Human papillomavirus (HPV) as the main cause of cervical and other related cancers: a review

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Abstract

Human papillomavirus (HPV) is a major cause of several cancers, most notably cervical cancer, which is the fourth most common cancer in women worldwide. HPV infections are typically spread through skin-to-skin contact during sexual activity, and while most infections are cleared by the immune system without symptoms, persistent infection with high-risk strains, such as HPV-16 and HPV-18, can lead to cellular changes in the body. These changes, over time, can result in precancerous lesions and, if untreated, progress to invasive cancer. Human papillomavirus (HPV) is a prevalent sexually transmitted infection recognised as the primary cause of cervical cancer, as well as other malignancies such as anal, oropharyngeal, penile, vulvar, and vaginal cancers. Recent advancements in HPV vaccines, including broader protection against multiple strains, have significantly contributed to reducing the incidence of HPV-related cancers. This review explores the role of HPV in oncogenesis, focusing on its types, mechanisms, and contribution to various cancers. Current prevention strategies, including vaccination, screening, and treatment options, are also discussed. The article emphasises the importance of widespread vaccination and early detection to reduce the global burden of HPV-associated cancers.

Keywords: Human papillomavirus, sexually transmitted infection, cervical cancer

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https://doi.org/10.36303/SAPJ.1164

Introduction

Human papillomavirus (HPV) is a group of over 100 related viruses, many of which infect the skin and mucous membranes of humans.[1] It is the most common sexually transmitted infection globally, affecting both men and women. HPV is primarily transmitted through direct skin-to-skin contact during sexual activity.[1] While many HPV infections are harmless and clear up on their own without causing symptoms, certain high-risk strains, particularly HPV-16 and HPV-18, can lead to serious health problems, including cervical cancer, as well as cancers of the anus, throat, vulva, vagina, and penis.[1]

HPV is not only the most common sexually transmitted infection but also a significant global health concern due to its role in multiple cancers. The high prevalence of HPV, especially in sexually active individuals, underscores the need for robust prevention strategies.[2] Apart from cervical cancer, HPV also contributes to other anogenital and oropharyngeal cancers. Globally, cervical cancer cases are predominantly found in low- and middle-income countries, where vaccination and screening programmes are less established. HPV vaccination is vital to lowering this burden and improving access to vaccines in under-resourced areas is a critical public health goal.[2]

Recent studies have expanded on these findings, delving deeper into the mechanisms of HPV-induced carcinogenesis.[3] The authors emphasise the importance of vaccination, early detection, and screening to reduce the global impact of HPV-associated cancers, advocating for a broader, population-based approach to prevention.[4] This call for prevention is echoed in subsequent studies, which highlight the evolving understanding of HPV's oncogenic potential in various anatomical sites.[4] While HPV infection is widespread, progression to invasive cancer is not immediate and depends on additional tumour-promoting factors.[5] This research underscores the importance of understanding these immunological mechanisms to enhance diagnostic accuracy and develop effective immunotherapies for HPV-related malignancies.[5]

Furthermore, research explores the emerging role of HPV in head and neck cancers, particularly oropharyngeal squamous cell carcinoma (OPSCC).[6] Their findings establish HPV as a significant risk factor for these cancers, distinguishing HPV-positive tumours from HPV-negative ones. This emerging recognition of HPV's role in head and neck cancers calls for a broader examination of its oncogenic potential beyond cervical cancer, particularly in light of increasing OPSCC cases globally.[6] These findings collectively highlight the critical importance of vaccination, early detection, and the development of immunotherapies in reducing the global burden of HPV-associated cancers. The literature from 2020 to 2024 reflects a growing recognition of HPV's impact across a range of cancers and underscores the need for comprehensive public health strategies.

In addition to its association with cancer, low-risk HPV strains can cause genital warts and other benign lesions.[1,2] Preventive measures, such as the HPV vaccine, have proven effective in reducing the risk of infection from the most dangerous strains.[1] Vaccination programmes, alongside routine screening like Pap smears for women, play a crucial role in early detection and prevention of HPV-related diseases.[2] A Pap smear is a procedure where cells are removed from the cervix for testing.[2]

Cervical cancer is the fourth most common cancer among women worldwide, with more than 90% of cases attributed to human papillomavirus (HPV) infection.[1] The primary cause of many epithelial lesions and cancers, primarily on cutaneous and mucosal surfaces, is the HPV.[2] Those who have multiple sexual partners and/or persistent HPV infection are particularly vulnerable to acquiring additional HPV subtypes.[2]

Understanding the relationship between HPV and cancer is critical for developing effective prevention, screening, and treatment strategies.[7] This review explores the role of HPV in the pathogenesis of cervical and other cancers, emphasising the need for global awareness and vaccination.

HPV and cancer development

HPV overview

HPV is a deoxyribonucleic acid (DNA) virus from the Papillomaviridae family, with over 200 identified types.[8] These types are categorised into "low-risk" and "high-risk" groups based on their oncogenic potential.[8] Low-risk types, such as HPV 6 and 11, are associated with benign conditions like genital warts, while high-risk types, particularly HPV 16 and 18, are implicated in cancer development.[8]

HPV primarily infects epithelial cells, leading to changes in the cell cycle and immune evasion.[9] Persistent infection with high-risk HPV types can cause cellular mutations and the progression to malignancy.[9]

Mechanisms of oncogenesis

The recent literature provides a comprehensive examination of human papillomavirus (HPV) as a necessary cause of cervical cancer and its association with other malignancies, such as anal, vulvar, vaginal, and penile cancers. Recent studies synthesise evidence on the critical role of HPV in oncogenesis, particularly its increasing prevalence in oropharyngeal cancer among younger adults.

HPV remains a critical factor in the aetiology of various cancers, particularly cervical cancer, which continues to be a significant global health issue.[4]

The pathogenesis of HPV is complex, involving intricate molecular mechanisms that lead to oncogenesis.[5] Research elucidated these mechanisms, particularly in cervical and other anogenital cancers. They highlighted the ongoing disparities in disease burden between high- and low-income countries, emphasising the need for enhanced public health initiatives and the development of innovative screening technologies to enable early detection and timely treatment.[5]

Recent research has expanded the understanding of HPV's impact beyond cervical cancer, notably in oropharyngeal squamous cell carcinoma (OPSCC). Research has shown that HPV-positive OPSCC cases tend to have better prognoses than HPV-negative cases, indicating the need for differentiated treatment strategies.[6]

Furthermore, advances in HPV genotyping have been identified as essential in improving prevention strategies, particularly through earlier diagnosis and more targeted interventions.[6]

The role of immunisation in preventing HPV infections remains a central focus in public health research. Research emphasised the effectiveness of prophylactic vaccines, advocating for gender-neutral vaccination campaigns to enhance herd immunity and reduce HPV-related diseases.[10] In addition, researchers explored therapeutic interventions for HPV-associated cervical lesions, highlighting the growing potential of immunotherapy in treatment protocols.[11]

Moreover, the epidemiology and molecular pathogenesis of HPV-related cancers have been further explored in recent years, particularly concerning immune evasion mechanisms employed by the virus. Researchers have provided insights into how understanding these mechanisms can inform the development of more effective vaccines and public health strategies.[12] Computational models simulating HPV transmission and prevention strategies have further emphasised the importance of addressing persistent oncogenic HPV infections to prevent cervical cancer progression.[13] Together, these advancements underscore the importance of vaccination, early detection through innovative screening methods, and targeted treatments in reducing the global burden of HPV-associated diseases.

HPV infection induces cancerous transformation primarily through its E6 and E7 oncoproteins, which disrupt the cell's normal regulatory pathways. E6 leads to the degradation of the p53 tumour suppressor protein, while E7 inactivates retinoblastoma protein (pRb).[14] These interactions result in the evasion of apoptosis, uncontrolled cell division, and accumulation of mutations over time. Persistent infection with high-risk strains such as HPV-16 and HPV-18 is most closely associated with cancer development.[14]

In cervical cancer, the transformation from normal epithelial cells to cancerous cells occurs through a series of stages, beginning with infection, progressing to pre-cancerous lesions, and ultimately developing into invasive cancer if left untreated.[14] This process can take several years or even decades, highlighting the importance of early detection.[6]

HPV-related cancers

Cervical cancer

Cervical cancer is the most well-established malignancy caused by HPV.[15] Virtually all cases of cervical cancer are linked to high-risk HPV types, with HPV-16 and -18 responsible for approximately 70% of cases.[15] HPV infects the cells of the cervix, particularly at the transformation zone, where squamous and columnar epithelial cells meet, making this area highly susceptible to viral infection and oncogenic transformation.[15]

The progression from infection to cervical cancer follows a distinct pathway, from low-grade cervical intraepithelial neoplasia (CIN1)

to high-grade CIN (CIN2/3) and, if not treated, to invasive cancer. Regular screening through Pap smears and HPV DNA testing is essential for early detection and treatment of pre-cancerous lesions.[16]

Anal cancer

HPV is responsible for approximately 90% of anal cancer cases, with HPV-16 being the most common type.[17] Anal cancer is more prevalent among individuals with a history of receptive anal intercourse, particularly in men who have sex with men (MSM), and immunocompromised individuals, such as those living with HIV.[17] HPV vaccination has the potential to reduce the incidence of anal cancer, especially in high-risk populations.[17]

Oropharyngeal cancer

HPV is also implicated in a rising number of oropharyngeal cancers, particularly those affecting the tonsils and base of the tongue. HPV-16 is the dominant type associated with these cancers.[18] Oropharyngeal cancer caused by HPV has distinct characteristics compared to those caused by smoking and alcohol, including a younger age of onset and better prognosis.[18] Vaccination against HPV offers a promising strategy for reducing the incidence of HPV-associated oropharyngeal cancers.[18]

Other HPV-related cancers

HPV contributes to approximately 40% of vulvar and vaginal cancers and about 60% of penile cancers.[19,20]These cancers are less common but still pose a significant health burden, particularly in low-resource settings where screening and vaccination rates may be low.[19]

Figure 1 illustatres how HPV is associated with a variety of cancers other than cervical cancer. This figure links HPV to several cancer types, such as anal, penile, valvular, vaginal, oropharyngeal, and colorectal cancers. Panel A in Figure 1 indicates that HPV is the primary causative factor linked to these malignancies; the iceberg theory is used in Panel B to illustrate the disparate percentages of HPV attribution. This depicts that HPV accounts for almost 99% of all cervical cancers and only 50% of penile cancers.

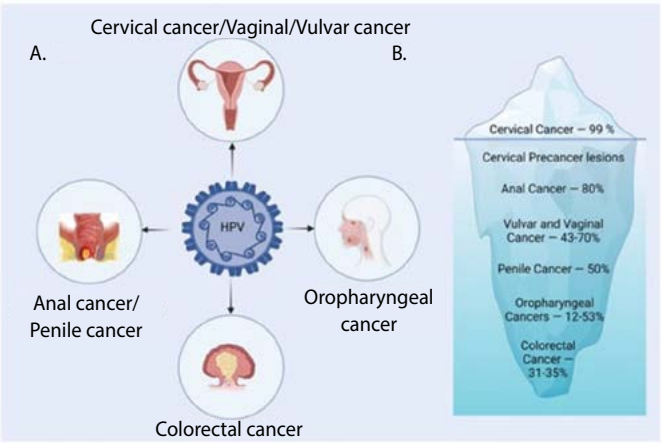

Figure 1: Depiction of HPV-associated malignancies and their prevalence. (A) A major group of malignancies attributed to HPV. (B) Burden of HPV-related malignancies.[20]

Prevention and screening

HPV vaccination

HPV vaccines are the most effective tool for preventing HPV-related cancers.[21] The three available vaccines – Cervarix®, Gardasil®, and Gardasil 9® – target high-risk HPV types, with Gardasil 9 offering the broadest protection against nine HPV types, including HPV-16 and -18. Vaccination is recommended for both males and females, ideally before the onset of sexual activity, but it can still offer protection for sexually active individuals.[21]

The introduction of HPV vaccination programmes has led to significant reductions in the prevalence of high-risk HPV infections and related conditions, such as genital warts and pre-cancerous cervical lesions.[22] However, global vaccination coverage remains uneven, with low-income countries facing challenges related to cost, infrastructure, and public awareness.[22]

Cervical cancer screening

Cervical cancer screening, primarily through Pap smears and HPV DNA testing, plays a crucial role in detecting pre-cancerous changes before they progress to invasive cancer.[23] Regular screening has significantly reduced cervical cancer incidence and mortality in countries with established screening programmes.[23]

HPV DNA testing, which detects the presence of high-risk HPV types, is becoming increasingly common as a primary screening tool.[24] It offers higher sensitivity than Pap smears, particularly in identifying women at risk for developing cervical cancer.[24] Combining HPV testing with traditional cytology (Pap smears) provides an effective approach to early detection.[24]

Screening for other HPV-related cancers

While cervical cancer screening is well-established, screening for other HPV-related cancers, such as anal and oropharyngeal cancers, is less widespread.[25] High-risk populations, such as MSM and individuals with HIV, may benefit from targeted anal cancer screening programmes.[25] Additionally, awareness of HPV's role in oropharyngeal cancers highlights the need for further research on effective screening strategies for this group.[25]

Treatment options for HPV-related diseases

The treatment of HPV-related diseases ranges from managing benign conditions, such as genital warts, to treating precancerous lesions and invasive cancers. The choice of treatment depends on the stage and location of the disease.

1. Treatment of precancerous lesions (Cervical Dysplasia)[20]

- Cryotherapy: This method uses extreme cold to destroy abnormal tissue. It is typically used to treat cervical intraepithelial neoplasia (CIN) and is especially valuable in low-resource settings due to its simplicity and low cost.
- Loop Electrosurgical Excision Procedure (LEEP): LEEP involves using a thin wire loop that carries an electric current to remove abnormal cervical tissue. It is commonly used for moderate to

severe dysplasia (CIN 2 and CIN 3).

- Conisation: This surgical procedure involves removing a cone-shaped section of abnormal tissue from the cervix. It is recommended for women with more severe dysplasia, or in cases where LEEP is insufficient.

2. Treatment of genital warts[20]

Genital warts, caused by low-risk HPV types such as HPV-6 and HPV-11, are typically managed through topical treatments or physical removal methods.

- Topical treatments: Imiquimod and podofilox are commonly used topical medications. Imiquimod stimulates the immune system to fight the virus, while podofilox works by destroying the wart tissue.
- Cryotherapy and electrocautery: Cryotherapy uses liquid nitrogen to freeze and destroy warts, while electrocautery involves burning off the warts with electric current.

3. Treatment of invasive cancer

The treatment of HPV-related cancers, such as cervical, anal, and oropharyngeal cancers, depends on the stage of the disease and may involve a combination of surgery, radiation, and chemotherapy.[26]

- Surgery: Early-stage cervical cancer can often be treated surgically, either through a hysterectomy (removal of the uterus) or conisation. For anal and oropharyngeal cancers, surgery is sometimes used to remove tumours, although these cancers are often treated with non-surgical methods.
- Radiation therapy: Radiation therapy is a mainstay of treatment for advanced HPV-related cancers. It can be used alone or in combination with chemotherapy to shrink tumours and destroy cancer cells.
- Chemotherapy: Chemotherapy is used in more advanced cases or when cancer has spread beyond the primary site. For example, cisplatin-based chemotherapy is commonly used in combination with radiation therapy for the treatment of advanced cervical cancer.
- Targeted therapy and immunotherapy: New treatments, such as immune checkpoint inhibitors (e.g. pembrolizumab), are being explored for HPV-related cancers. These therapies aim to enhance the body's immune response to target and destroy cancer cells. Clinical trials have shown promise in treating HPV-positive cancers, especially in cases where traditional therapies have failed.

The role of a pharmacist

Pharmacists have a significant role in the prevention and treatment of cervical cancer and other cancers associated with the human papillomavirus (HPV). As accessible healthcare professionals, pharmacists are well-positioned to educate the public on HPV, its connection to cancers, and the importance of prevention through vaccination and regular screenings. Pharmacists can promote the uptake of the HPV vaccine by providing counselling, addressing vaccine hesitancy and ensuring that patients understand its role in preventing cervical and other HPV-related cancers, such as anal, oropharyngeal, and genital cancers.[27] In addition, pharmacists can offer support for vaccine administration and adherence to vaccination schedules, particularly for young women and men within the recommended age range.

Pharmacists are essential in ensuring **continuous access to HPV-related treatments and vaccines** by:

- **Managing the supply chain** to prevent stockouts of **HPV vaccines, chemotherapy, and essential supportive care medicines**.
- Working with **health authorities, hospitals, and community pharmacies** to ensure **affordable and equitable access** to medicines.
- Advocating for **cost-effective procurement and distribution strategies**, particularly in **resource-limited settings**.

Pharmacists can advocate for early detection and timely screening, educating patients on the importance of routine Pap smears and HPV testing, which are essential for early intervention. Furthermore, pharmacists assist in the management of treatment for cervical cancer by ensuring patients receive accurate information on prescribed medications, managing side effects and supporting adherence to therapy, including chemotherapy and palliative care. As accessible healthcare professionals in the community, pharmacists can significantly contribute to public health efforts aimed at reducing the incidence and burden of HPV-related cancers.

Conclusion

The human papillomavirus (HPV) is a highly prevalent infection with both benign and serious health implications. While many HPV infections are harmless and resolve without intervention, persistent infections with high-risk strains can lead to various cancers, most including cervical cancer. Preventive strategies, such as vaccination and regular screening, have proven effective in reducing HPV-related cancers and other complications. However, the challenge remains in achieving vaccine coverage and ensuring access to health care, particularly in low-resource settings.

The continued support by pharmacists in public education and vaccination initiatives is essential to control the impact of HPV and reduce the global burden of HPV-related diseases. Pharmacists have an essential role in establishing and developing public health strategies to end HPV. As accessible healthcare professionals, they are instrumental in educating the public about HPV, its link to cancers and the importance of vaccination and screening. Pharmacists can address vaccine hesitancy and ensure adherence to vaccination schedules, particularly for adolescents and young adults. Additionally, they contribute to the management of HPV-related therapies by providing accurate medicine information and supporting treatment adherence. Their involvement in supply chain management ensures continuous access to HPV vaccines and essential therapy, even in resource-limited settings.

By collaborating with other healthcare providers and advocating for equitable access, pharmacists strengthen prevention and treatment strategies, making them a necessary component in the fight against HPV-associated cancers.

Further research is needed to optimise screening strategies for non-cervical HPV-related cancers to improve access to vaccines in low-resource settings. Public health initiatives that are aimed at increasing awareness of HPV and its role in cancer development, alongside the active involvement of pharmacists, will be important in order to achieve prevention and reducing the global impact of HPV-associated cancers.

Conflict of interest

The authors have no conflict of interest.

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