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Review Article

Cervical cancer: From bench to bedside- insights into pathogenesis, diagnosis, prevention, and therapy

Sanaz Aghajani[1], Seyed Ali Maboudi[2], Nasim Vousooghi[1,3], Iman Seyhoun[1,4], Masoumeh Majidizolbin[5], Alireza Namazi Shabestari[6], Arvin Namazi Shabestari[7], Javad Verdi[1*]

[1]Department of Applied Cell Sciences, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Nanotechnology, Tarbiat Modares University, Tehran, Iran
[3]Research Center for Cognitive and Behavioral Sciences, Tehran University of Medical Sciences, Tehran, Iran
[4]Gene, Cell & Tissue Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[5]Iranian Tissue Bank and Research Center, Tehran University of Medical Sciences, Tehran, Iran
[6]Department of Geriatrics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[7]College of Science, University of Tehran, Tehran, Iran

***Corresponding Author:** Javad Verdi, Email: jverdi49@gmail.com

Summary

Cervical cancer remains one of the most prevalent malignancies affecting women worldwide, with a particularly heavy burden in low- and middle-income countries. Persistent infection with high-risk human papillomavirus (HPV) types — most notably HPV-16 and HPV-18 — is firmly established as the primary etiological driver of this disease. This review takes a bench-to-bedside approach, examining the molecular and pathophysiological underpinnings of cervical carcinogenesis alongside the epidemiology, screening strategies, diagnostic tools, and the current treatment landscape. Special attention is given to recent progress in immunotherapy, targeted treatments, and prophylactic vaccines, as well as the growing body of research on exosome-based diagnostics and cell-based therapies. We also address persistent challenges that complicate global disease management — from inadequate access to vaccination in resource-limited settings to the emergence of therapeutic resistance. By bringing together insights from basic and clinical research, this article aims to bridge the gap between laboratory discovery and patient care in the ongoing fight against cervical cancer.

Keywords: Cervical cancer, Human papillomavirus (HPV), Cisplatin, Targeted therapy, Exosome

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Introduction

Cervical cancer ranks among the leading causes of cancer-related death in women globally, and the disparity between high-income and low-income countries remains stark. The World Health Organization reports that more than 500,000 new cases are diagnosed every year, with a significant proportion presenting at advanced stages — a reflection of inadequate screening infrastructure in many parts of the world.[1,2] Persistent infection with high-risk HPV types, particularly HPV-16 and HPV-18, has long been recognized as the central etiological factor.[3]

The past two decades have brought remarkable advances in our understanding of cervical carcinogenesis at the molecular level. These insights have informed the development of HPV vaccines and opened the door to novel therapeutic strategies, including immunotherapy and targeted agents. Yet substantial challenges persist: vaccine coverage remains uneven, screening access is limited in many regions, and a meaningful subset of patients continues to develop resistance to standard treatments.[4,5]

This review synthesizes current knowledge across the full spectrum of cervical cancer, from epidemiology and molecular pathogenesis to diagnostic innovation and emerging therapies, to provide a clinically meaningful, up-to-date resource for researchers and practitioners alike.

Epidemiology and Risk Factors

Global Burden

Cervical cancer is the fourth most common cancer among women worldwide and a significant contributor to cancer mortality on a global scale. In 2020, the World Health Organization documented over 604,000 new cases, with approximately 342,000 deaths attributable to the disease.[6] The regional distribution is deeply unequal — more than 85% of cases occur in low- and middle-income countries, where both HPV vaccination coverage and access to screening programs remain inadequate. Even in countries with comparatively lower baseline incidence, such as Iran, an upward trend has been observed in recent years, particularly among younger women.[7,8]

Risk Factors

The central risk factor for cervical cancer is persistent infection with high-risk HPV strains, particularly HPV-16 and HPV-18. However, HPV infection alone is generally insufficient to drive carcinogenesis — several co-factors are known to facilitate disease progression, including[9, 10]: High-risk sexual behavior, including early onset of sexual activity and multiple partners, increases exposure to HPV. Beyond that, Tobacco smoking impairs local immune defenses and introduces carcinogens that directly damage cervical DNA. Immunosuppression — whether from HIV infection or prolonged immunosuppressive therapy — substantially elevates risk. Multiple full-term pregnancies are associated with hormonal and structural changes at the cervix that may enhance susceptibility. Long-term use of oral contraceptives (beyond five years) has been linked to a modest increase in risk in several studies. Finally, host genetic factors — including certain HLA subtypes and immune response gene variants — may influence susceptibility to persistent HPV infection and subsequent malignant transformation.[11-13]

Understanding how these cofactors interact with HPV infection is essential for refining risk stratification and designing more effective prevention strategies.

Pathophysiology and Molecular Mechanisms

Cervical cancer arises, in the vast majority of cases, from long-standing infection with high-risk HPV types. While most HPV infections are transient and resolved by a competent immune response, a subset of individuals fails to clear the virus. In these cases, persistent infection leads to premalignant changes in the cervical epithelium that, over time, may progress to invasive carcinoma.[14,15]

HPV: Classification, Structure, and Biology

HPV belongs to the Papillomaviridae family and is classified as a Group I virus in the Baltimore system — meaning it encodes a double-stranded circular DNA genome of approximately 8,000 base pairs.[16] The virion itself is small (roughly 55 nm in diameter), non-enveloped, and assembled around an icosahedral protein capsid.

The HPV capsid is composed of two proteins: L1, the major structural protein that forms the outer shell and serves as the primary target for currently available vaccines; and L2, a minor protein that facilitates viral entry into host cells.[17] The viral genome is organized into early genes (E1, E2, E4–E7) responsible for replication and cellular transformation, and late genes (L1 and L2) encoding the capsid proteins. A non-coding long control region (LCR) regulates viral gene expression.[18,19]

The HPV life cycle is closely tied to the differentiation state of the epithelial cells it infects. The virus initially gains entry into basal epithelial cells at sites of microabrasion — commonly the cervical transformation zone — by binding heparan sulfate proteoglycans on the cell surface. Once internalized, the viral DNA is maintained as an extrachromosomal episome in undifferentiated basal cells. As infected cells differentiate, late viral genes are activated, capsid proteins are produced, and mature virions are shed from the epithelial surface. In persistent infections, however, the viral genome may integrate into the host chromosome — an event that disrupts the regulatory E2 gene and leads to unrestrained expression of the oncoproteins E6 and E7.[18,20]

Unlike RNA viruses such as HIV and hepatitis C, which accumulate mutations rapidly due to error-prone replication, HPV's DNA genome is replicated with high fidelity. This stability is a critical advantage for vaccine development: the L1 protein targeted by licensed vaccines (e.g., Gardasil, Cervarix) is structurally conserved, enabling durable and broadly protective immune responses.[21,22]

Oncogenic Mechanisms: E6 and E7

The oncogenic potential of high-risk HPV rests primarily on two viral proteins — E6 and E7 — which systematically dismantle the host cell's tumor suppressor machinery. E6 binds to and promotes the proteasomal degradation of p53, the cell's principal guardian against DNA damage and aberrant proliferation. By neutralizing p53, E6 impairs apoptosis and permits the accumulation of genetic mutations that would otherwise trigger programmed cell death.[23] E7, meanwhile, targets the retinoblastoma protein (pRb), whose normal function is to restrain cell cycle entry. By inactivating pRb, E7 releases transcription factors that drive uncontrolled cellular proliferation.[24]

These disruptions are compounded by a range of epigenetic alterations — including aberrant DNA methylation — and by the genomic instability that follows viral integration. The net effect is a progressive transition from low-grade cervical intraepithelial neoplasia (CIN I) through high-grade dysplasia (CIN II–III) to invasive carcinoma.[25,26] The pathophysiology and molecular mechanism of the HPV virus action are shown in Figure 1.

Molecular Biomarkers

The E7-driven inactivation of pRb results in compensatory overexpression of $p16^{IRP4a}$ — a cyclin-dependent kinase inhibitor that has become a widely used surrogate marker of high-risk HPV activity in pathological assessment. Concurrent overexpression of the proliferation marker Ki-67 further supports malignant transformation and has diagnostic utility in equivocal cytological specimens.[27,28]

Beyond these established markers, emerging genomic platforms — including RNA sequencing and DNA methylation profiling — are expanding the repertoire of molecular signatures available for early detection and for identifying patients likely to benefit from specific targeted therapies.

Diagnosis

Early-stage cervical cancer carries a substantially better prognosis than advanced disease, making robust screening and timely diagnostic workup central to

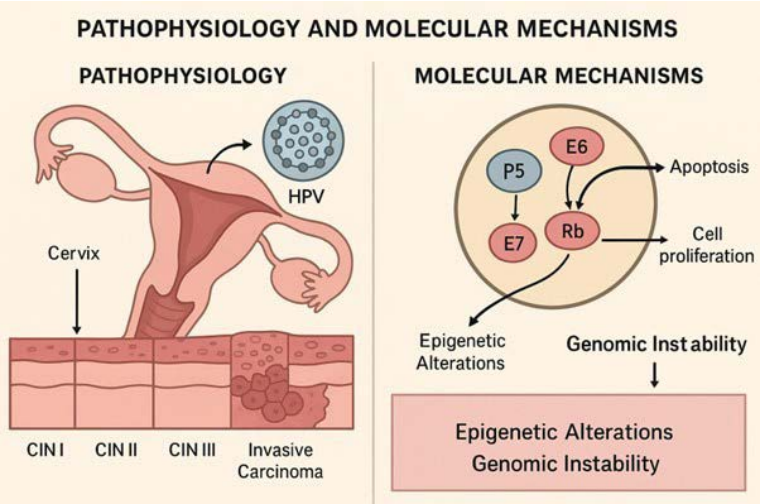

Figure 1. Overview of the pathophysiology of HPV associated cervical cancer. The schematic illustrates HPV infection of cervical epithelial cells, viral genome integration, and the expression of the viral oncoproteins E6 and E7. These oncoproteins disrupt key tumor suppressor pathways (p53 and pRb), leading to loss of cell cycle control, genomic instability, and progressive transformation from normal epithelium to cervical dysplasia and invasive carcinoma

reducing mortality. The diagnostic pathway encompasses three stages: population-level screening, follow-up investigation of abnormal findings, and formal disease staging.

1. Screening

Two primary modalities underpin cervical cancer screening: cytological examination (the Pap smear) and HPV DNA testing. The Pap smear identifies abnormal cellular morphology indicative of dysplasia, while HPV DNA testing directly detects high-risk viral genotypes with greater sensitivity. Co-testing — using both modalities simultaneously — offers the highest diagnostic accuracy and is increasingly endorsed by contemporary screening guidelines.[29,30] (Table 1)

2. Follow-Up Investigations

When screening identifies abnormal findings, further evaluation is required to characterize the lesion and guide management. Colposcopy — a magnified visual examination of the cervix with acetic acid application — is the standard next step, typically combined with targeted biopsy of suspicious areas. Histopathological analysis of biopsy specimens remains the gold standard for confirming CIN or invasive carcinoma. Where lesions are located within the endocervical canal, endocervical curettage or endoscopy may be required to obtain adequate tissue.[31,32]

3. Staging

Accurate staging is indispensable for treatment planning. The FIGO (International Federation of Gynecology and Obstetrics) 2018 staging system is internationally adopted and incorporates radiological findings — a significant update from earlier versions.[33]

Staging investigations typically include a pelvic examination, pelvic MRI or CT to assess local disease, and PET-CT to evaluate for distant metastatic spread.[34-36]

The FIGO 2018 classification system provides a comprehensive framework for the staging of cervical cancer, facilitating accurate diagnosis and treatment planning.[37,38]

Stage I designates disease confined to the cervix, with further subdivision into:

- **Stage IA**: Microscopic invasion characterized by IA1 (depth ≤ 3 mm) and IA2 (depth > 3 mm to ≤ 5 mm).
- **Stage IB**: Clinically visible or larger lesions, categorized as follows:
  - IB1: Lesions ≤ 2 cm
  - IB2: Lesions > 2 cm to ≤ 4 cm
  - IB3: Lesions > 4 cm

Stage II indicates that the disease has extended beyond the cervix without involving the pelvic wall or lower vagina, further divided into:

- **Stage IIA**: Involvement of the upper vagina
- **Stage IIB**: Involvement of the parametrium

Stage III reflects a more advanced disease state, with spread to the pelvic wall, lower vagina, or pelvic lymph nodes, delineated as:

- IIIA: Extension to the lower vagina
- IIIB: Involvement of the pelvic wall or resultant hydronephrosis (swelling of the kidney due to urine buildup)
- IIIC: Involvement of pelvic or para-aortic lymph nodes

Stage IV represents the most advanced disease, categorized by either involvement of adjacent pelvic organs (IVA) or distant metastases (IVB). These classifications highlight the urgency for early and accurate diagnosis and intervention.

Regarding screening methods for cervical cancer, the following are notable for their effectiveness:

- **Pap Smear (Cytology)**: Sensitivity ranges from 55% to 80%, with specificity between 90% and 97%. This method remains a cornerstone for detecting cellular abnormalities and is widely implemented across diverse healthcare settings.
- **HPV DNA Testing**: Sensitivity is reported at 90% to 97%, and specificity is between 84% and 90%. This test

Table 1. Comparative Overview of Cervical Cancer Screening Methods

Feature	Pap Smear (Cytology)	HPV DNA Testing	Co-testing (Pap + HPV)
Test Type	Cytological examination of cervical cells	Detection of high-risk HPV DNA	Combination of cytology and HPV DNA testing
Sensitivity for CIN2 +	Moderate (~55–70%)	High (~90–95%)	Very high (> 95%)
Specificity	High	Moderate	High
Advantages	Low-cost, widely available, well-established	High sensitivity for high-grade lesions	Early detection, reduced frequency of testing
Limitations	The risk of false negatives requires frequent testing	More expensive, potential false positives	Higher cost requires more resources
Recommended Screening Interval	Every 3 years (ages 21–65)	Every 5 years (ages ≥ 30)	Every 5 years (ages ≥ 30)
Best Use Setting	Resource-limited settings	Developed healthcare systems	Optimal in high-resource settings

Note: CIN2 + = cervical intraepithelial neoplasia grade 2 or higher. Current guidelines increasingly favor HPV-based primary screening from age 25–30.

identifies high-risk HPV types and is more sensitive than cytology alone, making it essential for early detection.

- **Co-Testing (Pap + HPV) **: This method demonstrates a sensitivity of 95% to 99% and a specificity of approximately 85%. By combining both tests, this approach enhances diagnostic accuracy and is increasingly endorsed by contemporary clinical guidelines.

- **Visual Inspection (VIA)**: Sensitivity ranges from 60% to 85%, with specificity between 70% and 85%. VIA is particularly beneficial in low-resource settings, requiring no laboratory infrastructure, thereby improving access to screening.

In conclusion, understanding the FIGO staging system and the various screening methods is crucial for optimizing cervical cancer management, ultimately enhancing patient outcomes through timely diagnosis and effective interventions.[38]

Treatment

Treatment selection in cervical cancer depends on disease stage, histopathological subtype, patient performance status, and, increasingly, molecular tumor characteristics. The main therapeutic modalities are surgery, chemotherapy, radiotherapy, and an expanding array of targeted and immune-based approaches.[39]

Early-Stage Disease

For patients with early-stage disease (stages IA to IB1), surgical resection is generally the preferred approach. Options include conization and a loop electrosurgical excision procedure (LEEP) for micro-invasive disease, or radical hysterectomy with lymph node dissection for larger stage IB1 lesions. In carefully selected younger patients who wish to preserve fertility, radical trachelectomy — with removal of the cervix while preserving the uterine body — offers a viable alternative.[40,41]

Locally Advanced Disease

The standard of care for locally advanced cervical cancer (stage II and beyond) is concurrent platinum-based chemoradiation: external beam radiotherapy (EBRT) combined with weekly cisplatin, followed by intracavitary brachytherapy. This approach has demonstrated robust survival benefits compared with radiotherapy alone, and remains the backbone of treatment for this population.[42,43]

Emerging and Future Therapies

Recent years have seen a significant expansion in the therapeutic armamentarium for recurrent, persistent, or metastatic cervical cancer:

Immunotherapy has emerged as one of the most consequential advances. Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis — particularly pembrolizumab and cemiplimab — have demonstrated meaningful survival benefits in patients with recurrent or metastatic disease. Pembrolizumab is now approved for PD-L1-positive tumors, while cemiplimab has shown superior outcomes compared with standard chemotherapy in the second-line setting. Response rates are further enhanced in tumors with high microsatellite instability (MSI-H) or elevated tumor mutation burden (TMB).[44]

Targeted therapy with bevacizumab — an anti-VEGF monoclonal antibody — has become a standard addition to platinum-based chemotherapy in patients with recurrent or metastatic disease, following demonstration of improved overall survival in the GOG 240 trial.[45]

Cell-based therapies, including CAR-T cells engineered to recognize HPV antigens and tumor-infiltrating lymphocyte (TIL) infusion, are under active clinical investigation for refractory disease. Therapeutic HPV vaccines, designed to elicit cytotoxic T-cell responses against E6 and E7, are also being explored in combination with other agents.[46,47]

Nanotechnology-based drug delivery systems — including lipid nanoparticles and polymeric nanocarriers — are being developed to improve the pharmacokinetics of existing cytotoxics, reduce systemic toxicity, and enable targeted delivery to tumor tissue.[48]

Bench Research and Preclinical Models

Progress in clinical cervical cancer management is inextricably linked to advances in laboratory research. Preclinical models are essential for studying tumor biology, identifying therapeutic targets, and evaluating candidate agents before clinical translation.[49]

Animal models, particularly transgenic and xenograft mouse systems, remain the workhorses of HPV research.

Transgenic mice expressing HPV-16 E6 and E7 develop spontaneous cervical lesions that faithfully recapitulate the human disease course, providing platforms for testing both preventive and therapeutic strategies. Xenograft models — in which human cervical cancer cells are implanted into immunodeficient mice — allow preclinical evaluation of novel drug candidates.[50]

Three-dimensional cervical organoid cultures represent a significant methodological advance. Derived from patient tumor tissue, these structures recapitulate the architectural complexity of the cervical epithelium and tumor microenvironment more faithfully than conventional two-dimensional cell lines. Organoids are increasingly used for drug sensitivity testing and immunotherapy evaluation, and may ultimately help guide individualized treatment decisions.[51]

High-dimensional omics platforms — encompassing genomics, transcriptomics, proteomics, and metabolomics — are being applied to cervical cancer to chart the molecular landscape of the disease, identify novel biomarkers, characterize resistance mechanisms, and stratify patients for targeted therapies.[52]

Cell-Based Therapies and Extracellular Vesicles

Cell-Based Therapies

Cell therapy has attracted growing interest as a treatment strategy for advanced and recurrent cervical cancer, particularly in cases where conventional therapies have failed. Several cell types have been investigated as therapeutic vehicles. Tumor-infiltrating lymphocytes (TILs) expanded from cervical tumor specimens and reinfused into patients have demonstrated the capacity to recognize and eliminate HPV-associated antigen targets, including the E6 and E7 oncoproteins. A landmark study by Stevanović and colleagues at the National Cancer Institute reported an overall response rate of 44% in patients treated with TIL therapy targeting HPV antigens, including one case of complete regression in metastatic disease.[53]

CAR-T cell therapy, in which T cells are genetically engineered to express chimeric antigen receptors targeting HPV-specific epitopes, is in active preclinical development. Early-phase clinical trials have demonstrated safety and preliminary efficacy signals, though the immunosuppressive nature of the tumor microenvironment presents a significant barrier.[54]

Natural killer (NK) cells, both autologous (from the same individual) and allogeneic (from a donor), have shown the ability to kill HPV-positive cervical cancer cells in laboratory studies. They are currently being evaluated as potential off-the-shelf therapeutic options. Another approach involves dendritic cell vaccines, where dendritic cells derived from patients are exposed to HPV antigens outside the body (ex vivo) to stimulate specific T-cell responses against the virus.[55,56]

Despite these promising signals, meaningful clinical translation remains challenged by the immunosuppressive tumor microenvironment, antigen escape mechanisms, and the difficulty of achieving adequate trafficking of adoptively transferred cells to tumor sites.

Extracellular Vesicles and Exosomes

Extracellular vesicles (EVs) — and in particular the nano-sized subset known as exosomes (30–150 nm in diameter) — have emerged as important mediators of intercellular communication in the tumor microenvironment. Secreted by virtually all cell types, exosomes carry a complex molecular cargo including proteins, lipids, mRNAs, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs) that reflect the physiological state of their cell of origin.[57]

Role in Tumor Progression

In cervical cancer, tumor-derived exosomes serve as vehicles for oncogenic cargo. HPV positive tumor cells release exosomes carrying E6/E7 mRNA transcripts, immunomodulatory microRNAs such as miR-21 and miR-146a, and surface molecules that suppress anti-tumor immune responses. These vesicles educate surrounding stromal and immune cells, remodel the tumor microenvironment to favor immune evasion, and may facilitate premetastatic niche formation.[58,59]

Diagnostic and Prognostic Potential

The exosomal cargo offers a rich and accessible source of biomarkers for non-invasive disease monitoring. Because exosomes can be isolated from blood, urine, and cervical secretions, they are well-suited to liquid biopsy applications — enabling longitudinal sampling without repeat tissue biopsy. Several exosomal miRNAs have been identified as diagnostically informative in cervical cancer. miR-21 is consistently upregulated in exosomes from cervical cancer patients and is associated with tumor aggressiveness, invasion, and immune modulation. Elevated levels of miR-146a, miR-200a, and miR-221 have also been detected in plasma-derived exosomes from affected patients. Conversely, miR-34a — which functions as a tumor suppressor — is frequently downregulated in cervical cancer-derived exosomes. These signatures have demonstrated high diagnostic accuracy (AUC > 0.85 in some studies) and may help distinguish between normal cervical tissue, premalignant lesions, and invasive cancer.[60,61] Table 2 lists some of the contents of exosomal miRNAs and their role in the diagnosis and treatment of cervical cancer

At the protein level, cervical cancer-derived exosomes are enriched for survivin — an antiapoptotic protein whose exosomal expression correlates with poor prognosis — as well as heat shock proteins HSP70 and HSP90, which promote immune evasion. Detection of HPV related oncoproteins E6 and E7 within exosomal fractions opens the intriguing possibility of non-invasive HPV subtype identification and treatment monitoring.[62,63]

Among lncRNAs, HOTAIR and MALAT1 are consistently elevated in cervical cancer-derived exosomes, particularly at advanced stages. Elevated exosomal levels

Table 2. Exosomal miRNA Content in Cervical Cancer: Diagnostic, Prognostic, and Therapeutic Relevance

miRNA / lncRNA	Expression	Sample Type	Clinical Role	Key Association
miR-21	Upregulated	Plasma	Early diagnosis	Tumor progression, immune modulation
miR-146a-5p	Upregulated	Plasma	Early diagnosis	Aggressive tumor behavior
miR-151a-3p	Upregulated	Plasma	Early diagnosis	Linked to invasion
miR-125a-5p	Downregulated	Plasma	Prognosis	Poor prognosis marker
MEG3 (lncRNA)	Downregulated	Plasma	Prognosis	Poor prognosis; drug resistance
miR-663b	Upregulated	Exosomal cells	Therapeutic target	Metastasis; EMT promotion

EMT = epithelial–mesenchymal transition.

of oncogenic mRNAs — including MYC and VEGFA transcripts — may additionally serve as indicators of tumor aggressiveness and metastatic potential.[64,65]

Therapeutic Applications of Exosomes

Beyond their diagnostic utility, engineered exosomes are being explored as delivery vehicles for therapeutic payloads. Their natural membrane composition confers inherent biocompatibility and the ability to traverse biological barriers that limit conventional nanoparticles. Proof-of-concept studies have demonstrated that exosomes loaded with siRNA targeting survivin — an oncogene critical for tumor cell survival — can effectively suppress tumor growth in cervical cancer xenograft models while minimizing off-target toxicity.[66]

Exosomes derived from activated dendritic cells or other immune effector cells have also been investigated as immunotherapy agents. These vesicles can present HPV-related antigens to T cells and stimulate tumor-specific cytotoxic responses, offering a cell-free alternative to dendritic cell vaccine approaches.[67,68] Ginger-derived exosome-like nanoparticles engineered to carry survivin siRNA represent another creative application, demonstrating anti-tumor efficacy in preclinical cervical cancer models.[58]

Standardization of exosome isolation and characterization methods remains one of the principal barriers to clinical translation. Techniques including ultracentrifugation, size exclusion chromatography, and precipitation-based approaches yield preparations of varying purity and reproducibility. Multi-center validation studies using harmonized protocols will be essential before exosomal biomarkers can be integrated into routine clinical practice.[69]

Emerging Cellular, Exosomal, and Immunotherapeutic Approaches: Key Developments

The past decade has witnessed an accelerating pace of innovation in cervical cancer treatment, with cell-based therapies, exosome-mediated strategies, and immune checkpoint blockade all contributing to an evolving therapeutic landscape.

Cell-Based Therapy

The clinical potential of adoptive TIL therapy for cervical cancer was compellingly demonstrated in work by Stevanović et al. at the National Cancer Institute. In their published study in the Journal of Clinical Oncology, TILs targeting HPV oncoproteins E6 and E7 achieved an overall response rate of 44% in heavily pre-treated patients with metastatic disease, including one complete response that was durable over follow-up.[53,54]

Computational modeling has complemented these clinical findings. In 2020, Cho, Wang, and Levy demonstrated that the timing and dose of interleukin-2 co-administration critically influence the expansion and anti-tumor activity of TCR-engineered T cells targeting HPV antigens, providing a framework for optimizing combination cell therapy regimens.[70]

CAR-T cell therapy for cervical cancer remains largely in preclinical development, though early-phase studies have shown encouraging safety profiles and laid the groundwork for ongoing investigation.[71]

Exosome Therapy

Research into exosome-based therapeutic strategies for cervical cancer has accelerated in recent years. Preclinical work has established the feasibility of using engineered exosomes to deliver chemotherapeutic agents — such as doxorubicin and paclitaxel — directly to cervical cancer cells, enhancing cytotoxic efficacy while limiting systemic exposure.[71,72]

Exosome-based vaccine platforms (so-called 'Dexosomes') derived from dendritic cells have successfully elicited cytotoxic CD8+T-cell responses against HPV-transformed cells in vitro, offering a promising direction for therapeutic vaccination. In parallel, Ayurvedic formulations such as Panchavalkala have been shown to modulate exosome secretion from HPV16/18-positive cells, with potential implications for immunomodulatory therapy.[73]

siRNA delivery via engineered exosomes — targeting oncogenes such as survivin — has demonstrated effectiveness in downregulating pro-survival pathways and sensitizing tumor cells to chemotherapy in xenograft models.[74]

Immunotherapy

The field of cervical cancer immunotherapy has arguably seen the most consequential clinical advances in recent years. Data presented by Melief and colleagues showed that robust HPV-specific T-cell responses following chemo-immunotherapy were strongly associated with prolonged overall survival, reinforcing the importance of

durable immune activation as a treatment endpoint.[75]

Cemiplimab, a PD-1 inhibitor, demonstrated a significant survival advantage over standard chemotherapy in a Phase III trial led by Monk and colleagues in patients with recurrent or metastatic cervical cancer — establishing it as a new standard of care in this setting [85]. More recently, Chen et al. reported high complete response rates and prolonged progression-free survival with camrelizumab combined with concurrent chemoradiation as neoadjuvant therapy in locally advanced disease.[76]

Therapeutic HPV vaccines have also generated notable results in combination strategies. PDS0101 — a lipid nanoparticle-based HPV-16 vaccine — combined with bintrafusp alfa (a bifunctional PD-L1/TGF-β inhibitor) and IL-12 achieved a 62.5% objective response rate in treatment-naive patients in a trial published in JAMA Oncology, pointing toward a new paradigm of combinatorial immunotherapy for this disease.[77]

Future Directions and Challenges

Despite the breadth of progress reviewed above, formidable obstacles continue to impede the equitable control of cervical cancer worldwide. Access to HPV vaccination remains profoundly inequitable. In many low-income countries, the logistical and financial barriers to implementing national vaccination programs mean that the populations carrying the highest disease burden are often the least protected.[78]

Bridging this gap will require coordinated international funding, cold-chain infrastructure, and community engagement strategies tailored to diverse cultural contexts. Drug resistance — both to platinum-based chemotherapy and, increasingly, to checkpoint immunotherapy — is an area of active concern. Understanding the molecular mechanisms underlying resistance, whether through antigen downregulation, upregulation of alternative immune checkpoints, or alterations in the tumor microenvironment, is essential for developing effective second-line strategies.[79]

The need for better biomarkers cuts across all aspects of cervical cancer management: earlier detection, more accurate prognostication, real-time monitoring of treatment response, and patient selection for targeted therapies. Exosomal profiling and advanced liquid biopsy platforms hold genuine promise in this regard, but require rigorous clinical validation before routine adoption.[69]

Artificial intelligence is beginning to demonstrate its potential in cervical cancer screening and diagnosis — from automated cytology reading to risk stratification using multimodal data. Thoughtful integration of AI tools into clinical workflows, with attention to equity, interpretability, and data quality, may substantially enhance the reach and efficiency of screening programs in under-resourced settings.[80-82]

Finally, the translation of cell-based and exosome-mediated therapies from the bench to the bedside will require concerted effort to address scalability, manufacturing standardization, and cost. These approaches hold genuine transformative potential — particularly for patients with refractory or metastatic disease, but realizing that potential will demand both scientific rigor and pragmatic thinking about implementation at scale.[83,84]

Discussion

This review has traced cervical cancer from its molecular origins to its clinical management, underscoring both the remarkable advances of recent decades and the challenges that remain. The central role of HPV in disease pathogenesis is now well established, and the molecular mechanisms by which E6 and E7 subvert host tumor suppressor function have informed biomarker development, vaccine design, and the identification of therapeutic targets. Yet translating these insights into equitably distributed clinical benefit remains an unfinished task.

HPV vaccination has unequivocally reduced cervical cancer incidence in vaccinated populations — a public health success story. However, vaccination coverage remains far from universal, and the time lag between vaccination and population-level cancer reduction means that current screening strategies remain indispensable for several decades to come. Optimizing screening protocols for diverse resource settings — balancing sensitivity, cost, and logistical feasibility — is an ongoing priority.[85,86]

The immunotherapy revolution has transformed the treatment landscape for recurrent and metastatic cervical cancer. Checkpoint inhibitors have demonstrated clinically meaningful survival benefits and established themselves as a standard component of care in this setting. However, the fraction of patients who derive durable benefit remains a minority, and predictive biomarkers beyond PD-L1 expression, such as tumor mutational burden, immune gene expression profiles, and exosomal signatures, are urgently needed to guide patient selection.[40,87,88]

Cell-based therapies represent one of the most intellectually compelling frontiers in the field, yet they face formidable translational hurdles. The immunosuppressive tumor microenvironment actively impairs the function of adoptively transferred lymphocytes; antigen heterogeneity enables immune escape; and the manufacturing complexity of individualized cell products limits scalability. Strategies to address these barriers, including combination with checkpoint blockade, engineering for TME resistance, and development of allogeneic off-the-shelf products, are in active development.[87]

Exosome research has illuminated previously unappreciated dimensions of tumor biology and opened genuinely exciting possibilities for non-invasive diagnostics and targeted drug delivery. The path to clinical integration, however, requires resolution of fundamental methodological challenges, particularly the lack of standardized isolation protocols and reference materials, that currently limit the reproducibility and comparability

of findings across studies.[60,69]

Integration of artificial intelligence into diagnostic and screening workflows holds considerable promise, but must be pursued with attention to equity. AI systems trained predominantly on data from high-income settings may perform less well in the populations bearing the greatest cervical cancer burden. Prospective evaluation in low-resource environments and the development of locally validated tools are necessary steps toward responsible implementation.[81,82]

Conclusion

Cervical cancer remains an important and preventable cause of cancer-related death in women worldwide, with an impact felt most acutely in low-resource settings where access to vaccination, screening, and treatment continues to lag. The scientific community has made extraordinary strides in characterizing the molecular biology of HPV-driven carcinogenesis, validating highly effective preventive vaccines, and developing an expanding array of therapeutic strategies — from precision immunotherapy to exosome-based diagnostics and drug delivery. Yet the gap between what is scientifically possible and what is equitably accessible remains wide. Closing this gap will require not only continued investment in research, to address resistance mechanisms, validate novel biomarkers, and optimize emerging therapies — but also sustained commitment to the public health infrastructure, healthcare financing, and global partnerships needed to make prevention and treatment universally available.

As the field moves toward greater integration of basic and clinical science, personalized medicine, and digital health tools, the prospect of substantially reducing — and ultimately eliminating — cervical cancer as a major public health threat is within reach. Realizing this prospect will demand both scientific ambition and unwavering attention to equity.

Authors' Contribution

Conceptualization: Sanaz Aghajani, Javad Verdi, and Nasim Vousooghi.
Supervision: Javad Verdi.
Writing–original draft: Sanaz Aghajani, Javad Verdi, and Nasim Vousooghi.
Writing–review & editing: Sanaz Aghajani, Seyed Ali Maboudi, Nasim Vousooghi, Iman Seyhoun, Masoumeh Majidizolbin, Alireza Namazi Shabestari, Arvin Namazi Shabestari, Javad Verdi.

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During the preparation of this work, the author used ChatGPT and Grammarly to correct grammatical mistakes. After using these tools/services, the author reviewed and edited the content as needed and takes full responsibility for the publication's content.

References

1. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. Lancet 2019;393(10167):169–82. doi:10.1016/s0140-6736(18)32470-x
2. Buskwofie A, David-West G, Clare CA. A Review of Cervical Cancer: Incidence and Disparities. J Natl Med Assoc 2020;112(2):229–32. doi:10.1016/j.jnma.2020.03.002
3. Bhatla N, Singhal S. Primary HPV screening for cervical cancer. Best Pract Res Clin Obstet Gynaecol 2020;65:98–108. doi:10.1016/j.bpobgyn.2020.02.008
4. Lechner M, Liu J, Masterson L, Fenton TR. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. Nat Rev Clin Oncol 2022;19(5):306–27. doi:10.1038/s41571-022-00603-7
5. Roman BR, Aragones A. Epidemiology and incidence of HPV-related cancers of the head and neck. J Surg Oncol 2021;124(6):920–2. doi:10.1002/jso.26687
6. Shen TT, Long CY, Wu MP. Favorable cervical cancer mortality-to-incidence ratios of countries with good human development index rankings and high health expenditures. BMC Womens Health 2023;23(1):284. doi:10.1186/s12905-023-02423-y
7. Hull R, Mbele M, Makhafola T, Hicks C, Wang SM, Reis RM, et al. Cervical cancer in low and middle-income countries. Oncol Lett 2020;20(3):2058–74. doi:10.3892/ol.2020.11754
8. Bedell SL, Goldstein LS, Goldstein AR, Goldstein AT. Cervical Cancer Screening: Past, Present, and Future. Sex Med Rev 2020;8(1):28–37. doi:10.1016/j.sxmr.2019.09.005
9. Petrelli F, De Santi G, Rampulla V, Ghidini A, Mercurio P, Mariani M, et al. Human papillomavirus (HPV) types 16 and 18 infection and esophageal squamous cell carcinoma: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2021;147(10):3011–23. doi:10.1007/s00432-021-03738-9
10. Lehtinen M, Gray P, Louvanto K, Vänskä S. In 30 years, gender-neutral vaccination eradicates oncogenic human papillomavirus (HPV) types while screening eliminates HPV-associated cancers. Expert Rev Vaccines 2022;21(6):735–8. doi:10.1080/14760584.2022.2064279
11. Oyouni AAA. Human papillomavirus in cancer: Infection, disease transmission, and progress in vaccines. J Infect Public Health 2023;16(4):626–31. doi:10.1016/j.jiph.2023.02.014
12. Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. The biology and life-cycle of human papillomaviruses. Vaccine 2012;30 Suppl 5:F55–70. doi:10.1016/j.vaccine.2012.06.083
13. Hemmat N, Bannazadeh Baghi H. Association of human papillomavirus infection and inflammation in cervical cancer. Pathog Dis 2019;77(5):ftz048. doi:10.1093/femspd/ftz048
14. Ma X, Yang M. The correlation between high-risk HPV infection and precancerous lesions and cervical cancer. Am J Transl Res 2021;13(9):10830–6.
15. Luo Q, Zeng X, Luo H, Pan L, Huang Y, Zhang H, et al. Epidemiologic characteristics of high-risk HPV and the correlation between multiple infections and cervical lesions. BMC Infect Dis 2023;23(1):667. doi:10.1186/s12879-023-08634-w
16. Song G, Luo J, Zou S, Lou F, Zhang T, Zhu X, et al. Molecular classification of human papillomavirus-positive cervical cancers based on immune signature enrichment. Front Public Health 2022;10:979933. doi:10.3389/fpubh.2022.979933
17. Han F, Guo XY, Jiang MX, Xia NS, Gu Y, Li SW. Structural biology of the human papillomavirus. Structure 2024;32(11):1877–92. doi:10.1016/j.str.2024.09.011
18. Cosper PF, Bradley S, Luo L, Kimple RJ. Biology of HPV Mediated Carcinogenesis and Tumor Progression. Semin Radiat Oncol 2021;31(4):265–73. doi:10.1016/j.semradonc.2021.02.006
19. Porter VL, Marra MA. The Drivers, Mechanisms, and Consequences of Genome Instability in HPV-Driven

Cancers. Cancers (Basel) 2022;14(19):4623. doi:10.3390/cancers14194623
20. Warowicka A, Broniarczyk J, Węglewska M, Kwaśniewski W, Goździcka-Józefiak A. Dual Role of YY1 in HPV Life Cycle and Cervical Cancer Development. Int J Mol Sci 2022;23(7):3453. doi:10.3390/ijms23073453
21. Speckhart K, Williams JM, Tsai B. How DNA and RNA Viruses Exploit Host Chaperones to Promote Infection. Viruses 2021;13(6):958. doi:10.3390/v13060958
22. Ashique S, Hussain A, Fatima N, Altamimi MA. HPV pathogenesis, various types of vaccines, safety concern, prophylactic and therapeutic applications to control cervical cancer, and future perspective. Virusdisease 2023;34(2):1–19. doi:10.1007/s13337-023-00824-z
23. Makgoo L, Mosebi S, Mbita Z. Molecular Mechanisms of HIV Protease Inhibitors Against HPV-Associated Cervical Cancer: Restoration of TP53 Tumour Suppressor Activities. Front Mol Biosci 2022;9:875208. doi:10.3389/fmolb.2022.875208
24. Baba SK, Alblooshi SSE, Yaqoob R, Behl S, Al Saleem M, Rakha EA, et al. Human papilloma virus (HPV) mediated cancers: an insightful update. J Transl Med 2025;23(1):483. doi:10.1186/s12967-025-06470-x
25. Da Silva MLR, De Albuquerque B, Allyrio T, De Almeida VD, Cobucci RNO, Bezerra FL, et al. The role of HPV-induced epigenetic changes in cervical carcinogenesis (Review). Biomed Rep 2021;15(1):60. doi:10.3892/br.2021.1436
26. Liu H, Ma H, Li Y, Zhao H. Advances in epigenetic modifications and cervical cancer research. Biochim Biophys Acta Rev Cancer 2023;1878(3):188894. doi:10.1016/j.bbcan.2023.188894
27. Ishikawa M, Nakayama K, Nakamura K, Yamashita H, Ishibashi T, Minamoto T, et al. P16(INK4A) expression might be associated with a favorable prognosis for cervical adenocarcinoma via dysregulation of the RB pathway. Sci Rep 2021;11(1):18236. doi:10.1038/s41598-021-97703-8
28. Del Moral-Hernández O, Hernández-Sotelo D, Alarcón-Romero LDC, Mendoza-Catalán MA, Flores-Alfaro E, Castro-Coronel Y, et al. TOP2A/MCM2, p16(INK4a), and cyclin E1 expression in liquid-based cytology: a biomarkers panel for progression risk of cervical premalignant lesions. BMC Cancer 2021;21(1):39. doi:10.1186/s12885-020-07740-1
29. Martins TR, Levi JE. Molecular Screening for Cervical Cancer. Genes (Basel) 2025;16(9):1041. doi:10.3390/genes16091041
30. Luu XQ, Jun JK, Suh M, Oh JK, Yu SY, Choi KS. Cervical Cancer Screening, HPV Vaccination, and Cervical Cancer Elimination. JAMA Netw Open 2025;8(8):e2526683. doi:10.1001/jamanetworkopen.2025.26683
31. Benard VB, Jackson JE, Greek A, Senkomago V, Huh WK, Thomas CC, et al. A population study of screening history and diagnostic outcomes of women with invasive cervical cancer. Cancer Med 2021;10(12):4127–37. doi:10.1002/cam4.3951
32. Perkins RB, Adcock R, Benard V, Cuzick J, Waxman A, Howe J, et al. Clinical follow-up practices after cervical cancer screening by co-testing: A population-based study of adherence to U.S. guideline recommendations. Prev Med 2021;153:106770. doi:10.1016/j.ypmed.2021.106770
33. Bhatla N, Singhal S, Dhamija E, Mathur S, Natarajan J, Maheshwari A. Implications of the revised cervical cancer FIGO staging system. Indian J Med Res 2021;154(2):273–83. doi:10.4103/ijmr.IJMR_4225_20
34. Boon SS, Luk HY, Xiao C, Chen Z, Chan PKS. Review of the Standard and Advanced Screening, Staging Systems and Treatment Modalities for Cervical Cancer. Cancers (Basel) 2022;14(12). doi:10.3390/cancers14122913
35. Fischerova D, Frühauf F, Burgetova A, Haldorsen IS, Gatti E, Cibula D. The Role of Imaging in Cervical Cancer Staging: ESGO/ESTRO/ESP Guidelines (Update 2023). Cancers (Basel) 2024;16(4). doi:10.3390/cancers16040775
36. Re GL, Cucinella G, Zaccaria G, Crapanzano A, Salerno S, Pinto A, et al. Role of MRI in the Assessment of Cervical Cancer. Semin Ultrasound CT MR 2023;44(3):228–37. doi:10.1053/j.sult.2023.03.010
37. Salib MY, Russell JHB, Stewart VR, Sudderuddin SA, Barwick TD, Rockall AG, et al. 2018 FIGO Staging Classification for Cervical Cancer: Added Benefits of Imaging. Radiographics 2020;40(6):1807–22. doi:10.1148/rg.2020200013
38. Grigsby PW, Massad LS, Mutch DG, Powell MA, Thaker PH, McCourt C, et al. FIGO 2018 staging criteria for cervical cancer: Impact on stage migration and survival. Gynecol Oncol 2020;157(3):639–43. doi:10.1016/j.ygyno.2020.03.027
39. Burmeister CA, Khan SF, Schäfer G, Mbatani N, Adams T, Moodley J, et al. Cervical cancer therapies: Current challenges and future perspectives. Tumour Virus Res 2022;13:200238. doi:10.1016/j.tvr.2022.200238
40. Xu M, Cao C, Wu P, Huang X, Ma D. Advances in cervical cancer: current insights and future directions. Cancer Commun (Lond) 2025;45(2):77–109. doi:10.1002/cac2.12629
41. D'Augè TG, Di Donato V, Giannini A. Strategic Approaches in Management of Early-Stage Cervical Cancer: A Comprehensive Editorial. Clin Exp Obstet Gynecol 2024;51(10):235. doi:10.31083/j.ceog5110235
42. Ni H, Huang C, Ran Z, Li S, Kuang C, Zhang Y, et al. Targeting HPV for the prevention, diagnosis, and treatment of cervical cancer. J Mol Cell Biol 2025;16(10):mjae046. doi:10.1093/jmcb/mjae046
43. Musa FB, Brouwer E, Ting J, Schwartz NRM, Surinach A, Bloudek L, et al. Trends in treatment patterns and costs of care among patients with advanced stage cervical cancer. Gynecol Oncol 2022;164(3):645–50. doi:10.1016/j.ygyno.2021.12.028
44. Ferrall L, Lin KY, Roden RBS, Hung CF, Wu TC. Cervical Cancer Immunotherapy: Facts and Hopes. Clin Cancer Res 2021;27(18):4953–73. doi:10.1158/1078-0432.Ccr-20-2833
45. Watkins DE, Craig DJ, Vellani SD, Hegazi A, Fredrickson KJ, Walter A, et al. Advances in Targeted Therapy for the Treatment of Cervical Cancer. J Clin Med 2023;12(18):5992. doi:10.3390/jcm12185992
46. Jasrotia R, Dhanjal DS, Bhardwaj S, Sharma P, Chopra C, Singh R, et al. Nanotechnology based vaccines: Cervical cancer management and perspectives. Journal of Drug Delivery Science and Technology 2022;71:103351. doi:10.1016/j.jddst.2022.103351
47. Zheng Q, He M, Mao Z, Huang Y, Li X, Long L, et al. Advancing the Fight Against Cervical Cancer: The Promise of Therapeutic HPV Vaccines. Vaccines (Basel) 2025;13(1):92. doi:10.3390/vaccines13010092
48. Hegde YM, Theivendren P, Srinivas G, Palanivel M, Shanmugam N, Kunjiappan S, et al. A Recent Advancement in Nanotechnology Approaches for the Treatment of Cervical Cancer. Anticancer Agents Med Chem 2023;23(1):37–59. doi:10.2174/1871520622666220513160706
49. Chambers L, Haight P, Chalif J, Mehra Y, Spakowicz D, Backes FJ, et al. Bridging the Gap from Bench to Bedside: A Call for In Vivo Preclinical Models to Advance Endometrial Cancer and Cervical Cancer Immuno-oncology Research. Clin Cancer Res 2024;30(14):2905–9. doi:10.1158/1078-0432.Ccr-23-2570
50. Larmour LI, Jobling TW, Gargett CE. A Review of Current Animal Models for the Study of Cervical Dysplasia and Cervical Carcinoma. Int J Gynecol Cancer 2015;25(8):1345–52. doi:10.1097/igc.0000000000000525
51. Lõhmussaar K, Oka R, Espejo Valle-Inclan J, Smits MHH, Wardak H, Korving J, et al. Patient-derived organoids model cervical tissue dynamics and viral oncogenesis in cervical cancer. Cell Stem Cell 2021;28(8):1380–96. doi:10.1016/j.stem.2021.03.012
52. Pang G, Li Y, Shi Q, Tian J, Lou H, Feng Y. Omics sciences for cervical cancer precision medicine from the perspective of the tumor immune microenvironment. Oncol Res

2025;33(4):821–36. doi:10.32604/or.2024.053772
53. Polten R, Kutle I, Hachenberg J, Klapdor R, Morgan M, Schambach A. Towards Novel Gene and Cell Therapy Approaches for Cervical Cancer. Cancers (Basel) 2022;15(1):263. doi:10.3390/cancers15010263
54. Yu L, Lanqing G, Huang Z, Xin X, Minglin L, Fa-Hui L, et al. T cell immunotherapy for cervical cancer: challenges and opportunities. Front Immunol 2023;14:1105265. doi:10.3389/fimmu.2023.1105265
55. Gutiérrez-Hoya A, Soto-Cruz I. NK Cell Regulation in Cervical Cancer and Strategies for Immunotherapy. Cells 2021;10(11):3104. doi:10.3390/cells10113104
56. Menshenina A, Goroshinskaya I, Frantsiyants E, Moiseenko T, Verenikina E, Kaplieva I, et al. Effect of dendritic cell vaccine on blood redox status in patients with cervical cancer. Research and Practical Medicine Journal 2023. doi:10.17709/2410-1893-2023-10-1-3
57. van der Merwe M, Myburgh K, Garnis C, Towle R, Engelbrecht AM. Unravelling the role of extracellular vesicles in cervical cancer: Mechanisms of progression, resistance, and emerging therapeutic strategies. Gene 2025;957:149467. doi:10.1016/j.gene.2025.149467
58. Bhat A, Yadav J, Thakur K, Aggarwal N, Chhokar A, Tripathi T, et al. Transcriptome analysis of cervical cancer exosomes and detection of HPVE6*I transcripts in exosomal RNA. BMC Cancer 2022;22(1):164. doi:10.1186/s12885-022-09262-4
59. Dong S, Zhang Y, Wang Y. Role of extracellular vesicle in human papillomavirus-associated cervical cancer. J Cancer Res Clin Oncol 2023;149(17):16203–12. doi:10.1007/s00432-023-05374-x
60. Ran Z, Wu S, Ma Z, Chen X, Liu J, Yang J. Advances in exosome biomarkers for cervical cancer. Cancer Med 2022;11(24):4966–78. doi:10.1002/cam4.4828
61. Raghani NR, Chorawala MR, Parekh K, Sharma A, Alsaidan OA, Alam P, et al. Exosomal miRNA-based theranostics in cervical cancer: bridging diagnostics and therapy. Med Oncol 2025;42(6):193. doi:10.1007/s12032-025-02752-y
62. Ye M, Wang J, Pan S, Zheng L, Wang ZW, Zhu X. Nucleic acids and proteins carried by exosomes of different origins as potential biomarkers for gynecologic cancers. Mol Ther Oncolytics 2022;24:101–13. doi:10.1016/j.omto.2021.12.005
63. Sommella E, Capaci V, Aloisio M, Salviati E, Campiglia P, Molinario G, et al. A Label-Free Proteomic Approach for the Identification of Biomarkers in the Exosome of Endometrial Cancer Serum. Cancers (Basel) 2022;14(24):6262. doi:10.3390/cancers14246262
64. Ding XZ, Zhang SQ, Deng XL, Qiang JH. Serum Exosomal lncRNA DLX6-AS1 Is a Promising Biomarker for Prognosis Prediction of Cervical Cancer. Technol Cancer Res Treat 2021;20:1533033821990060. doi:10.1177/1533033821990060
65. Hu Y, Li G, Ma Y, Luo G, Wang Q, Zhang S. Effect of Exosomal lncRNA MALAT1/miR-370-3p/STAT3 Positive Feedback Loop on PI3K/Akt Pathway Mediating Cisplatin Resistance in Cervical Cancer Cells. J Oncol 2023;2023:6341011. doi:10.1155/2023/6341011
66. Parashar D, Singh A, Gupta S, Sharma A, Sharma MK, Roy KK, et al. Emerging Roles and Potential Applications of Non-Coding RNAs in Cervical Cancer. Genes (Basel) 2022;13(7):1254. doi:10.3390/genes13071254
67. Zhou P, Liu W, Cheng Y, Qian D. Nanoparticle-based applications for cervical cancer treatment in drug delivery, gene editing, and therapeutic cancer vaccines. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2021;13(5):e1718. doi:10.1002/wnan.1718
68. Abas BI, Demirbolat GM, Cevik O. Wharton jelly-derived mesenchymal stem cell exosomes induce apoptosis and suppress EMT signaling in cervical cancer cells as an effective drug carrier system of paclitaxel. PLoS One 2022;17(9):e0274607. doi:10.1371/journal.pone.0274607
69. Andre M, Caobi A, Miles JS, Vashist A, Ruiz MA, Raymond AD. Diagnostic potential of exosomal extracellular vesicles in oncology. BMC Cancer 2024;24(1):322. doi:10.1186/s12885-024-11819-4
70. Cho H, Wang Z, Levy D. Study of dose-dependent combination immunotherapy using engineered T cells and IL-2 in cervical cancer. J Theor Biol 2020;505:110403. doi:10.1016/j.jtbi.2020.110403
71. Zhang Y, Li X, Zhang J, Mao L. Novel cellular immunotherapy using NKG2D CAR-T for the treatment of cervical cancer. Biomed Pharmacother 2020;131:110562. doi:10.1016/j.biopha.2020.110562
72. Zhou X, Lian H, Li H, Fan M, Xu W, Jin Y. Nanotechnology in cervical cancer immunotherapy: Therapeutic vaccines and adoptive cell therapy. Front Pharmacol 2022;13:1065793. doi:10.3389/fphar.2022.1065793
73. Bharti AC, Singh T, Bhat A, Pande D, Jadli M. Therapeutic startegies for human papillomavirus infection and associated cancers. Front Biosci (Elite Ed) 2018;10(1):15–73. doi:10.2741/e808
74. Li D, Hu C, Li H. Survivin as a novel target protein for reducing the proliferation of cancer cells. Biomed Rep 2018;8(5):399–406. doi:10.3892/br.2018.1077
75. Melief CJM, Welters MJP, Vergote I, Kroep JR, Kenter GG, Ottevanger PB, et al. Strong vaccine responses during chemotherapy are associated with prolonged cancer survival. Sci Transl Med 2020;12(535):eaaz8235. doi:10.1126/scitranslmed.aaz8235
76. Wang B, Gong C, Zhao Y, Hu X, Zhang J, Wang L, et al. Camrelizumab plus nab-paclitaxel and cisplatin as first-line treatment for metastatic triple-negative breast cancer: A prospective, single-arm, open-label phase II trial. Journal of Clinical Oncology 2025;43(16_suppl):1101. doi:10.1200/JCO.2025.43.16_suppl.1101
77. Birrer M, Li G, Yunokawa M, Lee JY, Kim BG, Oppermann CP, et al. Bintrafusp Alfa for Recurrent or Metastatic Cervical Cancer After Platinum Failure: A Nonrandomized Controlled Trial. JAMA Oncol 2024;10(9):1204–11. doi:10.1001/jamaoncol.2024.2145
78. Drolet M, Laprise JF, Martin D, Jit M, Bénard É, Gingras G, et al. Optimal human papillomavirus vaccination strategies to prevent cervical cancer in low-income and middle-income countries in the context of limited resources: a mathematical modelling analysis. Lancet Infect Dis 2021;21(11):1598–610. doi:10.1016/s1473-3099(20)30860-4
79. Sun Q, Wang L, Zhang C, Hong Z, Han Z. Cervical cancer heterogeneity: a constant battle against viruses and drugs. Biomark Res 2022;10(1):85. doi:10.1186/s40364-022-00428-7
80. Dellino M, Cerbone M, d'Amati A, Bochicchio M, Laganà AS, Etrusco A, et al. Artificial Intelligence in Cervical Cancer Screening: Opportunities and Challenges. AI 2024;5:2984–3000. doi:10.3390/ai5040144
81. Hou X, Shen G, Zhou L, Li Y, Wang T, Ma X. Artificial Intelligence in Cervical Cancer Screening and Diagnosis. Front Oncol 2022;12:851367. doi:10.3389/fonc.2022.851367
82. Wang J, Yu Y, Tan Y, Wan H, Zheng N, He Z, et al. Artificial intelligence enables precision diagnosis of cervical cytology grades and cervical cancer. Nat Commun 2024;15(1):4369. doi:10.1038/s41467-024-48705-3
83. Li X, Corbett AL, Taatizadeh E, Tasnim N, Little JP, Garnis C, et al. Challenges and opportunities in exosome research-Perspectives from biology, engineering, and cancer therapy. APL Bioeng 2019;3(1):011503. doi:10.1063/1.5087122
84. Li J, Wang J, Chen Z. Emerging role of exosomes in cancer therapy: progress and challenges. Mol Cancer 2025;24(1):13. doi:10.1186/s12943-024-02215-4

85. Malla R, Kamal MA. E6 and E7 Oncoproteins: Potential Targets of Cervical Cancer. Curr Med Chem 2021;28(39):8163–81. doi:10.2174/0929867327666201111145546
86. Ranasinghe V, McMillan N. Novel therapeutic strategies for targeting E6 and E7 oncoproteins in cervical cancer. Crit Rev Oncol Hematol 2025;211:104721. doi:10.1016/j.critrevonc.2025.104721
87. Nygård M, Nygård S. The Future of Cervical Cancer Prevention: From "One-Size-Fits-All" to Personalized Screening. J Pers Med 2023;13(2). doi:10.3390/jpm13020161
88. Garg P, Krishna M, Subbalakshmi AR, Ramisetty S, Mohanty A, Kulkarni P, et al. Emerging biomarkers and molecular targets for precision medicine in cervical cancer. Biochim Biophys Acta Rev Cancer 2024;1879(3):189106. doi:10.1016/j.bbcan.2024.189106