A Comprehensive Review of Cervical Cancer, Pathogenesis, Diagnosis, Prevention, and Multidisciplinary Management

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Abstract

Cervical cancer is a common yet preventable malignancy that predominantly affects women in low-resource settings. Persistent infection with high-risk human papillomavirus (HPV) is the major cause of cervical cancer and leads to molecular and cellular alterations involved in carcinogenesis (Doorbar et al., 2022). Despite advances in healthcare, cervical cancer remains a major cause of cancer-related mortality due to inadequate awareness, limited screening, and delayed diagnosis (Brisson et al., 2022). Modern treatment strategies involve surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy based on disease stage and patient condition (Ciavattini et al., 2023). Preventive measures such as HPV vaccination and regular cervical screening remain essential for reducing disease incidence and mortality. Recent research focusing on molecular mechanisms, biomarkers, and innovative therapeutic approaches has further improved cervical cancer management (Stanciu et al., 2023). This review summarizes recent advances in cervical cancer epidemiology, pathogenesis, diagnosis, prevention, and treatment, emphasizing the importance of multidisciplinary care and global preventive strategies.

Keywords: Cervical Cancer, Carcinogenesis, HPV Diagnostics, CIN Progression, Biomarkers.

1. Introduction: Cervical cancer is a serious global health problem and the fourth most frequent cancer among women with an estimated 604,000 cases diagnosed and over 340,000 deaths in 2020 (Sung et al., 2021). While cervical cancer is preventable, the cervical cancer burden is concentrated in the poor- and middle-income countries, which account for 85-90% of cervical cancer cases and deaths (Arbyn et al., 2020). High-risk human papillomavirus (HPV) infection is thought to be the primary cause of cervical cancer (Schiffman et al., 2016). HPV 16 and 18, two of over 200 HPV types, are the most common high-risk HPV types that cause nearly 70% of cervical cancer cases and other oncogenic types such as HPV 31, 33, 45, 52 and 58 also contribute to cervical cancer development (Martel et al., 2017). The better understanding of cervical cancer progression has led to preventive and screening strategies. The incorporation of human papillomavirus (HPV) vaccination,

cervical screening using cytology (Pap smear) and HPV DNA testing has resulted in a dramatic reduction in disease incidence and mortality in high-income settings (Ronco et al., 2014). However, the adoption of these prevention measures has varied globally due to a lack of awareness, access and health care facilities, resulting in a high burden of cervical disease in low- and middle-income countries (Arbyn et al., 2020). Cervical cancer treatment has become a multidisciplinary effort with gynaecologic oncologists, medical oncologists, radiation oncologists, radiologists and pathologists in recent decades (Rose et al., 1999). The strategy is to vaccinate 90% of girls by the age of 15, screen 70% of women at the appropriate ages for cervical disease using highly sensitive tests for human papillomavirus (HPV) infection and treat 90% of women with cervical disease (WHO, 2020). This could reduce the cervical cancer incidence to fewer than 4 cases per 100,000 women per year. This review provides an overview of the incidence, risk factors, aetiology, clinical presentation, diagnosis and management of cervical cancer. It also describes the recent advances in prevention and the impact of multidisciplinary involvement and global initiatives to reduce the impact of this preventable disease.

1.1.1 Pathogenesis and Role of HPV Infection: Cervical cancer develops through a multistep process that starts with infection by high-risk HPV. HPV is an epithelial DNA virus that is transmitted sexually. Although the majority of infections are cleared spontaneously by the host immune response, persistent infection with high-risk types of HPV can progress to the formation of precancerous cervical lesions and cervical cancer (Wang et al., 2024). Of the many HPV strains, high-risk HPV 16 and HPV 18 strains are most commonly associated with cervical cancer. These high-risk viruses can also integrate their DNA into the host cell genome, leading to disruption of cell regulatory pathways and transformation of the host cell (Doorbar et al., 2022). The viral oncogenes E6 and E7 are particularly important in this context as they target and disrupt key tumour suppressor proteins, such as p53 and retinoblastoma (Rb). Inactivation of these proteins results in deregulated cell growth, chromosomal instability and accumulation of mutations that drive the development of cancer (Wang et al., 2024). Emerging research has also shown that other pathways, such as epigenetic changes, immune evasion, and signalling pathway disruptions, are also involved. These play a role in the transformation from precancerous to

invasive cancer and offer new opportunities for treatment.

1.1.2 Natural History and Disease Progression: Cervical cancer progression occurs through a series of precancerous lesions called cervical intraepithelial neoplasia (CIN). These are graded according to the degree of abnormal changes in the epithelium. CIN1 is a low-grade dysplasia that may be caused by temporary HPV infection. These lesions tend to regress without treatment. CIN2 and CIN3 are moderate to severe dysplasia and have an increased risk of progression to invasive cervical cancer if not treated (Ronsini et al., 2022). The natural history of cervical cancer, from HPV infection to invasive cancer, is slow, and can take many years or decades. This latency period offers an opportunity for early detection and treatment through screening. But without screening and treatment, high-grade lesions can develop into invasive cancer, resulting in substantial disease burden and death. The progression of the cervical disease is influenced by a range of factors including immune status, co-infections, genetic and environmental factors.

1.1.3 Importance of Early Detection and Screening: The early detection of cervical cancer is crucial for better prognosis and survival (Doorbar et al., 2022). Early detection through screening programs helps to detect precancerous cervical lesions before they develop into invasive cancer, enabling early treatment. Traditional cytology screening (the Pap smear) has been in practice for many years and has greatly decreased cervical cancer rates in developed nations. But it has low sensitivity, prompting the emergence of more sophisticated screening techniques such as human papillomavirus (HPV) DNA testing (Fontham et al., 2023). HPV testing is more sensitive and enables the detection of infections at an earlier stage, facilitating prevention. Moreover, molecular diagnostic techniques, such as biomarker testing, have enhanced the sensitivity and specificity of screening (Stanciu et al., 2023). However, barriers still exist in the delivery of screening programs in resource-poor communities. Novel screening methods like self-sampling and point-of-care tests are being investigated to enhance screening rates.

2. Pathogenesis and Molecular Mechanism

2.1 HPV Infection and Cellular Changes: Cervical cancer begins with an infection of the cervical epithelium, usually the transformation zone, by a high-risk human papillomavirus (HPV). HPV penetrates the basal cells through micro abrasions and infects undifferentiated cells where it persists (Schiffman et al, 2016). During

productive infections, HPV replicates episomal without integrating into the host genome, resulting in benign lesions which can regress. However, in persistent infections with high-risk HPV, the viral DNA integrates with the host genome, which is crucial in cancer development (McBride, 2017). This disrupts viral E2 gene, a repressor of oncogenes E6 and E7. This results in deregulated expression of these genes and cell cycle dysregulation and DNA damage within the host cell (Moody & Laimins 2010). There is also recent evidence that HPV infection also alters host cell signalling pathways, including PI3K/AKT and Wnt/β-catenin to enhance cell survival, growth and block apoptosis (Wang et al., 2024). Finally, persistent HPV infection causes local inflammation and production of reactive oxygen species, promoting DNA damage and tumour development.

2.2 Precancerous Lesions (CIN Stages): The development of cervical cancer is characterised by a sequence of precancerous changes, cervical intraepithelial neoplasia (CIN). These are graded based on the extent of abnormal changes in cells of the epithelium, and are progressive steps in cervical cancer development (Arbyn et al., 2020). Low-grade CIN (CIN1 or mild dysplasia) is where the abnormal cells are limited to the lower third of the epithelium. It may be the result of a transient HPV infection and is likely to regress. CIN2, or moderate dysplasia, affects up to two-thirds of the epithelium and is more likely to progress. CIN3, or severe dysplasia/carcinoma in situ, involves the full thickness of the epithelium and is very likely to progress to invasive cancer (Bhatla et al., 2019). CIN progression to invasive cancer is complex, with factors including persistence of the HPV infection, the patient's immune system and genetics. While low-grade lesions are known to regress, high-grade lesions are persistent and progressive, and require prompt diagnosis and treatment (Doorbar et al., 2012). Recent reports have also suggested molecular markers of CIN progression, including p16INK4a expression and proliferation markers, which help to detect high-grade lesions and distinguish them from benign lesions (Wang et al., 2024).

2.3 Oncogene Activation (Role of E6 and E7 Proteins): Cervical cancer is caused by HPV through the actions of HPV oncoproteins E6 and E7, which interfere with tumour suppressors. They disrupt cell cycle regulation, leading to uncontrolled growth and mutation (Moody & Laimins, 2010). E6 protein binds to and degrades the tumour suppressor p53 protein, which responds to DNA damage and promotes cell

death. This allows the survival and growth of damaged cells, leading to mutation (McBride, 2017). The E7 protein, on the other hand, deactivates the retinoblastoma (Rb) protein, which is responsible for regulating the transition from G1 to S phase in the cell cycle. This enables the cell cycle to progress, leading to enhanced cell growth (Schiffman et al., 2016). Besides these classic mechanisms, recent studies highlight other oncogenic pathways that are triggered by HPV, including telomerase activation, epigenetic reprogramming and immune evasion. HPV-infected cells can escape immune surveillance through the suppression of antigen presentation and the change in cytokine signalling, leading to persistent infection and tumour growth (Stanley, 2012). Furthermore, the cervical cancer tumour microenvironment plays an important role. Inflammatory responses, angiogenesis and stromal cell interactions create a supportive microenvironment for tumour growth and invasion. This has led to new treatment strategies for cervical cancer, such as targeted therapies and immunotherapy (Wang et al., 2024).

2.4 Role of Human Papillomavirus (HPV): High-Risk Strains (HPV-16 and HPV-18): Human papillomavirus (HPV) infection is the major cause of cervical cancer, and is one of the best-studied virus-induced cancers. HPV-16 and HPV-18 are the most oncogenic types of HPV, and are responsible for the majority of cervical cancers globally (de Martel et al., 2017). HPV, which spreads through sexual transmission, infects basal cervical epithelial cells, especially in the transformation zone. While most HPV infections are cleared, persistent infection with high-risk types is closely linked to a high risk of cervical precancerous lesions and cervical cancer (Cohen et al., 2019). High risk HPV types are found worldwide, but the key role of HPV in cervical cancer development has enabled the development of vaccines that reduce infection and cancer risk (Bruni et al., 2019).

Mechanism of HPV-Induced Carcinogenesis: The oncogenic potential of HPV is mediated through its ability to disrupt host cellular regulatory pathways. After infection, the viral genome may become integrated into the host genome, forming a permanent source for the expression of the viral oncogenes, which disrupt the cell cycle (McBride, 2017). The E6 protein induces degradation of the tumour suppressor protein p53, disrupting apoptosis and DNA repair pathways, and the E7 protein disrupts the retinoblastoma (Rb) protein, resulting in unregulated cell growth (Moody & Laimins, 2010). This leads to DNA instability and mutation, leading to transformation into cancer.

Progress to cervical cancer following HPV infection can take many years, allowing for early detection through screening (Schiffman et al., 2016).

2.5 Classification and staging

FIGO Staging System

Stage I to IV Explanation: The International Federation of Gynaecology and Obstetrics (FIGO) staging system is used for cervical cancer. It's important for treatment and outcome (Bhatla et al., 2019).

Stage I the cancer is found only in the cervix. This is typically a localised cancer that is treated by surgery and has a good prognosis (Landoni et al, 1997).

Stage II is characterised by the cancer spreading to the upper vagina but not the pelvic wall. It generally requires surgery and radiotherapy (depending on the stage) (Rose et al., 1999).

Stage III is characterised by spread of the cancer to the pelvic wall or lower third of vagina and/or lymph nodes in the region. Chemoradiation is the most common treatment but the prognosis is worse than at earlier stages (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2010).

Stage IV, where the cancer has spread to organs adjacent to the cervix (bladder and rectum) or distant organs (lungs and liver) (Tewari et al., 2014). The main aim of treatment is now palliative care (Tewari et al., 2014). The most recent changes to the FIGO staging system include the use of imaging and pathology for staging, which improves staging accuracy and allows personalised treatment (Bhatla et al., 2019).

3. Treatment and Management

3.1 Chemotherapy: Chemotherapy plays a crucial role in cervical cancer treatment, especially in conjunction with radiation or in advanced stages. The most widely used chemotherapeutic drug is cisplatin, which is the backbone of treatment regimens because of its radio sensitising effect (Rose et al., 1999). Other agents include paclitaxel, carboplatin and topotecan, which are often used in combination to enhance the effectiveness of treatment in metastatic or recurrent disease (Monk et al., 2009). Neoadjuvant chemotherapy (given prior to surgery or radiation) is also being investigated to shrink tumours and enhance surgical outcomes (Rydzewska et al., 2012). However, chemotherapy can have systemic toxicities such as nausea, myelosuppression and nephrotoxicity, which need to be carefully monitored.

3.2 Targeted Therapy and Immunotherapy: Novel treatment approaches for cervical cancer include targeted therapy and immunotherapy,

which are particularly effective for advanced and recurrent cancers. Targeted therapies, like bevacizumab, work by blocking vascular endothelial growth factor (VEGF), which prevents the formation of new blood vessels that supply tumours (Tewari et al., 2014). Immunotherapy shows promise, particularly immune checkpoint inhibitors like pembrolizumab, which have been effective in treating cervical cancer patients with PD-L1 positive tumours. These therapies boost the immune response to better recognise and kill cancer cells (Colombo et al., 2021). Other emerging strategies include therapeutic vaccines against HPV oncogenes and adoptive T-cell therapies, which seek to offer more targeted and effective therapies (Trimble et al., 2015). These new therapies represent a move towards personalised medicine, targeting specific molecular features of tumours to enhance effectiveness and minimise side effects.

4. Prevention Strategies

4.1 HPV Vaccines (Gardasil, Cervarix): HPV vaccination is the most effective primary prevention strategy against cervical cancer, as it targets the cause of the disease. HPV vaccines (Gardasil and Cervarix) vaccine against high-risk HPV types, such as HPV-16 and HPV-18, that cause cervical cancer (Harper et al., 2006). Gardasil provides cross-protection against some other HPV types that are the cause of genital warts and cancers, making it more effective. HPV vaccines are highly effective in preventing HPV infection and cervical precancerous lesions in clinical trials and in population-based studies (Paavonen et al., 2009). The vaccines are most effective when administered prior to infection (typically in early teens). As a result, many countries have introduced nationwide vaccination programs for adolescent girls (and boys in some countries) to reduce the spread of infection and achieve herd immunity (Drolet et al., 2019).

4.2 Biomarkers in Diagnosis: Recent cervical cancer studies have sought to identify novel biomarkers to help improve the screening and detection, risk stratification and disease monitoring of cervical cancer. Traditional methods of detection (Pap smear, HPV tests) are effective but not completely specific and sensitive. One such biomarker is p16INK4a, which is overexpressed in oncogenic HPV-infected cells and a good indicator of high-grade cervical lesions (Sano et al., 1998). Another important marker is Ki-67, which is a marker for cell proliferation, and is used alongside p16 (Schmidt et al., 2011). Recent research has also looked at DNA methylation markers,

which can detect epigenetic changes during cervical carcinogenesis, and provide early indications of the disease (Wentzensen et al., 2009). In addition, liquid biopsy techniques, such as circulating tumour DNA (ctDNA), are emerging as a non-invasive diagnostic approach which allows dynamic monitoring of tumour behaviour (Bettegowda et al., 2014). Artificial intelligence (AI) diagnostic technologies are also in development to increase diagnostic accuracy and reduce false positives, particularly in cytology and radiology (Esteva et al., 2017).

4.3 New Treatment Approaches: Immunotherapy and Gene Therapy: Recent years have witnessed significant progress in the development of novel therapeutic approaches for cervical cancer, particularly in advanced and recurrent cases. Immunotherapy has emerged as a promising strategy, with immune checkpoint inhibitors such as pembrolizumab demonstrating efficacy in patients with PD-L1–positive tumours (Keynote-158 Study Group, 2019). These therapies work by blocking inhibitory pathways in the immune system, thereby enhancing the body's ability to recognize and destroy cancer cells. Another important development is the use of therapeutic vaccines targeting HPV oncogenes E6 and E7, which aim to stimulate an immune response against infected cells (Trimble et al., 2015). Gene therapy approaches are also being explored, focusing on restoring tumour suppressor gene function or silencing oncogenes involved in cervical carcinogenesis (Senzer et al., 2002).

5. Significance: Cervical cancer remains one of the most important public health concerns worldwide due to its high incidence, mortality, and socioeconomic impact, particularly in low- and middle-income countries. The introduction of HPV DNA testing and cytology-based screening has significantly reduced incidence and mortality rates in developed countries, demonstrating the effectiveness of early detection programs (Fontham et al., 2023). The disease commonly affects women during their reproductive and economically productive years, resulting in psychological, social, and financial consequences for patients and their families (Ronsini et al., 2022). Research on HPV-related molecular mechanisms, including the roles of viral oncoproteins E6 and E7, has provided valuable insights into cancer biology and contributed to the development of targeted therapies and immunotherapeutic approaches (Doorbar et al., 2022).

1. Cervical cancer remains one of the leading causes of cancer-related morbidity and mortality among women

worldwide, especially in low- and middle-income countries where healthcare access is limited (Brisson et al., 2022).

2. Persistent infection with high-risk human papillomavirus (HPV), particularly HPV 16 and 18, is the primary cause of cervical cancer, making it one of the few cancers with a clearly identified viral etiology (Doorbar et al., 2022).
3. Cervical cancer is largely preventable through HPV vaccination, regular screening, and early treatment of precancerous lesions, which significantly reduce incidence and mortality rates (Fontham et al., 2023).
4. Early diagnosis through Pap smear and HPV DNA testing improves treatment success and survival outcomes by identifying cervical abnormalities before progression to invasive cancer (Stanciu et al., 2023).
5. The disease commonly affects women during their reproductive years, leading to complications such as infertility, psychological distress, and reduced quality of life (Ronsini et al., 2022).

6. Future prospects: The future outlook for reducing the global burden of cervical cancer is promising, but it will depend on consistent and well-coordinated efforts across multiple areas. One of the most important prospects lies in expanding access to HPV vaccination, especially in low- and middle-income countries where coverage is still limited. Improving affordability and awareness, along with the adoption of simplified dosing schedules, could significantly increase vaccination rates and prevent a large number of future cases. Alongside prevention, advancements in screening methods such as HPV DNA testing and the use of digital or AI-supported tools are expected to improve early detection, even in resource-constrained settings. Strengthening healthcare systems will also play a critical role, particularly by ensuring better access to diagnostic services, treatment facilities, and trained healthcare professionals. In addition, the use of digital health platforms and mobile-based interventions may help reach remote populations more effectively. Future research is likely to focus on innovative treatment approaches, including targeted therapies and immunotherapy, which could improve survival outcomes.

7. Conclusion: Cervical cancer remains a significant global health challenge despite being one of the most preventable forms of cancer. Its strong association with HPV infection, along with the availability of effective vaccines and screening methods, provides a unique opportunity for disease

control and elimination. This review highlights the multifactorial nature of cervical cancer, including its epidemiology, aetiology, pathogenesis, clinical features, and management strategies. Early detection through screening and primary prevention through HPV vaccination are the most effective approaches to reducing disease burden. Advancements in molecular diagnostics, targeted therapies, and immunotherapy have significantly improved treatment outcomes, particularly in advanced cases. However, disparities in healthcare access and implementation of preventive measures continue to pose challenges, especially in low-resource settings. Future efforts should focus on expanding vaccination coverage, improving screening accessibility, and integrating innovative technologies into healthcare systems. With continued research and global collaboration, cervical cancer has the potential to be eliminated as a public health problem.

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