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# A Review on HR-HPV: An Increasing Cause of Concern for Cervical Carcinoma

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

Human Papilloma virus, leads to widely prevalent viral infection with worldwide distribution of variable genotypes, it is the major cause of cancer in women and a leading cause of deaths due to cancer in India. Cervical cancer is the second most common cancer in women worldwide and the most common cancer cause of death in the developing countries. Notably, four out of every five cases of cervical cancer reported in India were attributed to infections from HPV types 16 and 18. India has a population of 483.5 million women aged 15 years and older who are at risk of developing cervical cancer. Infections with high-risk HPV types impair the function of cellular proteins and interfere with the expression of biological gene products. In high-grade intraepithelial neoplasias and cancers, HPV DNA is typically integrated into the host genome. WHO has recommended Screening of cervical cancer among young sexually-active females for early detection of HPV induced cervical carcinoma. Detection of HPV at earlier stages is essential in

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prevention of invasive cervical carcinoma. Based on clinical stage categories upon diagnosis, standard of care for cervical cancer management includes surgery, radiation, systemic therapy, or a combination of these therapeutic modalities.

*Keywords: HPV; cervical carcinoma; World Health Organization; neoplasia; radiation.*

## 1. INTRODUCTION

"Concern over a sexually transmitted virus that can cause various grades of cervical cancer has been for many years. Worldwide distribution of several genotypes of a highly common viral infection is caused by the Human Papillomavirus (HPV). It is a primary cause of cancer in females and a significant factor in mortality from cancer, especially in India" [1]. "In poor nations, cervical cancer is the main cause of cancer-related fatalities and the second most frequent malignancy among women worldwide" [2]. "Every year, there are about 510,000 new cases of cervical cancer worldwide, which leads to about 288,000 deaths from the disease. High-risk HPV (Hr-HPV) is one of the several forms of Human Papillomavirus (HPV) that causes persistent infection and a higher risk of developing into invasive malignancy. Specifically, the HPV 16 AND 18 are considered the most commonly implicated in the development of cervical cancer, accounting for 60% of all cases. Additionally, the HPV types 31, 33, 35, 45, 52, and 58 are responsible for 20% of cervical cancer cases" [3].

In 2018, the World Health Organization (WHO) outlined a global initiative in the World Research ecancer 2022 publication, focusing on the termination of cervical cancer. The initiative set specific targets, known as the 90-70-90 goals, with the aim of achieving them by the year 2030 [4].

Cervical cancer affects women who have given birth multiple times in their early post-menopausal years, leading to a significant loss of life expectancy (Franco et al., 2003). Consequently, cervical cancer remains a substantial public health concern, ranking second only to breast cancer in terms of the overall disease burden for women worldwide [5].

## 2. PATHOGENESIS OF HR-HPV

"Human papillomavirus (HPV), a member of the Papillomaviridae family, is a small, double-stranded DNA virus. There are two categories of HPVs: low-risk HPVs (LR-HPVs), responsible for anogenital and cutaneous warts, and high-risk HPVs (HR-HPVs), responsible for oropharyngeal (oral, tonsil, and throat areas) cancers and anogenital cancers, including cervical, anal, vulvar, vaginal, and penile cancers" [6].

"HPVs are approximately 50–60 nm in diameter, possessing a non-enveloped structure. The viral capsid consists of 72 capsomeres that are pentameric monomers composed of five identical L1 proteins, anchoring one L2 protein. HPVs specifically infect the undifferentiated deeper layer cells of the skin and/or mucous membranes known as basal epithelial cells, which have a high mitotic capacity. Viruses on the outer apical surface of the skin and/or mucous membranes can reach their target cells only through microlesions in these upper layer cells occurring during trauma" [6].

"The viral entry into undifferentiated epithelial cells is determined by specific molecular interactions between viral antigens and host receptors. Structural studies of L1 have revealed the presence of four heparin-sulfate proteoglycan (HSPG)–specific binding sites rich in lysine (K), which are required for productive infection. The L1 protein is crucial in the infection process, particularly in viral entry" [6].

"It is well known that the initiation of cervical cancer is the continuous infection of the cervix with HR-HPV types 16 and 18. Thus, for premalignant lesions to begin and develop into squamous carcinoma, HR-HPV infection must be established, persist, and elude the host immune system" [7].
"It is thought that the HPV replication cycle starts when the virus enters the basal layer, or stratum germinativum, of the epithelium. The basal layer of the skin is more susceptible to HPV infection when there is a mild abrasion or microtrauma. In order to start HPV replication and transcription of the viral E6 and E7 genes, host cell factors interact with the long control region (LCR) of the HPV genome. The products of the E6 and E7 genes bind to and deactivate tumor suppressor proteins, cell cyclins, and cyclin-dependent kinases. Excessive proliferation of cells in the basal layer, accompanied by a large number of abnormal mitoses, is a characteristic feature of

malignant and premalignant diseases. Infections with high-risk HPV types impair the function of cellular proteins and interfere with the expression of biological gene products. In high-grade intraepithelial neoplasias and cancers, HPV DNA is typically integrated into the host genome" [8].

## 3. EPIDEMIOLOGY OF HPV INFECTION IN INDIAN SCENARIO

"In 2020, India accounted for 7% of the global cancer incidence and 24% of the global incidence of cancers related to Human Papillomavirus (HPV). Notably, four out of every five cases of cervical cancer reported in India were attributed to infections from HPV types 16 and 18".[4] "India has a population of 483.5 million women aged 15 years and older who are at risk of developing cervical cancer. According to current statistics, 77,348 women lose their lives to cervical cancer each year, while 123,907 women receive a diagnosis" [9]. "It is estimated that 5.0% of women in the general population are infected with HPV-16/18 at any given time, and that HPVs 16 or 18 are responsible for a sizable majority of invasive cervical malignancies, or 83.2%" [10]. "The incidence of cervical cancer peaks between the ages of 55 and 59. Breast cancer and cervical cancer are the most common cancers among women, according to recent data from the National Cancer Registry Program (NCRP). According to population-based surveys, just 19% of women in developing nations have cervical cancer screenings, compared to 63% in industrialized nations. Furthermore, the coverage of screenings varies greatly, from 1% in Bangladesh to 73% in Brazil" [11].

"The estimated risk of cervical cancer is approximately 1 in 53 for Indian women, as opposed to 1 in 100 for women in developed nations. Statistically, there are around 90,000 cases of cervical cancer reported annually in India, with an incidence rate of 45 per one lakh women. The disease is more prevalent among individuals living in poor household conditions and low-income groups. The prevention of cervical cancer is considered a highly sensitive and significant public health issue" [12].

## 4. RISK FACTORS ASSOCIATED WITH HPV INFECTION

"There is a strong correlation between living in a rural region, using outdated clothing more frequently, being illiterate, not practicing good personal hygiene, and being married young for cervical cancer. Factors include age, delivery method, not cleaning genitalia after sex, number of sexual partners the husband has had, history of STIs and genital warts, and ignorance of cervical cancer screening. Regular bathing and bathing during the menstrual cycle are strongly linked to a lower risk of cervical cancer. STI lack of access to healthcare services was significantly correlated with cervical cancer in multivariate analysis" [13]. "High-risk sexual behavior is the main risk factor associated with the acquisition and persistence of HPV infection and development of HPV-associated cancers. These sexual risk behaviors include age of first vaginal sex, age of first oral sex, and number of oral and vaginal sexual partners. Previous studies have shown that these HPV-associated sexual risk factors vary by socioeconomic status, age, race, and education level. However, there is a lack of information regarding how individuals, based on their race and gender, engage in these sexual behaviors in the context of HPV. It is crucial to make efforts to explore predictors of HPV infection, particularly in populations at a substantial risk of developing HPV infection. This is essential for addressing healthcare disparities, especially in understanding the variations in sexual behavior between males and females and among individuals from different racial backgrounds" [14].

A person with a high-risk HPV infection of the cervix is more likely to have a chronic infection due to certain risk factors, which can cause significant alterations in the cervical cells that may eventually lead to cervical cancer. One of these risk factors is a compromised immune system, which can make it more difficult for the body to fight off illnesses like HPV infection. Immunocompromised individuals are more vulnerable to HPV infections, which have the potential to become chronic and lead to cancer. "Smoking or breathing in secondhand smoke: Those who either smoke or breathe in second hand smoke have an increased risk of developing cervical cancer. The risk increases the more a person smokes per day and the longer a person has smoked. Becoming sexually active at an early age: The risk of high-risk HPV infection that is persistent and ultimately leads to cervical cancer is higher in people who become sexually active before age 18 and in those who have had multiple sexual partners. This sexual history increases the chances of exposure to high-risk HPV. Other reproductive factors: Both the use of oral contraceptives (birth control pills) and giving birth to many children have been

found to be associated with cervical cancer risk. Additionally, hormones used in contraception may encourage the integration of HPV-DNA into the host genome by binding to certain HPV-DNA sequences inside transcriptional regulatory areas. This can increase or decrease the transcription of various genes and perhaps affect the rate at which cells undergo apoptosis" [15].

## 5. HR-HPV INDUCED CERVICAL CANCER

The most common HPV-related illness is cervical cancer (Burd 2003). The cause of almost all occurrences of cervical cancer is long-term HPV infection.

Since the early 1980s, the connection between HPV and cervical squamous cell cancer has solidified. There is a far stronger correlation between HPV and cervix squamous cell carcinoma than there is between smoking and lung cancer (Franco 1995). There are approximately thirty different forms of HPV that are spread by intercourse and mostly affect the cervix, vagina, vulva, penis, and anus. Squamous cell carcinoma of the cervix has been linked to one or more of these HPV strains in 99.7% of instances [16]. The squamocolumnar junction, which connects the ectocervix (squamous epithelium) and endocervix (columnar epithelium), is where the majority of cervical malignancies begin. At this site, there are progressive metaplastic changes. There is a large probability of metaplastic activity in addition to HPV infection. After menopause, this metaplastic activity starts to decrease. It starts during adolescence and the first pregnancy. Sexually active young women, especially those between the ages of 18 and 30, are most likely to be infected with HPV. After the age of thirty, the prevalence drastically decreases. On the other hand, cervical cancer is more common in women over 35, which is associated with early infection and a slow but persistent rise in cancerous growth. Cervical cancer is largely caused by persistent infection, which is particularly prevalent in high-risk oncogenic HPV strains. It's possible that sexually transmitted infections contribute to the development of cervical cancer. Herpes simplex virus type 2 co-infection might be a major contributing factor to the initiation of cervical cancer [17]. According to Ssedyabane et al. (2019) and Martinelli et al. (2019), there is a significant frequency of HPV coinfection with CT (Chlamydia Trachomatis), and this coinfection may be linked to aberrant cervical cytology and a cervical intraepithelial lesion (CIL). Because co-infections of HPV and CT promote the duration of HPV infection and allow the introduction of numerous hr-HPV genotypes, they raise the risk of CN. The mucosal barrier is harmed by CT infections, which can also impair immune function and viral clearance, induce inflammation, reduce the number of effector T cells, activate DC, produce proinflammatory cytokines and chemokines, and alter regulatory T cells (Tregs), which prolongs the virus [18].

## 6. HR-HPV INDUCED CERVICAL CANCER CLINICAL CONSIDERATIONS

The majority of HPV infections have no symptoms and no clinical signs. Anogenital warts, recurrent respiratory papillomatosis, cervical intraepithelial neoplasia, and malignancies such as cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers are among the clinical consequences of HPV infection [19]. Though there is a wide range of ages involved, this condition most commonly presents in the fifth decade. Patients usually present with abdomino-pelvic symptoms such as vaginal bleeding or discharge, pelvic pain, or pelvic pressure. Rarely, patients may present with paraneoplastic syndromes like Cushing's syndrome, SIADH, carcinoid syndrome, and other neurological disorders. Some patients may also present with metastatic disease at presentation, and most often affected areas of metastasis are the liver, adrenals, bone, bone marrow, and the brain. On physical examination, a pelvic mass is a common finding. Based on examination alone, it is impossible to distinguish NCC from squamous cancer of the cervix [20]. HPV infection can manifest as clinical, subclinical, or latent. Either a high viral load infection combined with clinical illness or a low viral load infection without clinical disease could develop from it. Genital warts or low- or high-grade intraepithelial lesions are two possible manifestations of this disease. Multiple high-risk forms of infections appear to work in concert to cause cervical carcinogenesis. An HPV infection is active when cervical intraepithelial neoplasia (CIN1) is grade 1. Although CIN 2 is regarded as a high-grade lesion, 40% of women may experience spontaneous remission. Since CIN 3 is the least likely to recur, it is sometimes used in conjunction with CIN 2 as a surrogate result for cervical cancer [21].

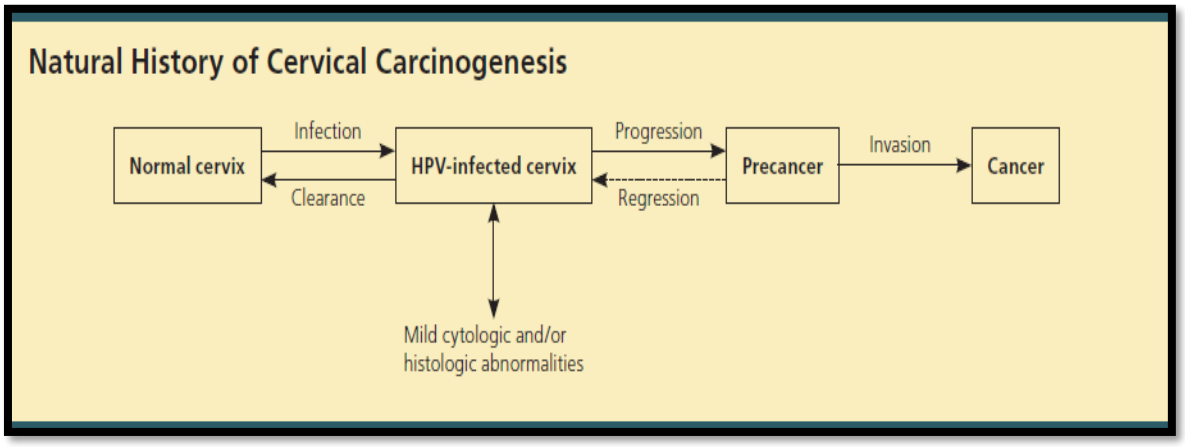


**Fig. 1. An epidemiological model for the development of cervical cancer. The three main stages of the development of cervical carcinogenesis are invasion, precancer progression (which is somewhat counteracted by precancer regression), and human papillomavirus (HPV) infection, which is balanced by viral clearance. For progression and invasion to occur, oncogenic HPV types must be persistent. Histologic and cytologic abnormalities are frequently, but not always, related with HPV infection**

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## 7. SCREENING STRATEGIES FOR HPV DETECTION

Awareness plays a crucial role in the early detection and prevention of cervical cancer. Cervical cancer is largely preventable through regular screening, early detection, and vaccination against the human papillomavirus (HPV), a major risk factor for cervical cancer. In India and many other parts of the world, barriers to screening and early detection include Insufficient cognition about risk factors, symptoms, and available screening methods.

Some of the common risk factors for cervical cancer include persistent infection with high-risk HPV types, lack of regular Pap smear or HPV testing, smoking, a weakened immune system, and long-term use of birth control pills. By addressing these factors, it is possible to increase awareness, encourage women to undergo regular screening, and ultimately reduce the morbidity and mortality associated with cervical cancer.

Periodic screening reduces the risk of developing invasive cancer by identifying precancerous lesions early on and treating them [22]. The aim of screening for cervical cancer is to evaluate precancerous cervical cell changes, where treatment can prevent progression into cervical cancer. Sometimes, cancer is detected accidentally during cervical screening. Early-stage cervical cancer is usually easier to treat. Once symptoms appear, the disease may have begun to spread, making treatment more challenging.

There are three main strategies for screening cervical cancer:

1. **HPV Test (Human Papillomavirus Test):** This test checks cells for infection with high-risk HPV types that can cause cervical cancer.
2. **Pap Test (Pap Smear or Cervical Cytology):** This test collects cervical cells to check for changes caused by HPV that may, if left untreated, progress into cervical cancer. It can find precancerous cells and cervical cancer cells. A Pap test may also identify conditions that are not cancer, such as infection or inflammation.
3. **HPV/Pap Co-Test:** This combines an HPV test and a Pap test to check for both high-risk HPV and cervical cell changes.

Regular screening, based on these strategies, plays a crucial role in early detection and intervention, reducing the probable risk of cervical cancer progression [23].

The World Health Organization recommends utilizing one of the following tactics to prevent cervical cancer:

The two methods of detecting HPV DNA are:

(1) Screen-and-treat, which begins at age 30, and frequent screening every 5 to 10 years; or
(2) Screen, triage, and treat, which begins at age 30 and continues regularly for 5 to 10 years [24].

As of 2021, the WHO suggests three HPV screening tests: 1) Nucleic acid amplification tests (NAAT) for hr-HPV types (hr-HPV DNA/NAAT and mRNA); 2) Visual inspection by camera or colposcope magnified or using acetic acid or Lugol's iodine (VIA/VILI); and 3) Cytology (Liquid-based cytology/Dual staining to identify p16 and Ki-67).

The World Health Organization suggests implementing a triple intervention plan (90-70-90) in order to achieve its 2030 aim of eliminating cervical cancer. The triple intervention strategy calls for 90% of girls to receive the HPV vaccine in its entirety by the age of 15; 70% of women to undergo screening with a high-performance test by the ages of 35 and 45; and 90% of women who are diagnosed with cervical disease to receive treatment (with 90% of those with invasive cancer being managed and 90% of those with pre-cancer receiving treatment) [25]. The global quest for exploring new chemotherapy and therapeutic interventions that are potentially less toxic and more effective has led to a renewed interest in herbal remedies. This renewed attention is due to several reasons, including cost-effectiveness, documented side effects, and the limitations of current treatment regimes [26]. Screening initiatives have played a significant role in reducing the overall incidence and mortality associated with cervical cancer (CCa). However, despite these efforts, the persistence of this precarious disease within the young female population remains a major concern [27].

## 8. DISCUSSION

Human papillomavirus (HPV) infection is the biggest risk factor for cervical cancer, which is still one of the most common cancers in women. Proper execution of primary and secondary prevention initiatives, such as cervical-vaginal cytology for the early detection of HPV infection and precancerous lesions and, accordingly, genotyping viral testing via DNA analysis could greatly lower mortality. Cytology has a number of drawbacks. Reports on specificity range from 56.6% to 99.2%, and reports on sensitivity range from 52.9% to 80%. Although primary HPV testing has been shown to be accurate, the method's implementation has been sluggish because of test availability issues and the need for sophisticated facilities equipped to perform polymerase chain reaction and nucleic acid amplification. Its implementation is particularly difficult in low-income and rural settings, where cervical cancer incidence, morbidity, and mortality are quite high. Artificial intelligence (AI)-based tools for histology or imaging diagnosis alternatives have recently been developed by the scientific community as a workable solution that might get over the aforementioned restrictions [28].

Utilizing research on HPV testing, AI learning technology enhances accuracy and expands the application of HPV testing in cervical cancer screening. Certain studies have discovered that cytological examination aided by AI can classify cervical cells to guide triage and improved the detection rate of CIN compared with that of standard pathological biopsy results after a good automated cytological detection model based on the AI method was established. The use of imaging and pathologic findings (if any) in staging was permitted by the FIGO in 2018. Artificial Intelligence (AI) has demonstrated positive outcomes when applied to colposcopy and magnetic resonance imaging (MRI) for cervical cancer diagnosis and staging. DL (Deep Learning) has become increasingly popular in medical imaging recently. By classifying colposcopy using DL technology, the diagnostic performance of traditional colposcopy can be enhanced and the bottleneck resolved [29].

Automated algorithms that use pictures obtained during VIA to identify precancerous and cancerous lesions show promise, particularly for developing nations where the majority of cervical cancer fatalities occur and where there is a lack of adequate healthcare infrastructure. It is possible to take these pictures by mobile devices, which are easier to use in LMICs than colposcopes, including cellphones or cameras, without causing any discernible decline in algorithm performance. When single or consecutive cervical images are used, the performance of AI systems may match or surpass human interpretation of the same images in terms of accuracy. Still, there are a lot of obstacles and limitations to be addressed [30].

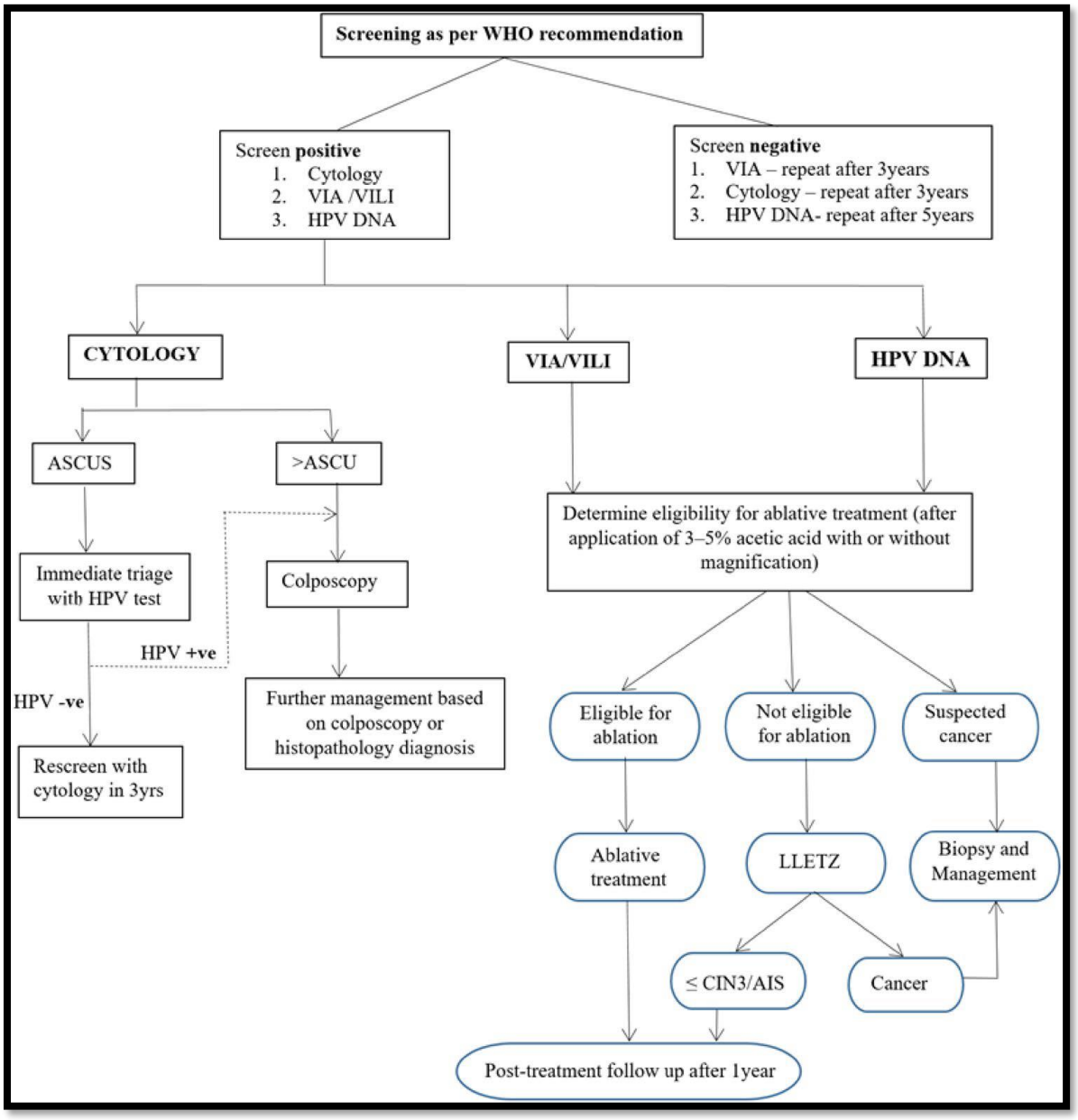


**Fig. 2. Management scheme for screen-positive women according to 2021 WHO guideline**

Pathania introduced the HPV AI surveillance, which reports 100% coincidence in sensitivity and specificity for identifying HPV 16 and HPV 18 DNA in cell lines using a deep learning (DL) algorithm and digital micro-holography [31]. Tian et al. used capture-based next generation sequencing to examine HPV integration status, somatic mutation, and copy number variation in order to identify enriched biomarkers of CIN 2. The identification of HPV kinds and related molecular markers that can help with the diagnosis of cervical lesions has demonstrated significant promise for AI application [32].

Based on clinical stage categories upon diagnosis, standard of care for cervical cancer management includes surgery, radiation, systemic therapy, or a combination of these therapeutic modalities. But clinical results are still not good, particularly when the illness is locally advanced and recurrent/metastatic. The latter scenario has demonstrated a median overall survival (OS) of up to 18 months with systemic chemotherapy based on paclitaxel and cisplatin or with bevacizumab in combination with doublet chemotherapy. However, once a progression starts, there are relatively few possibilities for further treatment [33]. With the release of the

Cancer Genome Atlas (TCGA) in 2017, our knowledge of the molecular profile of cervical cancer has improved. Amplifications in immunological targets, such as programmed death ligand 1 (PD-L1), PDL2, and BCAR4, and genes, such as ERBB2, CASP8, HLA-A, and TGFBR2, were discovered. Precision treatment for patients with cervical cancer may be available in the future thanks to knowledge about prospective targets and biomarkers [34].

Immunomodulatory medications are strongly justified in the treatment of cervical cancer due to the immune system's function in eliminating HPV and the higher prevalence of HIV-related cervical cancer in patients with. Immunotherapy is being used more often to treat metastatic cervical cancer, especially in patients whose tumors are PD-L1 positive. As a second-line treatment, immune monotherapy has poor response rates but shows promising durability. The treatment of hematologic malignancies has been revolutionized by genetically modified T-cell therapy, which is currently being researched for the treatment of HPV-associated epithelial tumors. Using a retrovirus expressing genes relevant to HPV, this technique isolates a patient's peripheral mononuclear blood cells and then primes the T lymphocytes to attack infected cells. Following preparatory chemotherapy, these cells are weeks manipulated, multiplied over several, and then infused back into the patient [35].

## 9. CONCLUSION

HPV induced cervical cancer is a common disease worldwide affecting female population. Various risk factors are involved in progression of the disease which can be minimized by precautionary initiatives such as sexual education and promotion of vaccination against cervical cancer. Recently upgrading technologies in diagnosis and management of cervical cancer can reduce the morbidity and mortality among the population. Artificial intelligence can be promising towards accurate and early diagnosis and therefore the treatment can be done at early stages. Treatment of cervical cancer by immunotherapies, T-cell therapy, gene therapy detecting mutations and their deletion can prove effective in eradicating the disease. However, several initiatives are required for inculcating awareness among population especially rural remote areas towards cervical cancer so that screening of cervical cancer can be increased on a wider platform involving women communities. Cervical cancer is indeed a serious and potentially life-threatening illness. Several government schemes and initiatives such as National Programme for Prevention and Control of Cancer, Universal Immunization Programme (UIP), Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (PMJAY), Rashtriya Kishor Swasthya Karyakram (RKSK) aim to reduce the burden of cervical cancer by promoting awareness, facilitating early detection, and providing access to affordable treatment and vaccination services. In India, 272.8 million women and 59.7 million girls are within the age range that qualifies them for screening and immunization against cervical cancer, respectively. Training and capacity development for cervical cancer screening are being provided to the health care community by the WHO, the International Agency for Research on Cancer, the Federation of Obstetric and Gynecological Societies of India, and the Indian Council of Medical Research. In India, the primary means of opportunistic HPV vaccine delivery are private healthcare facilities. As vaccination is a state-mandated program, states such as Uttar Pradesh (2022), Punjab (2018), Sikkim (2018), Delhi (2016), and Punjab (2018) have recently implemented school-based initiatives to provide girls between the ages of 11 and 13 with the bivalent HPV vaccine. In a few of these states' districts, immunization rates were reported to be higher than 95% [36]. As part of their social responsibility responsibilities, corporations like FOGSI, ISCCP, and AOGIN-India, as well as international organizations like WHO, should collaborate with public-private partnerships to support India's efforts to control cervical cancer. The World Health Organization has advised two rounds of HPV testing at the ages of 35 and 45. HPV self-sampling can be a perfect approach in the current pandemic era, when preventative efforts have faltered, as it minimizes contact with medical workers and prevents overcrowding in healthcare institutions [37].

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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