have a favorable safety profile, and their efficacy and immunogenicity have been confirmed in numerous randomized clinical trials and long-term observational studies. In countries that have achieved high population-level vaccination coverage, a substantial decline has been observed in the incidence of HPV infection, anogenital warts, and high-grade squamous intraepithelial lesions (CIN2+), translating into a reduced risk of cervical cancer and other HPV-associated malignancies. Current guidelines issued by international scientific societies and the World Health Organization recommend routine vaccination of both girls and boys as a key component of strategies aimed at eliminating HPV-related cancers, while simultaneously emphasizing the need to maintain cervical cancer screening programs (Drolet et al., 2019; Falcaro et al., 2021).

One of the most important bodies of evidence confirming the effectiveness of population-based HPV vaccination programs comes from the immunization program implemented in England in 2008. The program included routine vaccination of girls aged 12–13 years using the bivalent vaccine Cervarix, as well as a catch-up vaccination program for girls aged 14–18 years. An analysis of registry data comprising approximately 13.7 million person-years of follow-up demonstrated a significant reduction in the incidence of cervical cancer and of cervical intraepithelial neoplasia grade 3 among vaccinated cohorts compared with unvaccinated cohorts (Falcaro et al., 2021).

The greatest effectiveness was observed among girls vaccinated at 12–13 years of age, in whom the risk of developing cervical cancer was reduced by 87%, while the risk of CIN3 was reduced by 97%. A significant protective effect was also observed among individuals vaccinated at older ages, although the magnitude of the effect was smaller: the reduction in cervical cancer risk was 62% among those vaccinated at 14–16 years of age and 34% among those vaccinated at 16–18 years of age. A similar age-dependent relationship was observed for CIN3 lesions (Falcato et al., 2021). The authors estimated that, by June 2019, the vaccination program had prevented approximately 448 cases of cervical cancer and more than 17,000 cases of CIN3. These findings represent one of the first population-level confirmations that widespread HPV vaccination not only reduces the incidence of HPV infection and precancerous lesions but also substantially decreases the incidence of cervical cancer (Cruickshank & Grigore, 2021; Falcato et al., 2021).

3.3.2. Available Vaccine Products

Cervarix is a bivalent vaccine containing L1 proteins from HPV types 16 and 18, which are responsible for approximately 70% of cervical cancer cases. The antigens are produced in insect cells using recombinant baculovirus technology. A characteristic feature of the vaccine is the use of the AS04 adjuvant, consisting of an aluminum salt and monophosphoryl lipid A, a Toll-like receptor 4 agonist. The vaccine is indicated for the prevention of precancerous lesions and cancers of the cervix, vulva, vagina, and anus associated with infection with oncogenic HPV types (Fife et al., 2004; Monie et al., 2008).

In clinical trials, Cervarix demonstrated more than 90% efficacy in preventing HPV-16- and HPV-18-associated CIN2+ lesions. Partial cross-protection against HPV-31 and HPV-45 was also observed, potentially increasing the overall protection against cervical cancer to approximately 80%. Sustained immune responses were demonstrated for at least 5–6 years following vaccination, while subsequent follow-up studies confirmed the long-term durability of protection (Monie et al., 2008).

Gardasil 9 is a nine-valent vaccine providing protection against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. HPV types 16, 18, 31, 33, 45, 52, and 58 are classified as high-risk oncogenic types and collectively account for approximately 90% of cervical cancer cases. In addition, the vaccine protects against HPV types 6 and 11, which are responsible for approximately 90% of cases of anogenital warts. Owing to its broader spectrum of protection, Gardasil 9 reduces the risk of developing precancerous lesions and cancers of the cervix, vulva, vagina, and anus, as well as penile cancer and a proportion of HPV-associated cancers of the oral cavity and oropharynx (Cuzick, 2015; Huh et al., 2017; Monie et al., 2008).

3.3.3. The Universal Vaccination Program in Poland

In Poland, a universal publicly funded HPV vaccination program was introduced on 1 June 2023, ending the period during which vaccination was recommended but, in most cases, fully paid for by patients. The introduction of the program represents an implementation of the objectives of the National Oncology Strategy for 2020–2030 and aims to reduce the incidence of HPV-related malignancies by increasing the proportion of individuals vaccinated before the onset of sexual activity. The program covers girls and boys from the age of 9 years until their 14th birthday. Vaccination is administered according to a two-dose schedule, with an interval of 6–12 months between doses; the full vaccination course should be completed using the same vaccine product. Two vaccines are available free of charge under the program: the bivalent vaccine Cervarix and the nine-valent vaccine Gardasil 9. Vaccination is voluntary, does not require a referral, and may be administered at primary healthcare facilities participating in the program (Jankowski et al., 2023; Quinlan, 2021).

In addition to the universal vaccination program, a reimbursement system is also in place. Cervarix is available free of charge to girls and boys from the age of 9 up to their 18th birthday on a reimbursed prescription, and adults may obtain this vaccine with 50% reimbursement. By contrast, Gardasil 9 remains fully paid for outside the universal vaccination program (Jankowski et al., 2023; Quinlan, 2021).

An important component of the program is ensuring universal and convenient access to vaccination through an extensive network of healthcare facilities, multiple registration channels, and the involvement of various healthcare professional groups authorized to assess eligibility for vaccination and to administer vaccines. Parents or legal guardians are able to choose the vaccine product, which is consistent with the model of shared decision-making in healthcare (Jankowski et al., 2023; Rees et al., 2020).

Despite the removal of the financial barrier, initial HPV vaccination coverage in Poland remained low, indicating that economic constraints were not the sole factor influencing vaccination decisions. The literature emphasizes the need for comprehensive educational initiatives, increased public awareness, and consideration of school-based vaccination programs, which have contributed to achieving high vaccination coverage in many countries. At the same time, systematic monitoring of the program's effectiveness, its impact on participation in cervical cancer screening, and the long-term reduction in the incidence of HPV-related malignancies is essential (Michalek et al., 2024; Quinlan, 2021).

4. Discussion

4.1. Interpretation of the Findings

The evidence reviewed indicates that HPV is best understood not as a single disease entity but as a family of genotypes with divergent clinical programs. Low-risk types produce proliferative but essentially benign lesions, whereas high-risk types drive carcinogenesis through E6- and E7-mediated inactivation of the p53 and Rb pathways (Gillison et al., 2000; zur Hausen, 2002). Because the nine-valent vaccine covers both groups, a program justified primarily as cancer prevention also reduces the incidence of juvenile-onset recurrent respiratory papillomatosis (Jacobsen et al., 2025), a benefit largely absent from public discussion of HPV vaccination.

The strength of the causal association is, however, markedly site-dependent, and this gradient is obscured when HPV-associated cancers are discussed collectively. It is effectively definitive in the cervix (Bray et al., 2024; Saraiya et al., 2015), the anus (Clarke et al., 2022; Ebrahimi et al., 2024), and the oropharynx (Chaturvedi et al., 2011; Mehanna et al., 2013), whereas pooled detection rates of approximately 23.5% in the oral cavity and 24.0% in the larynx (Kreimer et al., 2005) fall short of establishing causation. Part of this heterogeneity is methodological: polymerase chain reaction detects viral DNA without establishing transcriptional activity, whereas p16 immunohistochemistry and E6/E7 mRNA assays reflect biologically active infection. HPV positivity should therefore be interpreted against the evidence base for the specific site rather than as a uniform attribute.

The same caution applies to HPV status as a biomarker. Its incorporation into the 8th edition of the AJCC classification (Lydiatt et al., 2017) is well justified by the survival data (Ang et al., 2010), but p16 is a surrogate of imperfect specificity whose validity is confined to the oropharynx (Bishop et al., 2015). This matters most for treatment de-escalation strategies (Mehanna et al., 2013), in which a false-positive classification carries the risk of undertreatment.

Finally, the English program data (Falcaro et al., 2021) establish that the timing of vaccination relative to sexual debut, rather than vaccination status alone, determines the magnitude of benefit. This does not make screening redundant, since available vaccines do not cover all oncogenic types and vaccinated cohorts have not yet reached the ages of peak incidence (Rees et al., 2020; Sasieni & Cuzick, 2020). The Polish experience is instructive in a further respect: the 2023 program removed the financial barrier entirely, yet uptake remained low (Michalek et al., 2024), which locates the binding constraint in awareness and access rather than in cost (Jankowski et al., 2023).

4.2. Limitations

This review is narrative rather than systematic: selection was not conducted in duplicate, no risk-of-bias instrument was applied, and no protocol was registered, so selection bias cannot be excluded. The included evidence is methodologically heterogeneous, and differences in HPV detection technique alone generate substantial variation in reported prevalence. The evidence base is geographically skewed toward high-income settings, whereas the greatest burden of HPV-associated cancer falls on low- and middle-income countries. Inclusion was restricted to English-language publications apart from official national sources. Finally, for several endpoints, particularly the effect of male vaccination on the incidence of oropharyngeal cancer, follow-up is not yet long enough for definitive outcome data to exist.

4.3. Directions for Future Research

Four priorities follow. First, transcriptionally informative assays are needed to resolve the causal status of HPV in the oral cavity and larynx. Second, long-term registry follow-up of vaccinated male cohorts is required to establish whether the reductions demonstrated for cervical endpoints extend to oropharyngeal cancer. Third, biomarkers more specific than p16 are needed if de-escalation strategies are to be applied safely. Fourth, the determinants of vaccine uptake in settings where cost has already been removed warrant direct investigation, since this is now the principal constraint on population-level impact.

5. Conclusions

HPV is a major public health concern because of its capacity to cause both benign lesions and malignant neoplasms, with clinical consequences determined by genotype. Low-risk types, particularly HPV-6 and HPV-11, are primarily associated with benign conditions such as anogenital warts and recurrent respiratory papillomatosis, whereas high-risk types, especially HPV-16 and HPV-18, play a central role in carcinogenesis through E6- and E7-mediated disruption of the p53 and Rb pathways (Jensen et al., 2024; Wolf et al., 2024; zur Hausen, 2002).

The association between HPV infection and cancer is best established for oropharyngeal squamous cell carcinoma and anogenital malignancies, and considerably weaker or unresolved in the oral cavity and larynx. In oropharyngeal carcinoma, HPV status distinguishes a biologically and clinically distinct tumor subgroup with characteristic molecular alterations, a better response to treatment, and a more favorable prognosis; its assessment, by p16 immunohistochemistry with molecular confirmation where indicated, therefore carries both diagnostic and prognostic value (Ang et al., 2010; Bishop et al., 2015). Within the anogenital tract, cervical cancer remains the most clinically significant HPV-associated malignancy, and the fact that it is preceded by detectable premalignant lesions creates the opportunity for effective secondary prevention (de Martel et al., 2017; Loopik et al., 2021).

Primary prevention through vaccination remains the key component of HPV control. Available vaccines are highly effective against infection with the covered types and against the associated premalignant lesions and cancers, and population-level data from countries with universal programs confirm real-world reductions in infection, precancerous lesions, and cervical cancer incidence (Drolet et al., 2019; Falcaro et al., 2021; Huh et al., 2017; Sasieni & Cuzick, 2020; World Health Organization, 2009). Effectiveness is greatest among those vaccinated before sexual debut, which makes the timing of immunization a determinant of program success rather than an operational detail (Falcaro et al., 2021; Huh et al., 2017).

In Poland, the universal program introduced in 2023 is an important element of the national cancer prevention strategy, but the availability of free vaccine has not by itself produced high coverage, and vaccination does not remove the need for screening (Bewley, 2022; Michalek et al., 2024; Quinlan, 2021). HPV infection is thus a modifiable risk factor for malignancy whose burden can be substantially reduced by combining effective primary prevention with organized screening and early diagnosis. Future work should concentrate on resolving the site-specific causal questions that remain open, on generating long-term outcome data for male vaccination, and on identifying the non-financial determinants of uptake, since these now represent the principal obstacle to realizing the preventive potential of existing vaccines (Drolet et al., 2019; Jankowski et al., 2023; World Health Organization, 2009).

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