WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 11, 1850-1867. Review Article ISSN 2277–7105

CERVICAL CANCER: A MULTIDIMENSIONAL REVIEW OF MOLECULAR PATHOGENESIS, DIAGNOSTIC CHALLENGES, AND EMERGING THERAPEUTIC STRATEGIES

Sneha S., Sruthi S., J. Anbu*, Sadhana Goswami

Department of Pharmacology, Faculty of Pharmacy, M. S. Ramaiah University of Applied Sciences, Bengaluru, India.

Article Received on 05 May 2026,
Article Revised on 25 May 2026,
Article Published on 01 June 2026

https://doi.org/10.5281/zenodo.20526749

***Corresponding Author**

J. Anbu

Department of Pharmacology, Faculty of Pharmacy, M. S. Ramaiah University of Applied Sciences, Bengaluru, India.

How to cite this Article: Sneha S., Sruthi S., J Anbu*, Sadhana Goswami (2026). Cervical Cancer: A Multidimensional Review of Molecular Pathogenesis, Diagnostic Challenges, and Emerging Therapeutic Strategies. World Journal of Pharmaceutical Research, 15(11), 1850–1867.

ABSTRACT

The relevance of the cervical cancer problem is evidenced by the prevalence of late diagnosis and inefficient screening tools in developing countries. The present paper addresses various aspects of pathogenetic mechanisms, current limitations of diagnostics, and innovative treatment approaches used to treat cervical cancer. Particular attention is paid to novel developments in immunotherapy, molecule-based treatment regimens, and delivery systems. The first reason is related to the role played by the human papillomavirus in the development of cervical cancer owing to its influence on the tumor suppression mechanism. Despite the high efficiency of traditional treatment approaches (surgical removal, chemotherapy, and radiotherapy), these methods have many limitations because of poor tolerance to therapy and the emergence of resistance. Newer treatment approaches based on immuno-modulation and precise therapy provide promising results. Moreover, certain natural components, e.g., fulvic acid, demonstrate positive effects for cancer patients' condition improvement. Recent developments related to advanced delivery systems (nanoparticles and thermosensitive in situ gel), also play a significant role in improving the quality of cancer treatment.

KEYWORDS: Cervical cancer; Human papillomavirus (HPV); Immunotherapy; Targeted therapy; Fulvic acid; Nanoparticle drug delivery.

1. INTRODUCTION

Cervical cancer continues to be a major public health concern and one of the main causes of cancer-related death for women, especially in developing nations.[1] In areas with limited resources, greater incidence and mortality rates are caused by inadequate vaccine access[2], a lack of structured examination, and a delay in early treatment, even though these factors can be largely prevented.[3] The continuous burden of the disease and the need to enhance prevention and treatment approaches worldwide are reflected in global cancer data reports.[4,5]

Long-term infection with high-risk human papillomavirus (hrHPV), mainly HPV-16 and HPV-18, is the main reason for cervical carcinogenesis.[6,7] While the majority of infections are short-term and cleared by the body's immune system, poor immune response can result in long-term presence of the virus and insertion into the host genome.[8,9] The virus-derived proteins involved in cancer are E5, E6, and E7 disrupt key systems that control cell activity. E6 promotes breakdown of the tumor suppressor protein p53, whereas E7 blocks the activity of retinoblastoma protein (pRB), leading to genetic instability, excessive cell growth, and reduced apoptotic activity.[10,11] Additionally, strategies to evade immune response, irregular cell signaling pathways, and changes in long non-coding RNA activity collectively contribute to HPV-related tumor progression.[12-14] The process of cervical carcinogenesis due to hrHPV infection is shown on Figure 1.

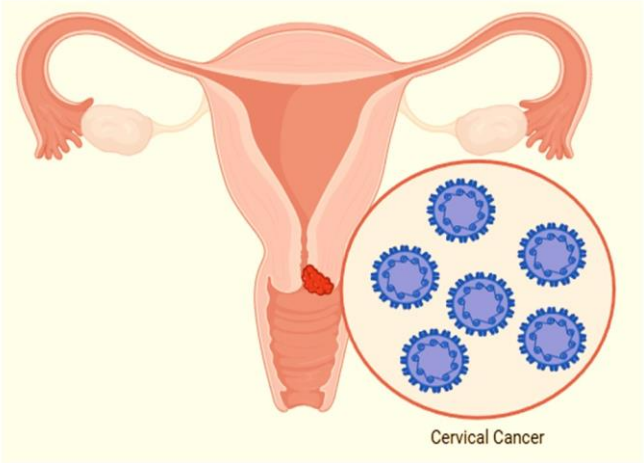

Figure 1: Cervical carcinogenesis due to infection with high-risk human papillomavirus (HPV), depicting the steps starting from HPV infection to cancerous change in cervical epithelial cells.

Cofactors such as prolonged use of hormonal contraceptives, sexual activity patterns, and irregular use of barrier protection influence spread of the virus and worsening of lesions.[15-17] Alterations in the cervicovaginal microbial community may also modulate local immune response and promote persistent inflammation, allowing the virus to persist and affecting therapeutic outcomes.[18] The care of severe disease is still difficult in clinical practice, despite the fact that vaccination and better diagnostic techniques have greatly increased preventative measures.[19] For example, there are reports of therapy being linked to relapse and toxicity as a result of the type of treatment and poor accessibility.[20] Even though new therapies such as the immune checkpoint inhibitors are effective, their cost and accessibility are major constraints.[21] Hence, it is important to ensure that a treatment method is realistic as well as effective.[22]

2. Epidemiology

Cervical cancer is one of the most common types of cancer among women worldwide. This type of cancer occupies the third place regarding its frequency. About 600,000 new cases of cervical cancer are diagnosed each year, which results in 340,000 deaths from the condition, meaning that it is one of the leading causes of cancer-related fatalities among women. Despite being preventable, this type of cancer remains a significant threat to the well-being of women worldwide.[23]

Cervical cancer is not evenly distributed around the world. Almost 90% of all newly diagnosed cases and deaths related to cervical cancer take place in low- and middle-income countries.[24] Meanwhile, in high-income nations, due to effective screening and widespread vaccination against HPV, both the number of people diagnosed with cervical cancer and the number of related deaths have decreased considerably. Yet there are regions where higher incidences of cervical cancer have been observed, for example, Sub-Saharan Africa and South Asia.[25]

3. Clinical Relevance and Risk Factors of Cervical Cancer

Cervical cancer remains a major contributor to the morbidity and mortality from cancer among women worldwide, particularly in developing countries that do not have sufficient preventive services.[26] Due to late diagnosis related to lack of screening, poor awareness, and poor access to health care, the survival rates for cervical cancer are lower than those for other types of cancer.[27-30] Although hrHPV infection is considered the most important risk factor, several other risk factors affect the onset of the disease.[31,32]

3.1 Modifiable Risk Factors

Several modifiable factors increase the risk of cervical cancer onset. Sexual activity at a young age, sexually promiscuous behavior, and non-adherence to barrier contraception increase the risk of persistent HPV infection.[33,34] Other factors include prolonged use of hormonal contraceptives, smoking, poor genital hygiene, immunosuppression, and sexually transmitted infections.[35,36] Absence of cervical cancer screenings and lack of HPV infection vaccinations remain the major modifiable risk factors in the development of cervical cancer.[37]

3.2 Non-modifiable Risk Factors

Age can be considered one of the important factors that influence the development of cervical cancer, since the highest prevalence of the disease occurs in women aged 30-44 years old.[38] Besides, genetic predisposition to the disease and familial factors might increase the risk. In addition, low socio-economic status in women is another factor that contributes to the higher prevalence and mortality rates because of poor accessibility to health care and lack of screening tests.[39,40] High parity is another risk factor that might contribute to the development of the disease.[41,42]

4. Pathophysiology

High-risk human papillomavirus (hrHPV) infection is the primary cause of the biological alterations that lead to cervical cancer. The most prevalent strains that cause cancer are HPV-16 and HPV-18, which infect the cervix's lining cells and incorporate their genetic material into the DNA of the host cell. Viral oncoproteins E6 and E7 are produced as a result of this integration, and they interfere with significant tumor-suppressor proteins such as p53 and retinoblastoma protein (pRb). Uncontrolled cellular proliferation and genomic instability emerge from the disruption of normal cell-cycle regulation, which permits aberrant cells to proliferate and divide uncontrollably.[43] The molecular pathway of hrHPV-associated cervical carcinogenesis is shown in Figure 2.

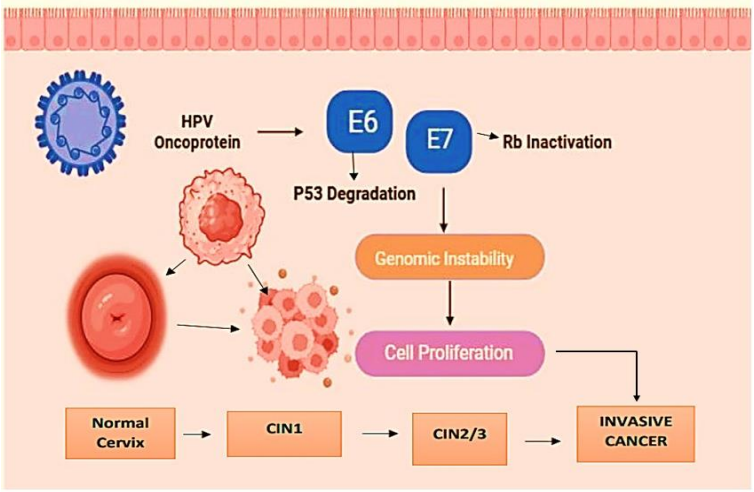

Figure 2: Pathogenesis of HPV-induced cervical carcinogenesis depicting the mechanism by which the viral oncogenes E6 and E7 lead to tumour suppressor malfunction and genome instability.

HPV infections can cause cervical intraepithelial neoplasia (CIN), which is a precancerous condition. It occurs in three forms, namely CIN1, CIN2, and CIN3, depending on the degree of epithelial dysplasia. CIN3 is considered the most severe form of precancer because it poses the highest chance of developing into cervical cancer in case no treatment measures are taken.[44] With further progression, other genetic and molecular modifications take place alongside changes in the tumor environment. This occurs mostly through the interaction between the viral proteins produced and the host's cell mechanisms.[45] At the same time, HPV has a means of evading the immune system of the host by modifying the immunological pathways, enabling the virus to persist within the body.[46]

5. Challenges in Diagnosis and Conventional Management of Cervical Cancer

Early detection of cervical cancer is challenging due to lack of symptoms. Techniques such as Pap smear have been effective in reducing incidences in high-resource settings.[47] However, these techniques require high-quality laboratories with skilled individuals. High-risk HPV DNA screening has shown more success than cytology in terms of sensitivity; however, the high cost of HPV screening limits its use in developing and middle-income countries.[48] Alternatives like visual inspection with acetic acid (VIA)[49] and fast HPV test could enhance accessibility of cervical screening despite the lower levels of accuracy.[50]

Treatment is dependent on the cervical cancer staging. Patients with locally advanced disease (FIGO IB3 to IVA) can be cured with cisplatin chemotherapy alongside external beam and

brachytherapy radiotherapy.[51] On the other hand, early cervical cancer patients (FIGO IA - IB1) can undergo radical hysterectomy and trachelectomy procedures.[52] In addition, LACC study showed poor survival rates for patients undergoing minimal surgical procedures rather than open surgery.[53] However, toxicity of treatment and recurrence remain critical aspects in treating cervical cancer.[54]

6. Emerging and Contemporary Therapeutic Strategies for Cervical Cancer

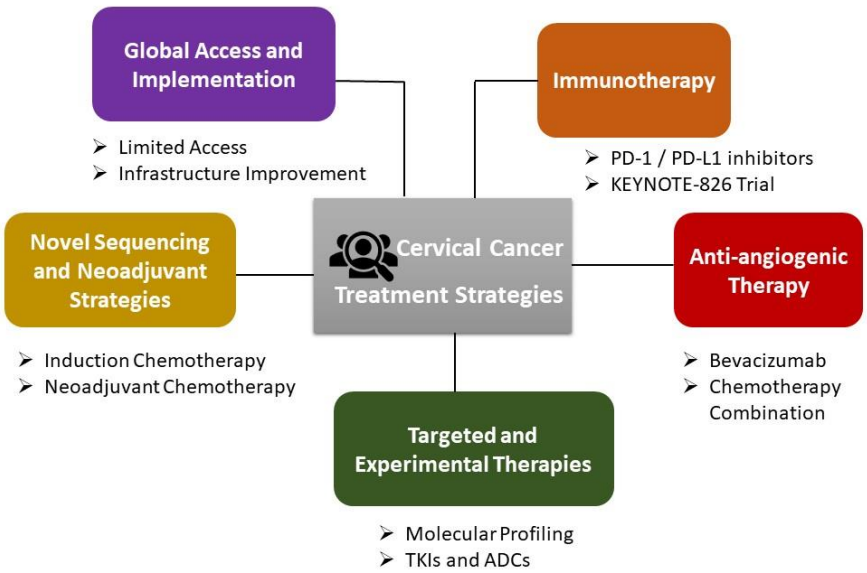

Figure 3: Modern treatment procedures of cervical cancer include Immunotherapy, angiogenesis inhibitors therapy, Targeted Therapy, and other new treatment procedures.

The progress made recently has allowed the improvement in existing treatment options for recurred or metastasized cervical cancers. As stated in the KEYNOTE-826 study, immunotherapy involving the inhibition of the PD-1/PD-L1 axis via pembrolizumab resulted in better outcomes for survival rates combined with platinum-based chemotherapy and/or bevacizumab.[55] Bevacizumab has also been indicated to be significant for the primary treatment option.[56] Additionally, due to advances in the field of molecular profiling, potential targets in cancer cases were discovered, such as mutation of PI3K signaling pathway and status of HER2 receptors, which led to encouraging results in developing tyrosine kinase inhibitors and antibody-drug conjugates for treatment.[57] The current therapies used to treat cervical cancer are described in Figure 3.

Further research is being conducted for the advancement in brachytherapy and neoadjuvant treatment options.[58] Access to the new methods for treatment in lower- and middle-income countries makes it difficult for the patients in such countries to achieve improved outcomes in survival rates.[59] Current research-based personalized medicine includes immuno-oncology via targeting immune checkpoints, ADCs, tumor-infiltrating lymphocytes, HPV vaccination, and biomarker analysis for recurrence prediction and treatment strategy.[60-62] A comparative analysis of currently employed treatment regimens for cervical cancer is presented in Table 1.

Table 1: Comparative analysis of treatment regimens employed for cervical cancer.

Regimen Type	Description	Advantages	Disadvantages
Chemoradiotherapy	Combination therapy Administration of both radiation and platinum-based agents to induce damage to DNA of cancerous cells	Commonly employed and well-known method	May have adverse effects; possible development of resistance
Immunotherapy	Immunotherapy Eliciting an immune response by facilitating the recognition of cancer cells through stimulation of PD-1/PD-L1 pathway	Life-long remission in certain cases	Pricy and not readily accessible
Antibody–Drug Conjugate Therapy	Conjugate Therapy Targeted therapy Delivery of cytotoxic drugs via targeted transport to cancer cells via antibody-antigen binding	Selective mechanism with minimal harm to healthy cells	May produce adverse reactions and not readily available
FA-Gel Loaded With Nanoparticles	Provides localized administration and long-lasting effect using nanoparticles	Prevents systemic circulation and improves specificity	Still experimental and not frequently utilized

Abbreviations: PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ADCs, antibody–drug conjugates; FA, fulvic acid; DNA, deoxyribonucleic acid; NPs, nanoparticles.

7. Role of Fulvic Acid in Cancer Therapy

Low-molecular-weight humic fraction fulvic acid (FA) has immunomodulatory, pro-apoptotic, chemosensitizing, and antiproliferative properties. It increases xenobiotic-metabolizing enzymes in vitro,[63] and in certain cancer cell lines, it triggers caspase activation, apoptosis, G0/G1 arrest, and ROS signaling.[64] By modifying cytokines and boosting mediators generated from macrophages, FA may also modify the tumor

microenvironment.[65] However, because the evidence is primarily preclinical, clinical translation necessitates deeper mechanistic research and standardized FA formulations.[66]

8. Future Perspectives

Further advancements in cancer therapy are inevitably going to be achieved with the help of more efficient drug delivery systems that will help make this process much safer, more accurate, and effective. Using such systems, including nanoparticles and ligand-based targeting approaches, it will be possible to deliver the necessary amount of medication to a tumor without harming healthy cells.[67] Additionally, the application of drug delivery systems employing nanoparticles will most likely make medications more efficient by increasing their solubility, stability, and sustained release.[68]

Finally, the development of targeted drug delivery systems, for example, involving antibodies and nanocarriers, will allow doctors to create a more personalized approach to the treatment, thus providing them with more options when it comes to the therapy of each particular patient.[69] Moreover, one can consider combining various drug delivery approaches to help overcome the problems associated with drug resistance among patients using a combination of chemotherapy and siRNA delivery.[70]

9. Advanced Drug Delivery Approaches

Nanoparticle utilization for drug delivery in cancer treatment has been extensively researched because of their ability to improve drug targeting. The various kinds of nanoparticle carriers such as liposome, polymer, solid lipid, dendrimer, and inorganic nanoparticles allow drugs to accumulate in the tumor tissue in the EPR effect.[71] Moreover, the addition of other materials like folic acid, antibody, and peptides to these carriers allows them to target the cancer cells specifically. They can deliver different classes of drugs ranging from chemotherapy, nucleic acids, and immunomodulators. Despite a variety of well-developed nanoparticle-based experiments, their use in medicine remains challenging due to several factors.[72]

The inclusion of fulvic acid into nanocarrier systems can be applied in order to enhance drug delivery processes and increase their mucosal permeability.[73] In combination with nanoparticles and thermoreversible in situ gels, it provides sustained drug release and maintenance of the drug in its location.[74] There are several important considerations that need to be made during the process of formulating a system. These include particle size, rate of drug release, mucoadhesiveness, and toxicity.[75] Thermosensitive gel that changes its state

upon reaching the temperature of tissue in the body is particularly useful for targeted delivery because it increases the period of residence and decreases systemic absorption.[76] In addition, the effectiveness of such systems may be improved by incorporating mucoadhesive polymers or nanoparticles.[77]. Several formulations have been formulated for targeted delivery, including chitosan-based systems, PLGA-PEG-PLGA hydrogel, and poloxamer.[78-81]

10. In Vitro and In Vivo Experimental Models for Evaluation

10.1 In vitro models

Cancer cells of cervix can be subjected to intervention studies in vitro for analysis of how they react to the intervention. In these studies, parameters that can be analyzed include proliferation, apoptosis, cell cycle alterations, as well as invasion and migration of the cells using cancer cell lines such as HeLa, SiHa, CaSki, and ME-180. Three-dimensional (3D) systems have been used for tumor-like conditions to analyze their structural characteristics, including other factors such as hypoxia and diffusion of drugs in the tumor.[82,83]

10.2 In vivo models

In vivo modeling is necessary in assessing antineoplastic agents against cervical cancer due to the ability to monitor the development of the tumor, drug penetration into tissue, and the tumor response towards the treatment. In particular, some common in vivo models include subcutaneous xenografts, which involve the implantation of cancer cells in an immunocompromised mouse host. Although this model is rather easy and useful in assessing how well the tumor is suppressed, it does not provide a full replication of the natural conditions in which the tumor is growing and may metastasize.[84] In order to compensate for that drawback, patient-derived xenograft (PDX) models may be used because they allow keeping the features of the primary tumor and are useful especially when assessing local administration methods like intravaginal administration. Furthermore, syngeneic models and genetically engineered mouse models (GEMMs) can provide information about the influence of immune reactions on the tumor and its response to treatment.[85] The development of research usually includes a stepwise approach, from in vitro experiments to xenografts and in vivo models.[86]

11. Future Prospects and Research Deficits

Further investigations for fulvic acid (FA) as a potential anti-cancer agent for cervical cancer must be conducted focusing on several aspects that have yet to be clarified. The first aspect relates to the problem of standardization since the structure of fulvic acid depends on the

origin and therefore leads to different results and may hinder regulatory approval.[87] Moreover, in order to elucidate its therapeutic mechanisms of action in association with HPV-induced signaling and assess the safety profile as well as any toxic effects associated with fulvic acid, further investigations should be carried out.[88] Another aspect that requires attention involves the further optimization of delivery vehicles by improving the current approaches that involve nanoparticles and thermosensitive hydrogels for FA delivery in order to allow efficient large-scale drug production.[89,90] Additionally, the use of more physiologically-relevant models, such as orthotropic and immune-competent ones, will provide information regarding its effectiveness and pharmacokinetics.[91]

12. CONCLUSION

Cervical cancer is still a significant health problem worldwide, mainly because of persistent HPV infections and the presence of molecular abnormalities. Although the traditional methods of treatment, such as surgery, radiotherapy, and chemotherapy, are quite effective, their disadvantages, including therapy resistance, side effects, and recurrence of the disease, necessitate the search for more efficient methods of treatment.

Additionally, some of the recent trends in the field of medicine are the application of newer treatment modalities like immune-checkpoint inhibition therapy, biomarker therapy, and T-cell adoptive therapy. Also, using bioactive agents like fulvic acid along with the modern drug delivery system involving nanoparticles and thermosensitive hydrogel will help in increasing the concentration of drugs in the targeted area while lowering the toxicity of drugs. Nanotechnology, immunotherapy, and molecular treatments may contribute to providing personalized treatments for patients.

REFERENCES

1. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: World Health Organization; 2020.
2. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health.* 2020; 8(2): e191–e203.
3. Ekezie W, Awwad S, Krauchenberg A, Karara N, Dembiński Ł, Grossman Z, Del Torso S, Dornbusch HJ, Neves A, Copley S, Mazur A. Access to vaccination among disadvantaged, isolated and difficult-to-reach communities in the WHO European region: a systematic review. Vaccines. 2022 Jun 28; 10(7): 1038.

4. Crafton SM, Venkat P, Salani R. A review of the state of cervical cancer: updates from prevention to recurrent disease. *Curr. Opin. Obstet. Gynecol.*, 2024; 36(1): 28-33.
5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide. *CA Cancer J. Clin.*, 2021; 71(3): 209-249.
6. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin., 2024; 74(3): 229–263.
7. Ojha PS, Maste MM, Tubachi S, Patil VS. Human papillomavirus and cervical cancer: an insight highlighting pathogenesis and targeting strategies. *Virusdisease.* 2022; 33(2): 132-154.
8. Basukala O, Banks L. HPV E5, E6 and E7 oncoproteins in carcinogenesis. *Viruses.* 2021; 13(10): 1892.
9. Akaaboune M, Kenfack B, Viviano M, Temogne L, Catarino R, Tincho E, et al. Clearance and persistence of HPV infection. *Health Care Women Int.* 2018; 39(10): 1106-1124.
10. Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Holmes KK, et al. Condom use and the risk of genital human papillomavirus infection in young women. N. Engl. J. Med., 2006; 354(25): 2645–2654.
11. Skelin J, Sabol I, Tomaić V. HPV E5, E6 and E7 in cell death evasion. *Pathogens.* 2022; 11(9): 1027.
12. Medda A, Duca D, Chiocca S. HPV and cellular pathways. *Pathogens.* 2021; 10(3): 262.
13. Jiang S, Zhou Y, Ye M, Li X, Zhang L, Yang Y. Immune-related ceRNA network in cervical cancer. *Front Oncol.* 2022; 12: 979884.
14. Dias TR, Santos JMO, Gil da Costa RM, Medeiros R. Long non-coding RNAs in HPV malignancies. *Crit Rev Oncol Hematol.* 2021; 161: 103310.
15. Stern PL. Harnessing immunity for therapy in HPV-driven cancers. *Tumour Virus Res.* 2021; 11: 200212.
16. Iversen E, Green J, Kjaer SK, Adami HO, Baandrup L, Bertelsen L, et al. Hormonal contraception and cervical cancer. *Int J Cancer.* 2021; 149(9): 1720-1732.
17. Hogewoning CJ, Bleeker MC, van den Brule AJ, Voorhorst FJ, Snijders PJ, Berkhof J, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. Int. J. Cancer. 2003; 107(5): 811–816.

18. Frett BM, Hogewoning CJA, Bleeker MC, Berkhof J, Starink TM, Snijders PJF, et al. Condom use and regression of CIN2–3. *Infect Agents Cancer*. 2012; 7: 30.
19. Wu L, Yan H, Wang K, Wang Y, Li M, Hu Y, et al. Cervicovaginal microbiota in cervical cancer. *Infect Agents Cancer*. 2024; 19(1): 19.
20. Su L, Peng H, He X. HPV detection and vaccine research. *Clin Exp Obstet Gynecol.* 2023; 50(3): 304-348.
21. Tewari KS, Monk BJ. Developments in advanced cervical cancer. *Am. Soc. Clin. Oncol. Educ., Book.* 2019; 39: e65-e74.
22. Lu Z, Haghollahi S, Afzal M. Therapeutic targets for HPV-associated malignancies. Cancers (Basel). 2024; 16(20): 3474.
23. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Pembrolizumab for advanced cervical cancer. N. Engl. J. Med., 2021; 385(20): 1856–1867.
24. Pimple SA, Mishra GA. Global strategies for cervical cancer prevention and screening. Minerva. Med., 2022; 113(3): 413–425.
25. Vali S, Pallavi P, Chowhan AK. Cervical cancer in low- and middle-income countries: epidemiology, prevention and control strategies. Asian Pac J Cancer Prev., 2023; 24(3): 649–657.
26. Ojha S, Thakur N, Chapagain S. Late presentation of cervical cancer patients: clinical features and management challenges in resource-limited settings. J Nepal Health Res. Counc., 2022; 20(1): 68–74.
27. Tekalign T, Teshome M. Prevalence and determinants of late-stage presentation among cervical cancer patients: a systematic review and meta-analysis. PLoS One. 2022; 17(5): e0268524.
28. Vali M, Maleki Z, Nikbakht HA, Hassanipour S, Kouhi A, Nazemi S, et al. Survival rate of cervical cancer in Asian countries: a systematic review and meta-analysis. BMC Womens Health. 2023; 23: 671.
29. Bhatla N, Aoki D, Sharma DN. Morbidity after surgical management of cervical cancer in low and middle-income countries: a systematic review and meta-analysis. Int J Gynaecol Obstet. 2019; 145(1): 1–12.
30. Ojha N, Jha M, Shrestha E, Dangal G. Late-stage cervical cancer among confirmed cervical cancer cases in a tertiary care centre: a descriptive cross-sectional study. Kathmandu Univ. Med. J., 2022; 20(79): 21–25.

31. Gopalkrishnan K, Karim R. Addressing global disparities in cervical cancer burden: a narrative review of emerging strategies. Curr HIV/AIDS Rep., 2025; 22(1): 18.
32. Chan CK, Aimagambetova G, Kongrtay K, Ukybassova T, Azizan A. Human papillomavirus infection and cervical cancer: epidemiology, screening, and vaccination—review of current perspectives. J Oncol. 2019; 2019: 3257939.
33. Mekonnen AG, Mittiku YM. Early-onset of sexual activity as a potential risk of cervical cancer in Africa: a review of literature. PLoS Glob Public Health. 2023; 3(2): e0000941.
34. Choi S, Ismail A, Pappas-Gogos G, Boussios S. Human papillomavirus and cervical cancer: a review of epidemiology and screening uptake in the UK. Pathogens. 2023; 12(2): 298.
35. Garces AH, de Melo AC, Paulino E, Nogueira-Rodrigues A, Grazziotin R, Reisner ML, Dias MS, Guitmann G, Iglesias G, Ferreira CG. Approach and Management of Cervical Cancer. In: International Manual of Oncology Practice: iMOP-Principles of Oncology 2019 Oct 16: 491-549. Cham: Springer International Publishing.
36. Glick SB, Clarke AR, Blanchard A, Whitaker AK. Cervical cancer screening, diagnosis and treatment interventions for racial and ethnic minorities: a systematic review. Journal of general internal medicine. 2012 Aug; 27(8): 1016-32.
37. Singh GK, Azuine RE, Siahpush M. Global inequalities in cervical cancer incidence and mortality are linked to deprivation, low socioeconomic status, and human development. International Journal of MCH and AIDS. 2012; 1(1): 17.
38. Bonello K, Blundell R. The role of the human papillomavirus (HPV) in cervical cancer: A review about HPV-induced carcinogenesis and its epidemiology, diagnosis, management and prevention. International Journal of Medical Students. 2016 Apr 30; 4(1): 26-32.
39. Small W Jr, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, et al. Cervical cancer: a global health crisis. Cancer. 2017; 123(13): 2404–2412.
40. Van den Brule AJC, et al. Familial cervical cancer: three-generation case reports and review. Cancer Epidemiol Biomarkers Prev., 2010; 19(5): 1160–1165.
41. International Agency for Research on Cancer. Cervical cancer and parity as a cofactor in HPV-mediated carcinogenesis. IARC Monogr Eval Carcinog Risks Hum. 2012; 100B: 261–276.
42. Tekalegn Y, Sahiledengle B, Woldeyohannes D, Atlaw D, Degno S, Desta F, et al. High parity is associated with increased risk of cervical cancer: systematic review and meta-analysis of case-control studies. Womens Health (Lond). 2022; 18: 17455065221075904.

43. Narisawa-Saito M, Kiyono T. Basic mechanisms of high-risk human papillomavirus-induced carcinogenesis: roles of E6 and E7 proteins. Cancer Sci., 2007; 98(10): 1505–1511.
44. McLaughlin-Drubin ME, Munger K. Mechanistic role of HPV-associated early proteins in cervical cancer: molecular pathways and targeted therapeutic strategies. Front Oncol. 2022; 12: 789603.
45. Hoppe-Seyler K, Bossler F, Braun JA, Herrmann AL, Hoppe-Seyler F. The HPV E6/E7 oncogenes: key factors for viral carcinogenesis and therapeutic targets. Trends Microbiol., 2018; 26(2): 158–168.
46. Da Silva MLR, De Albuquerque BHDR, Allyrio TAMF, De Almeida VD, Cobucci RNO, Bezerra FL, et al. The role of HPV-induced epigenetic changes in cervical carcinogenesis. Biomed. Rep., 2021; 15(1): 60.
47. Petersen Z, Jaca A, Ginindza TG, et al. Barriers to uptake of cervical cancer screening services in low- and middle-income countries: a systematic review. BMC Womens Health. 2022; 22: 486.
48. Gupta R, Gupta S, Mehrotra R, Sodhani P. Cervical cancer screening in resource-constrained countries: current status and future directions. Asian Pac J Cancer Prev., 2017; 18(6): 1461–1467.
49. Petignat P, Kenfack B, Wisniak A, Saiji E, Tille JC, Tsuala Fouogue J, Catarino R, Tincho E, Vassilakos P. ABCD criteria to improve visual inspection with acetic acid (VIA) triage in HPV-positive women: a prospective study of diagnostic accuracy. BMJ open. 2022 Apr; 12(4): e052504.
50. Ferrari F, De Vincenzo R, Cuschieri KS, et al. Barriers to cervical cancer screening in low-income and middle-income countries: a systematic review. Lancet Glob Health. 2022; 10(1): e56–e68.
51. Musunuru HB, et al. Advances in management of locally advanced cervical cancer. Indian J. Med. Res., 2021; 154(2): 248–261.
52. Ramirez PT, Robledo KP, Frumovitz M, Pareja R, Ribeiro R, Lopez A, et al. LACC trial: final analysis on overall survival comparing open versus minimally invasive radical hysterectomy for early-stage cervical cancer. J. Clin. Oncol., 2024; 42(23): 2741–2746.
53. Alim S, Siddiqui SA, Akram M, Hakim S, Khan MA. Clinical outcomes in locally advanced cervical cancer treated with EBRT and HDR intracavitary brachytherapy with or without concurrent cisplatin. Asian Pac. J. Cancer Prev., 2024; 25(4): 1333–1338.

54. Zhang GY, Zhang R, Bai P, Li SM, Zhang YY, Chen YR, et al. Concurrent definitive chemoradiation incorporating intensity-modulated radiotherapy followed by adjuvant chemotherapy in high-risk locally advanced cervical squamous cancer: a phase II study. BMC Cancer. 2022; 22: 1331.
55. Monk BJ, Colombo N, Tewari KS, Dubot C, Caceres MV, Hasegawa K, et al. First-line pembrolizumab plus chemotherapy versus placebo plus chemotherapy for persistent, recurrent, or metastatic cervical cancer: final overall survival results of KEYNOTE-826. J. Clin. Oncol., 2023; 41(36): 5505–5511.
56. Tewari KS, Sill MW, Long HJ III, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. N. Engl. J. Med., 2014; 370(8): 734–743.
57. Bogani G, Coleman RL, Vergote I, Raspagliesi F, Lorusso D, Monk BJ. Tisotumab vedotin in recurrent or metastatic cervical cancer. Curr Probl Cancer. 2023; 47(3): 100952.
58. Jiang P, Wei S, Li C, et al. Safety and efficacy of toripalimab plus concurrent chemoradiotherapy for locally advanced cervical cancer: a phase Ib trial. BMC Cancer. 2025; 25: 1566.
59. LaVigne AW, Triedman SA, Randall TC, Trimble EL, Viswanathan AN. Cervical cancer in low- and middle-income countries: addressing barriers to radiotherapy delivery. Gynecol. Oncol. Rep., 2017; 22: 16–20.
60. Zhang X, Zeng Q, Cai W, Ruan W. Trends of cervical cancer at global, regional, and national level: data from the Global Burden of Disease study 2019. BMC Public Health. 2021; 21: 894.
61. Monk BJ, et al. Integration of immunotherapy into treatment of cervical cancer: recent data and ongoing trials. Cancer Treat Rev., 2022; 106: 102385.
62. Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin. Oncol., 2019; 37(17): 1470–1478.
63. Chen M, Cheng M, Shao C, Liang W, Tang Y, Ding F. Fulvic acid exhibits antitumor effects in ovarian cancer cells by upregulating cytochrome P450 family 1 subfamily A member 1 expression. Discov. Oncol., 2025; 16(1): 523.
64. Salehi M, Piri H, Farasat A, Pakbin B, Gheibi N. Activation of apoptosis and G0/G1 cell cycle arrest along with inhibition of melanogenesis by humic acid and fulvic acid in A375 human melanoma cells. Iran J. Basic Med. Sci., 2022; 25(4): 489–496.

65. Xin P, Li X, Zhang Y, Zhang L, Wang Y, Li S, et al. Natural fulvic acids inhibit non-small-cell lung cancer through the COX-2/PGE2/EP4 axis: in silico and in vivo assessments. Heliyon. 2023; 9(6): e17080.
66. Schellekens J, Buurman P, Kalbitz K, van Zomeren AV, Vidal-Torrado P, Cerli C, et al. Molecular features of humic acids and fulvic acids from contrasting environments. Environ. Sci. Technol., 2017; 51(3): 1330–1339.
67. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MP, Acosta-Torres LS, et al. Nano-based drug delivery systems: recent developments and future prospects. J Nanobiotechnol., 2018; 16: 71.
68. Al-Samydai A, et al. Advancements of metallic nanoparticles: a promising frontier in cancer treatment. Sci Prog., 2024; 107(4): 368504241274967.
69. Wang Y, Liu C, Zhang Y, Zhou Y. Peptide-mediated nanocarriers for targeted drug delivery: advances and prospects. Pharmaceutics (Basel). 2024; 16(2): 256.
70. Viegas C, Rodrigues M, Rodrigues MA. Advances in pancreatic cancer treatment by nano-based drug delivery systems. Cancers (Basel). 2023; 15(16): 3732.
71. Yuan Y, Chiba P, Cai T, Callaghan R, Bai L, Cole SPC, et al. Fabrication of psoralen-loaded lipid–polymer hybrid nanoparticles and their reversal effect on drug resistance of cancer cells. Oncol. Rep., 2018; 40(5): 2853–2860.
72. Mohanty A, Uthaman S, Park IK. Utilization of polymer-lipid hybrid nanoparticles for targeted anti-cancer therapy. Molecules. 2020; 25(19): 4377.
73. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, et al. Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. Front Mol. Biosci., 2020; 7: 193.
74. Fernandes DA. Liposomes for cancer theranostics. Pharmaceutics. 2023; 15(10): 2448.
75. Jayasooriya RGPT, Dilshara MG, Kang CH, Lee S, Choi YH, Jeong YK, et al. Fulvic acid promotes extracellular anticancer mediators from RAW 264.7 cells causing cancer cell death in vitro. Int Immunopharmacol. 2016; 36: 241–248.
76. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat. Rev. Drug Discov., 2021; 20(2): 101–124.
77. Qian Q, Shi L, Gao X, Ma Y, Yang J, Zhang Z, et al. A paclitaxel-based mucoadhesive nanogel with multivalent interactions for cervical cancer therapy. Small. 2019; 15(47): e1903208.

78. Osmałek T, Froelich A, Jadach B, Tatarek A, Gadziński P, Falana A, et al. Recent advances in polymer-based vaginal drug delivery systems. Pharmaceutics. 2021; 13(6): 884.bmj
79. Zhao Y, Wang T, Chen Z, et al. Development and evaluation of a thermosensitive in situ gel formulation for intravaginal delivery of *Lactobacillus gasseri*. Pharmaceutics. 2022; 14(9): 1934.
80. Qian H, Wang L, Zhang Y, Yan M, Zhang J, Wang D. PLGA-PEG-PLGA thermosensitive hydrogels as injectable drug carriers. J Biomater Appl. 2018; 32(5): 622–630.
81. Yin L, Song Z, Kim KH, et al. Injectable biodegradable hydrogels and their application in drug delivery and tissue engineering. Int J Biol Macromol. 2020; 152: 1135–1144.
82. Fan R, Cheng Y, Wang R, Zhang T, Zhang H, Li J, et al. Thermosensitive hydrogels and advances in their application in disease therapy. Polymers (Basel). 2022; 14(12): 2379.
83. Ensign LM, Cone R, Hanes J. Nanoparticle-based drug delivery to the vagina: a review. J Control Release. 2014; 190: 500–514.
84. Kutle I, Polten R, Hachenberg J, Klapdor R, Morgan M, Schambach A. Tumor organoid and spheroid models for cervical cancer. Cancers (Basel). 2023; 15(9): 2518.
85. Daum AK, Dittmann J, Jansen L, Peters S, Dahmen U, Heger JI, et al. ITIH5 shows tumor suppressive properties in cervical cancer cells grown as multicellular tumor spheroids. Am. J. Transl. Res., 2021; 13(9): 10298–10314.
86. Pedraza-Brindis EJ, Sánchez-Reyes K, Hernández-Flores G, Bravo-Cuellar A, Jave-Suárez LF, Aguilar-Lemarroy A, et al. Culture supernatants of cervical cancer cells induce an M2 phenotypic profile in THP-1 macrophages. Cell Immunol. 2016; 310: 42–52.
87. Zhang Y, Zhou Q, Xu Y, Yang L. Patient-derived xenograft models in cervical cancer: a systematic review. Int. J. Mol. Sci., 2021; 22(17): 9369.
88. Zou S, Ye M, Zhang JA, Ji H, Chen Y, Zhu X. Establishment and genetic characterization of patient-derived xenograft models of cervical cancer. BMC Med Genomics. 2022; 15(1): 191.
89. Li Y, Zhang X, Liu J, Wang H. Biological activities and potential therapeutic applications of fulvic acid: a review**.** J. Agric. Food Chem., 2019; 67(23): 6553–6564.
90. Winkler J, Ghosh S. Therapeutic potential of fulvic acid in chronic inflammatory diseases and diabetes. J Diabetes Res., 2018; 2018: 5391014.

91. Su S, Kang PM. Recent advances in nanocarrier-assisted therapeutics delivery systems. Pharmaceutics. 2020; 12(9): 837.