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Understanding the Risk Factors and Diagnosis of Cervical Cancer: A Review of Vaccination and Drug Delivery Materials

Shubhanshu Goel[1]*, Monika Singh[1], Shubh Deep Yadav[1], Moumita Barman[1]

[1] *I.T.S. College of Pharmacy Murad Nagar, Ghaziabad, Uttar Pradesh, 201206, INDIA*

*Corresponding Author: shubhanshugeol@its.edu.in
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Abstract

Cervical cancer remains a prevalent health issue globally, with risk factors such as multiple sexual partners, use of certain contraceptives, smoking, and specific dietary patterns contributing to its incidence. This review aims to provide a comprehensive overview of cervical cancer epidemiology, etiological factors, diagnostic methods, and current treatment strategies. Although cervical cancer often progresses without noticeable symptoms initially, once it affects other organs, symptoms may include pelvic pain, abnormal vaginal bleeding, and gynecological infections. Preventive measures are crucial, particularly vaccination between ages 9 and 15, to reduce the risk of high-risk HPV strains known to cause cervical cancer. Additionally, radiotherapy, immunotherapy, chemotherapy and novel drug delivery methods are instrumental in cervical cancer management. This review highlights recent advancements in cervical cancer management, especially focusing on materials engineering aspects of drug delivery and the role of screening techniques in early diagnosis. These insights aim to enhance clinical and public health approaches to reduce the global burden of cervical cancer effectively.

1. Introduction

After lung, breast, and colon cancers, cervical cancer is the fourth most common malignancy among women globally. Many reports show how this illness affects female mortality in different parts of Africa, such as the eastern, western, central, and southern regions. Every year, cervical cancer claims the lives of 50,000 to 60,000 people; more than one-third of new cases worldwide are reported from China and India. It is the third most common cause of cancer-related deaths among women and the second most common type of cancer identified in less developed nations. Women are diagnosed with cervical cancer on average at the age of 53, and the average age of death is 59. The occurrence of this cancer has seen a decline in developed nations, attributed mainly to lifestyle modifications like quitting smoking and the advancement of screening and medical interventions [1]. Cervical carcinoma manifests in diverse forms, ranging from asymptomatic early-stage conditions identified through screenings to more severe symptoms such as abnormal vaginal bleeding, bacterial infections, pelvic discomfort, or advanced stages involving cyst formation or metastasis. The cancer primarily spreads via direct extension into the cervix, uterus, vagina, surrounding tissues, and lymphatic system, eventually reaching distant organs. Surgical intervention is the preferred treatment in the initial stages, particularly stages 1 and 2, with procedures varying from complete hysterectomy to localized cone biopsies. In contrast, primary radiotherapy remains the standard care in economically challenged regions, serving both palliative and curative purposes. Studies have demonstrated that combining chemotherapy with radiation therapy significantly enhances survival rates [2].

1.1 Cervical Cancer Epidemiology

Cervical cancer is primarily caused by the human papillomavirus (HPV). Having multiple pregnancies, having multiple sexual partners, and sexually transmitted diseases (STDs) can also contribute to the disease. There are approximately 100 types of HPV, and types 16 and 18 are linked to 70% of cases of cervical cancer. The HPV vaccine can prevent over 90% of precancerous conditions and cervical cancer, especially in children between the ages of 9 and 12. Since these high-risk strains are responsible for a large number of cancer cases, especially in India, vaccinations against these strains are necessary. Cervical cancer typically develops slowly over ten to fifteen years, allowing for early detection and treatment with straightforward procedures [3,4].

1.2 Human Papillomavirus (HPV) Genome and Functions

Cervical cancer is mostly caused by the human papillomavirus (HPV), which comes in two varieties: high-risk and low-risk. More than 99% of occurrences of cervical cancer are caused by high-risk kinds, whereas low-risk types may result in warts or no symptoms at all. About 40 of the approximately 200 HPV strains are human-pathogenic, with types 16 and 18 accounting for 70% of occurrences of cervical cancer. About one-fifth of adenocarcinomas are type 18 cases, while type 16 is associated with half of all cervical cancer cases. HPV infections can result in cervical intraepithelial neoplasia (CIN), which can advance through stages (CIN1, CIN2, and CIN3) and, in the case of chronic, high-risk HPV infections, may eventually lead to cancer [5]. The compact DNA virus HPV has about 8,000 base pairs and a genome that includes eight to ten open reading frames. It has three main parts: the early gene area, the late gene area, and a long control region (LCR) in the non-coding section. The early genes are important for regulating proteins and helping the virus replicate at different stages of its cycle. The late genes produce capsid proteins. The LCR has regulatory elements that control how genetic information is passed in the open reading frames, including the p97 core promoter [6].

1.3 Causes of Cervical Cancer

Genetic material from HPV has been detected in about 95% of cervical cancer cases, highlighting a significant association between the virus and this form of cancer. Persistent HPV infections can lead to severe conditions like cervical intraepithelial neoplasia or adenocarcinoma in situ, although most infections are temporary and resolve on their own. Without treatment, many women undergo years or even decades of progression from dysplasia to aggressive cancer. However, in approximately 10% of affected individuals, this progression can occur in less than a year. Furthermore, adenocarcinoma in situ often evades detection through Pap tests, underscoring its importance as a prevalent type of cervical cancer [7].

1.4 Role of Female Sex Hormones in Cervical Cancer

Cervical cancer incidence in unscreened populations peaks between 40 and 45 years of age, although most carcinomas worsen with age. This age pattern is comparable to that of estrogen-dependent breast cancer. Reanalyzes of data on women infected with HPV have revealed that the risk of cervical cancer is considerably higher in women who have used oral contraceptives for a longer period of time than in those who have never used them. But after ten or more years, when a woman stops taking oral contraceptives, her risk goes back to what it was before. Cervical cancer risk is three times higher in women who have had seven or more full-term pregnancies, beginning at age 17 or younger, than in nulliparous women [8,9].

1.4.1 Estrogen, Progesterone, and Their Roles in Nuclear Receptor Signaling

G-protein coupled estrogen receptor (GPER), estrogen receptor β (ERβ), and estrogen receptor α (ERα) all interact with estrogen. Progesterone binds to membrane progesterone receptors (mPRs), progesterone receptor membrane components (PGRMCs), and progesterone receptors (PRs). ERα, ERβ, and PR are part of a group of transcription factors that rely on ligands. Targeting these receptors has been effective in treating various disorders, including cancer [10]. A rise in estrogen during a person's hormonal cycle causes physical changes, such as the proliferation of cells in the female reproductive system, which includes the cervix. Progesterone receptors (PR) in the cervix are expressed more when estrogen levels are higher, but because progesterone levels are low during this period, PR activity is also low. PR levels fall in along with a reduction in estrogen levels. PR activates when progesterone levels rise. While ERβ levels rise in the cervix during pregnancy, its precise function in this situation is still unclear [11,12]. It has been discovered that Erα and Erβ, respectively, stimulate and inhibit the formation of breast tumors. Compared to estrogen receptors, the function of progesterone receptors (PR) in the proliferation of epithelial cells is less well characterized. The N-terminus of the two PR variants produced by the PGR gene, PR-A and PR-B, differ by an extra 164 amino acids. In uterine muscle cells, progesterone has anti-inflammatory actions that are enhanced by PR-B and inhibited by PR-A [13,14].

1.5 Distinct Aspects of Cervical Cancer

1.5.1 Dietary Factors

Diet plays a crucial role in this study. Vitamin C and beta-carotene have been shown to protect against cervical cancer. A Chinese study found that eating green vegetables had a protective role against cervical cancer [15].

1.5.2 Family Planning Practices

Several studies have shown the effect of different contraceptive methods shows the risk of cervical cancer. Using contraception is among the most prevalent methods of family planning. Most studies have shown a high risk of cervical neoplasia as pill use increases. The barrier method has been recommended as a preventive measure to prevent cervical cancer because it prevents some sexually transmitted diseases [15].

1.5.3 Multiple Sex Partner

Cervical cancer is primarily caused by sexually transmitted infections, especially those brought on by the human papillomavirus (HPV). Having several sexual partners and maintaining poor genital cleanliness are significant risk factors for HPV transmission. Types 16 and 18 of the 100 known HPV types are categorized as high-risk variations for cervical cancer. Interestingly, these two kinds account for over 70% of cervical cancer incidences in India.

1.5.4 Smoking

Tobacco use has also been identified as an important cause of the processes leading to cervical cancer. Cigarette-related tumors are primarily squamous cell tumors, such as lung or esophageal tumors. It has been assumed that the effect of smoking is most pronounced in the oncogenic response of squamous cells. Therefore, cervical cancer may be linked to smoking [15].

1.6 Symptoms

Following are the most typical signs of cervical cancer:

- Vaginal bleeding that is not associated with periods
- Discomfort during sexual activity
- Foul-smelling discharge
- Pelvic and abdominal pain
- Postmenopausal bleeding
- Postcoital bleeding
- Gynecological Infection
- Endometriosis [16,17]

1.7 Disease Management

In its initial stages, cervical cancer might not present any symptoms and can be detected during routine pelvic examinations. The most common symptom observed is excessive or abnormal vaginal bleeding, particularly post-coital. Some women might also experience a discharge that could be foul-smelling, thick, or clear. Advanced-stage patients might suffer from pain in the pelvic region or lower back, pain along the side of the body, and swelling in the lower extremities. Additionally, complications involving the digestive or urinary systems, such as altered pressure sensations or the unintended passage of stool or urine into the vaginal area, may indicate that the cancer has spread to the rectum or bladder. A pelvic exam, which includes a biopsy and an evaluation of the vaginal lining and cervix, is conducted when symptoms suggestive of cervical cancer are present. The cervix might look normal if the cancer is in a microinvasive stage or located within the endocervical canal. Conversely, large tumors may appear to engulf the cervix, and the presence of swollen lymph nodes could suggest metastatic spread [18,19]. A colposcopy is conducted if a patient's Pap smear test indicates an advanced precancerous condition or persistent low-grade cellular changes. Large loop excision of the transformation zone (LLETZ) is a medical procedure employed to eliminate precancerous cells and deter cancer progression, particularly following a biopsy or colposcopy [20].

1.8 Diagnosis

Numerous studies have demonstrated the frequent association between high-risk Human Papillomavirus strain infections and cervical cancer. The progression of cervical cancer, spanning from its early detection to advanced stages, impacts the strategies employed in secondary prevention, diagnosis, and treatment. Cervical intraepithelial neoplasia (CIN1) is a modest abnormality that begins a steady progression to more significant

neoplastic disorders and microinvasive growths, which ultimately lead to invasive carcinoma. This progression is logical, considering that high-risk HPV infections typically begin early in an individual's life, persist over extended periods, and may evolve into more aggressive forms when coupled with other factors that promote cellular changes. Early detection and treatment of HPV in precancerous stages are universally recognized as critical steps in halting the progression to cancer. Conventional immunological techniques struggle to detect HPV infections because it's challenging to culture the virus from clinical samples. Historically, histological and cytological analyses have served as the main diagnostic methods. Nevertheless, recent progress in molecular biology has enabled the creation of techniques capable of detecting HPV DNA in clinical specimens [21].

1.9 Cervical Cancer Screening

Cervical cancer screening is critical for detecting precancerous changes in the cervix, allowing for early management before cervical cancer occurs. Several screening approaches are used, with a focus on HPV testing, cytology screening (also known as the Pap test), or a combination of the two (referred to as "co-testing") and visual screening.

1.9.1 HPV Testing

Cervical cancer can result from high-risk HPV strain infection, which is checked for during this treatment. It provides helpful details on a person's risk profile [22].

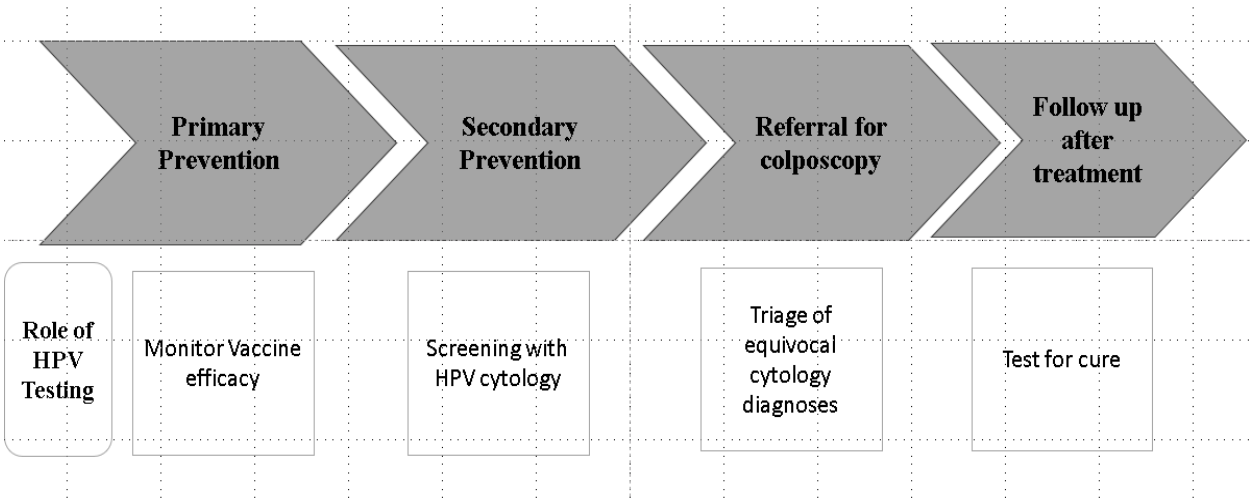

Fig. 1 *Role of HPV testing in cervical cancer*

1.9.2 Assay to Detect HPV: HPV DNA Assays

HPV DNA Assays can be categorized into the following subgroups:

1. Assays that detect the presence of carcinogenic HPV types without providing specific genotyping information.
2. Assays that offer genotyping information for a few key carcinogenic HPV types, primarily HPV 16 and HPV 18.
3. Assays capable of genotyping a wide range of HPV types simultaneously.

The most widely used HPV DNA assay globally is the Hybrid Capture 2 and HPV DNA test. This hybridization-based assay identifies 13 carcinogenic HPV types, along with HPV 66, though it has been noted that it may cross-react with non-carcinogenic HPV types [23].

1.9.3 Assay to Detect HPV: HPV RNA Assays

During an HPV infection, specific proteins are expressed, with the E6 and E7 proteins playing crucial roles in cancer development. The overexpression of these proteins leads to the inactivation of the tumor suppressor proteins p53 and retinoblastoma, contributing to malignant transformation. Since the expression of E6 and E7 is essential for carcinogenesis, they may serve as valuable biomarkers for infections associated with cervical cancer or precancerous conditions. Moreover, E6 and E7 levels are generally higher in transforming infections than in transient infections that resolve spontaneously, suggesting that measuring their expression could help identify clinically significant HPV infections. Two tests are currently available for detecting mRNA levels of E6 and E7: APTIMA (by GenProbe) and PreTect HPV-Proofer (by Norchip). The APTIMA HPV Assay identifies E6/E7

mRNA from 14 different HPV genotypes. In contrast, the PreTect HPV-Proofer assay detects E6/E7 mRNA from only five carcinogenic HPV types and has not received FDA approval for cervical cancer screening [24].

- Cytology Screening (Pap Test): Cytological screening has demonstrated its effectiveness in reducing both the occurrence and death rate associated with cervical cancer over many years. In this procedure, cells are obtained from both the external surface (ectocervix) and the cervical canal (endocervix) of the cervix. Pathologists analyze these cells to evaluate the transformation zone (squamocolumnar junction), which is particularly susceptible to neoplasia. The advantages of cytology screening include its relatively high specificity and cost-effectiveness [22].
- Visual screening Tests: Once 3-5% diluted acetic acid has been applied, the cervix is visually examined under bright light for one minute. This process is known as Visual Inspection with Acetic Acid (VIA). Good results are indicated by a prominent, thick acetowhite region. VIA is suitable for premenopausal women below the age of 50, especially when the transformation zone (TZ) on the ectocervix is visible. However, VIA is not recommended for women over the age of 50. It is a straightforward, practical, and cost-effective method that provides rapid results, allowing women with positive screening to be diagnosed or treated during the same visit [25].

1.10 Treatment of Cervical Cancer

There are now three HPV vaccinations that are authorized for use:

- The quadrivalent vaccine Gardasil targets HPV6, HPV11, HPV16, and HPV18.
- The bivalent vaccine Cervarix targets both HPV16 and HPV18.
- Vaccination against HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, and HPV58 is covered by the nonvalent Gardasil 9.

Licenses were granted for Gardasil and Gardasil 9 in 2006 and 2014, respectively. These vaccines contain the amorphous aluminum hydroxy phosphate sulfate adjuvant and are made with the Saccharomyces cerevisiae expression system. For those ages 9 to 26, Gardasil is advised as a preventative measure against dysplastic lesions, genital warts, and cervical cancer. On the other hand, Gardasil 9 is licensed to prevent genital warts, precancerous or dysplastic lesions, cervical, vulvar, vaginal, and anal cancers in both boys and females between the ages of 9 and 45. It also offers protection against an extra five HPV strains [26].

2. Vaccination Schedules

Initially, a three-dose vaccination schedule was used to approve HPV vaccines. According to recent research, receiving two or even just one dose of the Cervarix vaccine may increase its effectiveness. Studies have shown that when girls between the ages of 9 and 14 receive two doses of the Cervarix vaccine at months 0 and 6, their HPV-16/18 antibody responses are better than those of those who receive two doses of the Gardasil vaccine at the same intervals or three doses at months 0, 2, and 6 [27,28].

This new information has led the World Health Organization (WHO) to recommend a two-dose HPV vaccination schedule for people between the ages of 9 and 15 years, with the second dose given at least six months after the first. A number of randomized trials have shown that women who follow the two-dose schedule either show similar or inconclusive immune responses to those who follow the three-dose regimen [29].

2.1 Vaccines Based on Live Vectors

Live vector vaccines are known for their high immunogenicity and minimal toxicity, rendering them ideal for conveying HPV E6 and HPV E7 antigens to dendritic cells. They offer several advantages, such as the flexibility to choose an appropriate vector from a diverse range for delivering antigens tailored for specific effects. These vectors, categorized into viral and bacterial vectors, have been scrutinized as promising tools for developing therapeutic HPV vaccines [30]. Attenuated bacterial vector-based vaccines have been investigated for HPV therapeutic applications, including those derived from Listeria monocytogenes, Lactobacillus lactis, Lactobacillus plantarum, and Salmonella enterica. Among these, Listeria monocytogenes has garnered significant attention due to its ability to replicate in the cytosol of antigen-presenting cells (APCs) and to infect monocytes and macrophages. Viral vector-based vaccines also present a compelling option for HPV therapy, as they demonstrate high immunogenicity and efficient infection rates, leading to effective expression of encoded antigens within infected cells. Several preclinical studies have highlighted the effectiveness of live viral vectors, such as vaccinia virus, adenovirus, adeno-associated virus, and fowl pox virus. In particular, vaccinia virus is viewed as a promising candidate for antigen-specific immunotherapy due to its high infection efficiency [31].

2.1.1 Vaccines Based on Peptides and Proteins

Peptide-based HPV vaccinations entail the injection of peptides extracted from HPV antigens into the body. Subsequently, dendritic cells (DCs) uptake these peptides and present them alongside MHC class I and class II molecules. Despite their ease of production, stability, and safety profile, these vaccines have demonstrated limited immunogenicity [32]. Protein-based vaccines for HPV-related cervical cancer are favored for their safety and simple manufacturing process. These vaccines facilitate the digestion and presentation of protein antigens on dendritic cells, encompassing a wide range of HLA epitopes. Nonetheless, their immunogenicity is moderately constrained, prompting the frequent use of adjuvants and fusion protein strategies to augment vaccine efficacy [33].

2.1.2 Vaccines Based on Tumor Cells

The use of tumor cell-based vaccinations presents an innovative approach by circumventing the requirement for precise identification of tumor antigens. Given the well-defined nature of HPV-associated tumor antigens, modifying and isolating tumor cells to express immunomodulatory proteins such as IL-2 and IL-12 can amplify their immunogenicity in vivo. However, scaling up the production of tumor cell-based vaccines poses challenges due to cost and the complexities of ensuring consistent purity and efficacy. Consequently, this approach has restricted utility in advancing HPV vaccine development [30].

2.1.3 Vaccines Based on Dendritic Cells

By loading dendritic cells (DCs) with HPV antigens ex vivo and then delivering these cells to HPV-associated lesions, a natural adjuvant has been developed to improve T-cell mediated immunity. DCs can be produced ex vivo using a variety of techniques, including the use of viral vectors, DNA or RNA encoding the antigen transfection, and stimulation of DCs with protein antigens, peptides, or lysates obtained from cancer cells [34].

2.1.4 Prophylactic Vaccination Against HPV

In most cases, the immune system successfully eliminates the infection. However, a small percentage of individuals experience chronic infection, where the viral genome integrates into the host DNA. This dysregulation is primarily driven by HPV oncogenes E6 and E7. Prophylactic vaccination aims to stimulate high levels of HPV-specific neutralizing antibodies, effectively preventing cervical infection. Two vaccines, developed using virus-like particles of HPV types 16 and 18 with different adjuvants, have been introduced. One vaccine is bivalent, targeting types 16 and 18, while the other is quadrivalent, covering types 6 and 11, responsible for genital warts. Extensive testing occurred across phase 1, phase 2, and pivotal phase 3 trials. However, findings from these trials indicated that the vaccines did not protect females already infected with HPV [35,36].

2.2 Recent Advances in Preventive Vaccination

Three doses were initially needed for the initial vaccination program, and they were to be given at 0, 2, and 6 months. Recent studies, however, indicate that if a second dose is administered six to twelve months after the first dose, it may be just as effective as three doses. Additionally, a significant advancement in the development of vaccines has been made: a non-covalent vaccination that targets not only the current kinds 6, 11, 16, and 18, but also types 31, 33, 52, 58, and 45. According to phase 3 trials, this novel vaccine exhibits great efficacy against recently discovered kinds and comparable efficiency versus the original types (6, 11, 16, and 18) [37].

2.3 Radiotherapy

Radiotherapy, a vital component in the treatment of cervical cancer, uses high-energy X-rays to target cancer cells. Cervical cancer is presently treated using three basic methods of radiation treatment [38]:

- External Beam Radiation Therapy (EBRT) administers high-intensity X-rays to the tumor from an external machine. While similar to standard X-rays, EBRT delivers significantly higher radiation doses. EBRT is commonly the primary treatment for cervical cancer, often combined with chemotherapy (referred to as concurrent chemoradiation) to enhance its efficacy. Typically, treatment spans 5 weeks, with radiation sessions occurring 5 days per week. If the cancer hasn't spread to distant sites, brachytherapy (explained below) may follow concurrent chemoradiation.
- Intensity-Modulated Radiation Therapy (IMRT) represents an advanced radiation approach. It precisely shapes photon and proton radiation beams to match the tumor's contours. IMRT is effective for both malignant and non-cancerous tumors.
- Brachytherapy administers high-dose radiation directly to the tumor or places a radioactive implant at the tumor site, thereby minimizing harm to nearby healthy tissues. This targeted method reduces the impact on surrounding structures.

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Even if radiation therapy is effective, side effects might occur, such as lymphedema, skin toxicity, pelvic pain, diarrhea, and abdominal cramps.

2.4 Chemotherapy

Chemotherapy is commonly administered after surgery for cervical cancer, particularly when high-risk tumor characteristics elevate the risk of cancer returning. Cisplatin, a platinum-based chemotherapy medication, has been a cornerstone of cervical cancer treatment for many years. However, despite its initial effectiveness, patients frequently develop resistance to cisplatin over time, diminishing the efficacy of subsequent platinum-based therapies. In response, researchers have investigated combination therapies to enhance cisplatin's effectiveness. Chemotherapy is often paired with radiation therapy (chemoradiotherapy), primarily used to treat locally advanced cervical cancer. While this combined approach aims to decrease the likelihood of cancer recurrence, it may also lead to significant side effects and long-term health concerns. Systematic reviews and meta-analyses consistently indicate that chemoradiotherapy improves overall survival, and progression-free survival, and reduces the chances of both local and distant recurrence of cervical cancer [39,40].

2.5 Various Approaches for Delivering Drugs in Cervical Cancer Therapy

2.5.1 Nanoparticles

Biodegradable polymeric nanoparticles are increasingly important in delivering anticancer drugs due to their ability to carry high drug payloads, self-stabilize, improve cellular uptake, promote favorable biodistribution, and transport both hydrophilic and hydrophobic drugs. These polymers, whether natural or synthetic, undergo degradation either chemically or enzymatically. Biodegradable polymers offer advantages in controlling drug release kinetics based on their degradation rates, enabling sustained and controlled drug delivery. Moreover, these polymeric carriers transform into non-toxic, absorbable subunits that can be metabolized, thereby eliminating the need for surgical removal after drug depletion [41].

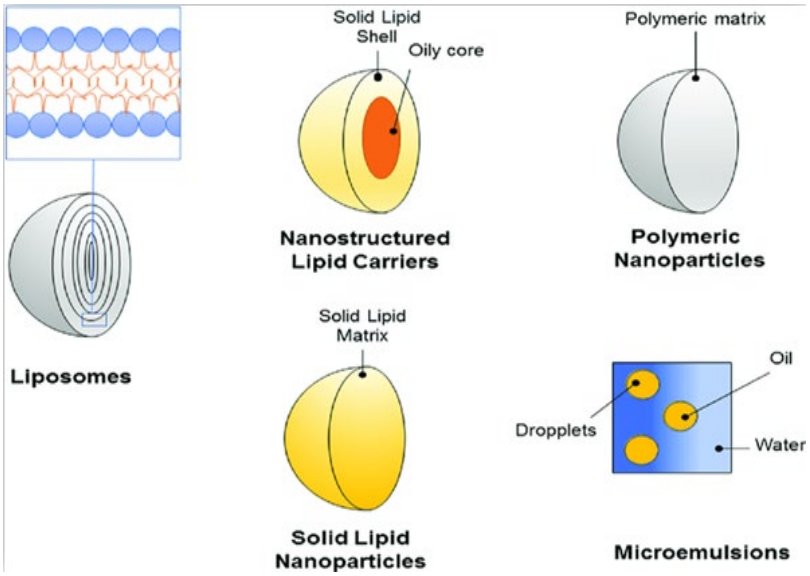

Fig. 2 *Illustration of nanostructured drug delivery systems*

2.5.2 Nano Emulsion

Nano emulsions are complex systems where tiny oil droplets are dispersed in water, stabilized by surfactants or emulsifying agents, often amphiphilic surfactants that reduce the tension between oil and water phases [42,43]. Effective vascularization is critical for tumor tissues, as inadequate vascularization can lead to abnormalities in the basement membrane and lymphatic vessels, causing poor drainage and increased permeability (pores ranging from 380-780 nm). Nanotherapeutic drugs have been developed as a result of this need. Greater than 100 nm in size, larger particles may be identified by the mononuclear phagocyte system, whereas smaller nanoscale devices can be filtered by the kidneys [44]. Smaller than 200 nm is the usual range for nano emulsions. With a larger surface area provided by smaller droplet sizes, drugs can be administered and absorbed more quickly and consistently. As such, they are efficient drug transporters, increasing the effectiveness of delivery while decreasing toxicity [45].

2.5.3 Polymeric Nanoparticles (PNPs)

Polymeric nanoparticles (PNPs) possess notable features such as resistance to enzymatic degradation, controlled drug release, and superior penetration capabilities. These nanoparticles vary in size from 1 to 100 nm and are constructed from a range of polymers, including polyacrylamide, polyacrylate, gelatin, chitosan, and polylactic acid. PNPs have proven effective in treating bacterial infections and in the chemotherapy of cervical cancer. For instance, chitosan-graft-poly was dissolved in water to form an aqueous dispersion, which facilitated the production of silver nanoparticles that demonstrated significant cytotoxic effects on human cervical HeLa carcinoma cells. Due to their flexible controlled release properties, responsiveness to the tumor microenvironment (TME), and enhanced solubility for insoluble anti-cancer drugs, PNPs are being explored as drug carriers specifically for cervical cancer. A recent study involved the grafting of a reduction-sensitive prodrug of 6-mercaptopurine (6MP) and pH-responsive doxorubicin (DOX) onto Poly (DEA)-b-Poly (ABMA-co-OEGMA) (referred to as PDPAO). Characterization revealed that these pH and reduction-sensitive polymers had an average particle size of 116 ± 2 nm, exhibiting stable spherical structures with a low dispersion index. Additionally, another study focused on the development of polymeric prodrugs based on hyaluronan and DOX through a self-assembly approach. These prodrugs demonstrated pH-dependent release characteristics and maintained stability in vitro. The polymeric vehicles exhibited enhanced cytotoxicity and increased apoptotic rates specifically in HeLa cells. Furthermore, the pH-dependent release system has the potential to mitigate dose-related toxicity associated with the anticancer agent chlorambucil (CBL) [46-48].

2.5.4 Metallic Nanoparticles

Metallic nanoparticles play a crucial role in biomedical applications, especially in targeted drug delivery, gene therapy, and diagnostics. Their distinctive physical, chemical, and optical properties position them as promising candidates for advancing cancer therapy. For example, they can serve as carriers for drugs like doxorubicin, a commonly used chemotherapy agent, or co-deliver drugs to enhance their penetration into tumor cells. This approach allows for reduced drug dosage while improving effectiveness against cancer cells. In one approach, nanoparticles combined with resveratrol (GNPs) form stable supramolecular nano assemblies with doxorubicin (Dox). These complexes demonstrate strong stability and potent anticancer effects against human cervical carcinoma cell lines, showcasing the potential of advanced drug delivery platforms in both cancer diagnosis and treatment [49-51].

2.5.5 Micelles

Micelles, composed of amphiphilic block copolymers, are colloidal particles capable of self-assembly. Their stability within the body, ability to solubilize water-insoluble drugs, extended circulation time in the bloodstream, and small size (usually between 10 and 100 nm) make them promising for cancer therapy. For instance, targeted polymeric composite micelles enhanced with folic acid and loaded with paclitaxel (PTX) have demonstrated encouraging outcomes in inhibiting tumor growth and promoting cell death in cervical cancer tumors, as evidenced by both laboratory studies and animal models [16,17]. PTX-loaded polymeric micelles made from a candesartan-g-polyethyleneimine-cis-1,2-cyclohexanedicarboxylic anhydride polymer with negative surface charges demonstrated significant antitumor efficacy. This effect is attributed to their ability to facilitate amidase-responsive drug release and enable rapid endosomal escape [52].

2.5.6 Liposomes

Liposomes were originally discovered by Bangham and colleagues in 1965 and have since become valuable carriers for drugs. They can be formulated using a variety of phospholipids and excipients, offering versatile systems with adjustable formulation parameters. These modifications significantly influence drug encapsulation capacity, permeability, stability, liposome size, and lamellarity [53,54]. Preparation methods for liposomes include agitation, sonication, extrusion, lyophilization, freeze-thaw cycles, reverse phase evaporation, detergent depletion, ether/ethanol injection [55,56], as well as emulsification and transmembrane pH gradient-driven encapsulation techniques. Alternative techniques such as dense gas or supercritical fluid methods are also employed, providing environmental benefits by eliminating potentially harmful organic solvents [57,58]. Comprising a single lipid bilayer, liposomes efficiently encapsulate both water-soluble and lipid-soluble drugs. These versatile vesicles are widely used in delivering anticancer drugs like cisplatin, bleomycin sulfate, and curcumin for treating cervical cancer. Targeted liposomes, such as those with transferrin targeting, have demonstrated enhanced specificity in delivering paclitaxel to cervical cancer cell lines compared to non-targeted liposomes, thereby enhancing the bioavailability, stability, and uptake of encapsulated chemotherapeutic agents [59,60].

Table 1 *Overview of liposomal nanocarriers utilized in cancer therapy*

Liposomes	Drug or Active Ingredient	Major Results	Ref
Liposomal AS-ODNs	Antisense oligode oxynucleotide	Additional research is still necessary.	55
Liposome-protamine-DNA (LPD) NPs	Cholesterol-conjugated mannan	Improved anti-tumor efficacy	56
Cationic liposomes	RNA duplexes or small-hairpin	I-RNA specifically regulates the expression of HPV-6b/11 E7 genes, offering a valuable approach for managing condyloma acuminatum.	57
Biphasic vesicles	INF-α	Biphasic vesicles, like the INF-α delivery system, effectively transport INF-α across intact skin, leading to therapeutic benefits in patients.	58
Liposome polycation DNA	E7 antigens	Regression of a model cervical cancer tumor. Potent carrier and/or adjuvant for various antigens in vaccines.	59
Agarose/liposome/ siRNA formulation	iRNA	Effective delivery of RNAi inducers to human epithelial cancer cells via topical gel.	60

2.5.7 Dendrimers

Dendrimers are distinguished by their large branching, amazing symmetry, and spherical form. They are very uniform because of their well-defined molecule size, surface charge, and structure. They are incredibly versatile because of their special architecture, which allows antigen molecules to adhere and present on their outer surface [61,62]. Their structure enables the attachment and display of antigen molecules on their surface, making them primarily multifunctional. Drugs can be incorporated into their core cavities through chemical bonds, hydrophobic interactions, hydrogen bonding, or conjugation to the polymer framework. A polyacrylate star polymer linked to the HPV E7 protein has been employed to enhance the immunogenicity of peptide-based vaccines for cervical cancer. Studies indicated that these conjugates, both alone and following a single immunization, effectively reduced tumor growth and eliminated E7-expressing TC-1 tumors in mice [52].

2.6 Recent Developments in Cervical Cancer Therapy

2.6.1 Immunotherapy for Cervical Cancer

Immunotherapy, focused on HPV oncoproteins, is gaining recognition as a promising treatment for cervical cancer. This strategy targets dysplastic precancerous and malignant cervical epithelial cells expressing these oncoproteins, resulting in substantial advancements in both laboratory research and clinical practice. Notably, it has driven the advancement of vaccines, checkpoint inhibitors, and adoptive T cell therapies tailored for cervical cancer. While success rates of different immunotherapies vary, many are presently undergoing clinical trials [63].

2.6.2 Therapeutic Targeting for Cervical Cancer

Chemotherapy drugs eradicate both cancerous cells and healthy rapidly dividing cells without discrimination, resulting in severe side effects such as anemia. In contrast, targeted therapies are specifically designed to inhibit substances, usually proteins, that are exclusively expressed by cancer cells, thereby controlling cancer progression, proliferation, and metastasis. Furthermore, targeted therapy focuses on overcoming the pathways of tumor drug resistance, which remains a significant hurdle in current treatment approaches [64].

2.6.3 Genetic Strategies in Addressing Cervical Cancer

Recent studies indicate strong potential for genome-editing technologies and genetic strategies aimed at targeting the HPV E6 and E7 genes in the treatment of cervical cancer. Notable examples include the CRISPR/Cas9 system utilizing clustered regularly interspaced short palindromic repeats (CRISPR) technology, as well as RNA interference (RNAi) [65].

2.6.4 Role of Combination Therapy in Cervical Cancer

Cervical cancer is a complex and resilient disease, and current treatment options often have limited effectiveness, largely due to tumor drug resistance associated with monotherapy. Utilizing a combination of therapeutic strategies can provide benefits over single-agent treatments, as these combinations are more likely to target multiple or redundant signaling pathways that are critical for the survival of cervical cells. Additionally, combination therapies can reduce treatment intensity, lower costs, decrease the number of cycles, and lessen the side effects typically seen with high-dose monotherapy. Chemotherapy is commonly administered alongside radiotherapy in cervical cancer treatment, which can lead to a reduction in tumor volume, inhibition of micro metastasis, prevention of damage repair and drug resistance, and increased radiosensitivity of hypoxic cells in the cervix. Some studies suggest that integrating immunotherapy with chemotherapy can enhance the sensitivity of cervical cancer tumors to subsequent chemotherapy. However, this approach may be limited by the immunosuppressive effects that chemotherapeutic agents can have on proliferating immune cells. Consequently, combining chemotherapy with immunotherapy could represent a promising advancement in cervical cancer treatment [66].

3. Conclusion

This study comprehensively examines the epidemiology, causative factors, and treatment approaches for cervical cancer, emphasizing the disease's complex interaction with lifestyle and preventive healthcare measures. Cervical cancer remains a prominent global health challenge, particularly due to its association with high-risk HPV types 16 and 18. These HPV strains contribute to over 70% of cases, highlighting the importance of early HPV vaccination, ideally administered between ages 9 to 15. Current vaccines, including Gardasil, Cervarix, and Gardasil 9, offer protection against multiple HPV strains, significantly reducing cervical cancer incidence.

Early screening of Pap tests, HPV DNA testing and visual inspection methods facilitates timely detection of precancerous changes, allowing for more effective intervention and improved patient outcomes. For those diagnosed with cervical cancer, a combination of radiotherapy, immunotherapy, and chemotherapy presents promising treatment pathways, particularly with HPV-targeted therapeutics focusing on viral proteins like E6 and E7, which play crucial roles in malignant transformation.

Further research should focus on refining HPV-based diagnostics and therapeutic approaches, particularly live-vector vaccine strategies, which show potential in targeting persistent infections. Addressing barriers to HPV vaccination and expanding access to screening in low-resource settings could significantly reduce the cervical cancer burden worldwide. Ultimately, advancing cervical cancer management requires a multi-faceted approach that integrates prevention, early detection, and innovative treatments to improve patient survival and quality of life.

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Conflict of Interest

Authors declare that there is no conflict of interests regarding the publication of the paper.

Author Contribution

The authors confirm contribution to the paper as follows: ***study conception and design:*** *Monika Singh;* ***data collection:*** *Shubhdeep Yadav;* ***analysis and interpretation of results:*** *Moumita Barman, Shubhanshu Geol;* ***draft manuscript preparation:*** *Shubhanshu Goel, Monika Singh. All authors reviewed the results and approved the final version of the manuscript.*

References

[1] Pimple, S., & Mishra, G. (2022). Cancer cervix: Epidemiology and disease burden. Cytojournal, 19.
[2] Denny, L. (2012). Cervical cancer: prevention and treatment. Discovery medicine, 14(75), 125-131.
[3] Perkins, R. B., Wentzensen, N., Guido, R. S., & Schiffman, M. (2023). Cervical cancer screening: a review. Jama, 330(6), 547-558.
[4] Bhatla, N., Meena, J., Kumari, S., Banerjee, D., Singh, P., & Natarajan, J. (2021). Cervical cancer prevention efforts in India. Indian Journal of Gynecologic Oncology, 19(3), 41.
[5] Bedell, S. L., Goldstein, L. S., Goldstein, A. R., & Goldstein, A. T. (2020). Cervical cancer screening: past, present, and future. Sexual medicine reviews, 8(1), 28-37.

[6] Zhang, J., Fan, J., Skwarczynski, M., Stephenson, R. J., Toth, I., & Hussein, W. M. (2022). Peptide-based nanovaccines in the treatment of cervical cancer: a review of recent advances. International Journal of Nanomedicine, 869-900.
[7] Small Jr, W., Bacon, M. A., Bajaj, A., Chuang, L. T., Fisher, B. J., Harkenrider, M. M., ... & Gaffney, D. K. (2017). Cervical cancer: a global health crisis. Cancer, 123(13), 2404-2412.
[8] Moreno, V., Bosch, F. X., Muñoz, N., Meijer, C. J., Shah, K. V., Walboomers, J. M., ... & Franceschi, S. (2002). Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. The Lancet, 359(9312), 1085-1092.
[9] International Collaboration of Epidemiological Studies of Cervical Cancer. (2006). Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. International journal of cancer, 119(5), 1108-1124.
[10] Robinson-Rechavi, M., Garcia, H. E., & Laudet, V. (2003). The nuclear receptor superfamily. Journal of cell science, 116(4), 585-586.
[11] Larsen, B., & Hwang, J. (2011). Progesterone interactions with the cervix: translational implications for term and preterm birth. Infectious diseases in obstetrics and gynecology, 2011(1), 353297.
[12] Wang, H., Stjernholm, Y., Ekman, G., Eriksson, H., & Sahlin, L. (2001). Different regulation of oestrogen receptors α and β in the human cervix at term pregnancy. Molecular human reproduction, 7(3), 293-300.
[13] Patel, B., Elguero, S., Thakore, S., Dahoud, W., Bedaiwy, M., & Mesiano, S. (2015). Role of nuclear progesterone receptor isoforms in uterine pathophysiology. Human reproduction update, 21(2), 155-173.
[14] Yang, S., Thiel, K. W., & Leslie, K. K. (2011). Progesterone: the ultimate endometrial tumor suppressor. Trends in Endocrinology & Metabolism, 22(4), 145-152.
[15] Juneja, A., Sehgal, A., Mitra, A. B., & Pandey, A. (2003). A survey on risk factors associated with cervical cancer. Indian Journal of Cancer, 40(1), 15-22.
[16] Singh, S., Narayan, N., Sinha, R., Sinha, P., Sinha, V. P., & Upadhye, J. J. (2018). Awareness about cervical cancer risk factors and symptoms. Int J Reprod Contracept Obstet Gynecol, 7(12), 4987-4991.
[17] Stapley, S., & Hamilton, W. (2011). Gynaecological symptoms reported by young women: examining the potential for earlier diagnosis of cervical cancer. Family practice, 28(6), 592-598.
[18] Lim, A. W., Ramirez, A. J., Hamilton, W., Sasieni, P., Patnick, J., & Forbes, L. J. (2014). Delays in diagnosis of young females with symptomatic cervical cancer in England: an interview-based study. British Journal of General Practice, 64(627), e602-e610.
[19] Rajaram, S., Chitrathara, K., & Maheshwari, A. (2012). Cervical cancer: contemporary management. JP Medical Ltd.
[20] Wuerthner, B. A., & Avila-Wallace, M. (2016). Cervical cancer: Screening, management, and prevention. The Nurse Practitioner, 41(9), 18-23.
[21] Burd, E. M. (2003). Human papillomavirus and cervical cancer. Clinical microbiology reviews, 16(1), 1-17.
[22] Ji, L., Chen, M., & Yao, L. (2023). Strategies to eliminate cervical cancer in China. Frontiers in Oncology, 13, 1105468.
[23] Castle, P. E., Schiffman, M., Burk, R. D., Wacholder, S., Hildesheim, A., Herrero, R., ... & Lorincz, A. (2002). Restricted cross-reactivity of hybrid capture 2 with nononcogenic human papillomavirus types. Cancer Epidemiology Biomarkers & Prevention, 11(11), 1394-1399.
[24] Mietz, J. (2012). M. Scheffner, H. Romanczuk, K. Münger, Jm Huibregtse, Ja Mietz, And Pm Howley. Human Pathogenic Papillomaviruses, 186, 83.
[25] Banerjee, D., Mittal, S., Mandal, R., & Basu, P. (2022). Screening technologies for cervical cancer: Overview. Cytojournal, 19.
[26] Wang, R., Pan, W., Jin, L., Huang, W., Li, Y., Wu, D., ... & Liao, S. (2020). Human papillomavirus vaccine against cervical cancer: Opportunity and challenge. Cancer letters, 471, 88-102.
[27] Kreimer, A. R., Rodriguez, A. C., Hildesheim, A., Herrero, R., Porras, C., Schiffman, M., ... & CVT Vaccine Group. (2011). Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. Journal of the National Cancer Institute, 103(19), 1444-1451.
[28] Leung, T. F., Liu, A. P. Y., Lim, F. S., Thollot, F., Oh, H. M. L., Lee, B. W., ... & Struyf, F. (2018). Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and 4vHPV vaccine administered according to two-or three-dose schedules in girls aged 9–14 years: Results to month 36 from a randomized trial. Vaccine, 36(1), 98-106.
[29] Dobson, S. R., McNeil, S., Dionne, M., Dawar, M., Ogilvie, G., Krajden, M., ... & Young, E. (2013). Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. Jama, 309(17), 1793-1802.

[30] Bergot, A. S., Kassianos, A., Frazer, I. H., & Mittal, D. (2011). New approaches to immunotherapy for HPV associated cancers. Cancers, 3(3), 3461-3495.
[31] Peralta-Zaragoza, O., Bermúdez-Morales, V. H., Pérez-Plasencia, C., Salazar-León, J., Gómez-Cerón, C., & Madrid-Marina, V. (2012). Targeted treatments for cervical cancer: a review. OncoTargets and therapy, 315-328.
[32] Vambutas, A., DeVoti, J., Nouri, M., Drijfhout, J. W., Lipford, G. B., Bonagura, V. R., ... & Melief, C. J. M. (2005). Therapeutic vaccination with papillomavirus E6 and E7 long peptides results in the control of both established virus-induced lesions and latently infected sites in a pre-clinical cottontail rabbit papillomavirus model. Vaccine, 23(45), 5271-5280.
[33] Frazer, I. H., Quinn, M., Nicklin, J. L., Tan, J., Perrin, L. C., Ng, P., ... & Basser, R. L. (2004). Phase 1 study of HPV16-specific immunotherapy with E6E7 fusion protein and ISCOMATRIX™ adjuvant in women with cervical intraepithelial neoplasia. Vaccine, 23(2), 172-181.
[34] Kim, J. H., Kang, T. H., Noh, K. H., Bae, H. C., Kim, S. H., Do Yoo, Y., ... & Kim, T. W. (2009). Enhancement of dendritic cell-based vaccine potency by anti-apoptotic siRNAs targeting key pro-apoptotic proteins in cytotoxic CD8+ T cell-mediated cell death. Immunology letters, 122(1), 58-67.
[35] Zhao, Q., Modis, Y., High, K., Towne, V., Meng, Y., Wang, Y., ... & Sitrin, R. D. (2012). Disassembly and reassembly of human papillomavirus virus-like particles produces more virion-like antibody reactivity. Virology journal, 9, 1-14.
[36] Future II Study Group. (2007). Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. New England Journal of Medicine, 356(19), 1915-1927.
[37] Small Jr, W., Bacon, M. A., Bajaj, A., Chuang, L. T., Fisher, B. J., Harkenrider, M. M., ... & Gaffney, D. K. (2017). Cervical cancer: a global health crisis. Cancer, 123(13), 2404-2412.
[38] Burmeister, C. A., Khan, S. F., Schäfer, G., Mbatani, N., Adams, T., Moodley, J., & Prince, S. (2022). Cervical cancer therapies: Current challenges and future perspectives. Tumour Virus Research, 13, 200238.
[39] Tewari, K. S., & Monk, B. J. (2005). Gynecologic oncology group trials of chemotherapy for metastatic and recurrent cervical cancer. Current oncology reports, 7, 419-434.
[40] Green, J. A., Kirwan, J. J., Tierney, J., Vale, C. L., Symonds, P. R., Fresco, L. L., ... & Collingwood, M. (2005). Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. Cochrane database of systematic reviews, (3).
[41] Joshi, J. R., & Patel, R. P. (2012). Role of biodegradable polymers in drug delivery. Int J Curr Pharm Res, 4(4), 74-81.
[42] Shafiq, S., Shakeel, F., Talegaonkar, S., Ahmad, F. J., Khar, R. K., & Ali, M. (2007). Development and bioavailability assessment of ramipril nanoemulsion formulation. European journal of pharmaceutics and biopharmaceutics, 66(2), 227-243.
[43] Hippalgaonkar, K., Majumdar, S., & Kansara, V. (2010). Injectable lipid emulsions—advancements, opportunities and challenges. Aaps Pharmscitech, 11, 1526-1540.
[44] Caron, W. P., Lay, J. C., Fong, A. M., La-Beck, N. M., Kumar, P., Newman, S. E., ... & Zamboni, W. C. (2013). Translational studies of phenotypic probes for the mononuclear phagocyte system and liposomal pharmacology. Journal of Pharmacology and Experimental Therapeutics, 347(3), 599-606.
[45] Kang, B. K., Chon, S. K., Kim, S. H., Jeong, S. Y., Kim, M. S., Cho, S. H., ... & Khang, G. (2004). Controlled release of paclitaxel from microemulsion containing PLGA and evaluation of anti-tumor activity in vitro and in vivo. International journal of pharmaceutics, 286(1-2), 147-156.
[46] Wilczewska, A. Z., Niemirowicz, K., Markiewicz, K. H., & Car, H. (2012). Nanoparticles as drug delivery systems. Pharmacological reports, 64(5), 1020-1037.
[47] Ranghar, S., Sirohi, P., Verma, P., & Agarwal, V. (2014). Nanoparticle-based drug delivery systems: promising approaches against infections. Brazilian Archives of Biology and Technology, 57, 209-222.
[48] Zhou, P., Liu, W., Cheng, Y., & Qian, D. (2021). Nanoparticle‐based applications for cervical cancer treatment in drug delivery, gene editing, and therapeutic cancer vaccines. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 13(5), e1718.
[49] Arvizo, R. R., Bhattacharyya, S., Kudgus, R. A., Giri, K., Bhattacharya, R., & Mukherjee, P. (2012). Intrinsic therapeutic applications of noble metal nanoparticles: past, present and future. Chemical Society Reviews, 41(7), 2943-2970.
[50] Tang, M., Lei, L., Guo, S., & Huang, W. (2010). Recent progress in nanotechnology for cancer therapy. Chin J Cancer, 29(9), 775-80.
[51] Tomoaia, G., Horovitz, O., Mocanu, A., Nita, A., Avram, A., Racz, C. P., ... & Tomoaia-Cotisel, M. (2015). Effects of doxorubicin mediated by gold nanoparticles and resveratrol in two human cervical tumor cell lines. Colloids and Surfaces B: Biointerfaces, 135, 726-734.
[52] Gupta, S., & Gupta, M. K. (2017). Possible role of nanocarriers in drug delivery against cervical cancer. Nano reviews & experiments, 8(1), 1335567.

[53] C Silva, A., Santos, D., Ferreira, D., & M Lopes, C. (2012). Lipid-based nanocarriers as an alternative for oral delivery of poorly water-soluble drugs: peroral and mucosal routes. Current medicinal chemistry, 19(26), 4495-4510.
[54] Couvreur, P., Fattal, E., & Andremont, A. (1991). Liposomes and nanoparticles in the treatment of intracellular bacterial infections. Pharmaceutical research, 8, 1079-1086.
[55] Jiskoot, W., Teerlink, T., Beuvery, E. C., & Crommelin, D. J. (1986). Preparation of liposomes via detergent removal from mixed micelles by dilution: The effect of bilayer composition and process parameters on liposome characteristics. Pharmaceutisch Weekblad, 8, 259-265.
[56] Deamer, D. W. (1978). Preparation and properties of ether‐injection liposomes. Annals of the New York Academy of Sciences, 308(1), 250-258.
[57] Szoka Jr, F., & Papahadjopoulos, D. (1978). Procedure for preparation of liposomes with large internal aqueous space and high capture by reverse-phase evaporation. Proceedings of the national academy of sciences, 75(9), 4194-4198.
[58] Meure, L. A., Foster, N. R., & Dehghani, F. (2008). Conventional and dense gas techniques for the production of liposomes: a review. Aaps Pharmscitech, 9, 798-809.
[59] Movahedi, F., Hu, R. G., Becker, D. L., & Xu, C. (2015). Stimuli-responsive liposomes for the delivery of nucleic acid therapeutics. Nanomedicine: Nanotechnology, Biology and Medicine, 11(6), 1575-1584.
[60] Sriraman, S. K., Salzano, G., Sarisozen, C., & Torchilin, V. (2016). Anti-cancer activity of doxorubicin-loaded liposomes co-modified with transferrin and folic acid. European Journal of Pharmaceutics and Biopharmaceutics, 105, 40-49.
[61] Kesharwani, P., Banerjee, S., Gupta, U., Amin, M. C. I. M., Padhye, S., Sarkar, F. H., & Iyer, A. K. (2015). PAMAM dendrimers as promising nanocarriers for RNAi therapeutics. Materials Today, 18(10), 565-572.
[62] Wang, A. Z., Langer, R., & Farokhzad, O. C. (2012). Nanoparticle delivery of cancer drugs. Annual review of medicine, 63(1), 185-198.
[63] Kagabu, M., Nagasawa, T., Sato, C., Fukagawa, Y., Kawamura, H., Tomabechi, H., ... & Baba, T. (2020). Immunotherapy for uterine cervical cancer using checkpoint inhibitors: future directions. International journal of molecular sciences, 21(7), 2335.
[64] Chabner, B. A., & Roberts Jr, T. G. (2005). Chemotherapy and the war on cancer. Nature Reviews Cancer, 5(1), 65-72.
[65] Aghamiri, S., Talaei, S., Roshanzamiri, S., Zandsalimi, F., Fazeli, E., Aliyu, M., ... & Ghanbarian, H. (2020). Delivery of genome editing tools: A promising strategy for HPV-related cervical malignancy therapy. Expert opinion on drug delivery, 17(6), 753-766.
[66] Burmeister, C. A., Khan, S. F., Schäfer, G., Mbatani, N., Adams, T., Moodley, J., & Prince, S. (2022). Cervical cancer therapies: Current challenges and future perspectives. Tumour Virus Research, 13, 200238.