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Human Papillomavirus, its coinfection and Patho-demographic determinants of cervical carcinoma

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Abstract: The most common sexually transmitted virus in the world is the human papillomavirus, or HPV. Cervical cancer and precancerous lesions can be caused by a persistent high-risk HPV infection; high-risk HPV16 and 18 are linked to 70% of cervical cancer cases. There is a substantial financial and psychological cost associated with HPV infection. Thus, research into ways to eliminate HPV infection and stop the development of precancerous lesions is still essential. The mechanisms behind HPV-related cervical lesions are thoroughly examined in this review, including the host and environmental contributing factors, immune factors, epithelial cell malignant transformation, and the viral life cycle. Furthermore, we offer a thorough review of cervical cancer and HPV-related cervical precancerous lesions treatment options. We concentrate on immunotherapy, which includes advanced adoptive T cell therapy, immune checkpoint inhibitors, and HPV therapeutic vaccines. For the management of HPV infection and related cervical lesions, we also provide an overview of the commonly used medications and additional nonsurgical therapies currently used in clinical practice. Clinical research is currently being conducted on gene editing technology, and while it has not yet been formally used to treat cervical lesions in clinical settings, a number of preclinical studies have confirmed its effectiveness. For cervical lesions caused by HPV, it therefore has potential as a targeted treatment approach. Cervical cancer is primarily caused by an infection with the human papillomavirus (HPV).

Index Terms – Cervical Cancer, HPV, Therapeutic Vaccines, Immunotherapy.

1. INTRODUCTION

Cervical cancer is primarily caused by an infection with the human papillomavirus (HPV).**[1]** High-risk HPV (HR-HPV) infections account for 99 percent of cervical cancer cases. **[2].** More than 200 HPV genotypes have been found so far [**3**]. For women aged 25 to 65, HPV screening alone is the recommended approach, according to the American Cancer Society (ACS) **[4]**. As a result, HPV screening is crucial for both preventing and detecting cervical cancer. Cervical carcinogenicities vary among HPV subtypes. Approximately 70% of invasive cervical cancers worldwide are caused by
HPV-16 and HPV-18 **[5],** but other HR-HPV genotypes can also cause cervical cancer. It has been recently reported that HPV-16 and HPV-33 are the most common single HR-HPV genotypes in patients with cervical intraepithelial neoplasia (CIN)2 + **[6].** It has a also been recently reported that HPV-35 is one of the most common high-risk types and should be dominant types among South African women with CIN3, only behind HPV-16 **[7].** Another study showed that the most common carcinogenic HPV subtypes are HPV-16, HPV-58 and HPV-33 in southwest China **[8]**. Therefore, in addition to HPV-16 and HPV-18, other putative HPV carcinogenic types warrant our attention. There has been an increased trend in recent years towards multiple HPV infections **[9]**. however, the clinically significant of the multiple HPV infections controversial [**10**].it is highly effective strategies for detecting cervical cancers **[11].**

Furthermore, whether there are differences between HR-HPV genotypes and whether a specific combination of HR-HPV genotypes will increase or reduce the risk of cervical cancer warrants further study **[12,13]**. In the present investigation, we ascertained the genotype-specific distribution of cervical cytologic abnormalities in Chongqing, China, as well as the prevalence of HPV **[14]**. Additionally, it was established whether multiple HR-HPV infections were associated with cervical pathological abnormalities, such as TCT and colposcopy biopsies. Investigations were conducted into the type-type interactions of multiple HPV

infections on the risk of cervical disease. This study set out to give a comprehensive estimate of the frequency of multiple HR-HPV infections.

2.EPIDEMIOLOGY

2.1) HPV types and global distribution

The prevalence of specific HPV types can vary across regions due to factors such as geographical location, The prevalence rates of HPV types vary by region and population, indicating their global distribution. The following are important details about the distribution of HPV types worldwide: Most HPV-related cancers worldwide are caused by high-risk HPV types, especially HPV-16 and HPV-18. Cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers are among them. HPV-16 Is the most common high-risk kind and is responsible for a sizable fraction of cancers linked to HPV worldwide. **[15,16,17,18] Geographical** location, among other factors, can affect the prevalence of particular HPV types in different regions. demographics of the populace, customs, and medical facilities. For instance, specific HPV types might be more common in areas with greater cervical cancer incidence, like sub-Saharan Africa, portions of Latin America and Asia. Conversely, HPV-associated oropharyngeal infections may be more common in other areas.

cancers, including those in Western Europe and North America. **[19, 20, 17]**. Often, genital warts are linked to low-risk HPV types like HPV-6 and HPV-11. The prevalent Although the prevalence of particular low-risk types can also differ by region, research on them is typically less common. because they are less likely to cause cancer than high-risk varieties. **[19,21,16,18]**. Many nations have instituted HPV vaccination programs to prevent HPV infections and associated illnesses. Numerous factors influence how vaccination affects the distribution of HPV types, including the vaccine effectiveness, targeted HPV types, and vaccination coverage rate. The most prevalent high-risk strains, such as HPV-16 and HPV-, are the main targets of HPV vaccinations. The distribution of HPV types may change over time as vaccination campaigns continue to grow. **[22, 23, 24, 25, 30]**. Diseases linked to HPV, especially cervical cancer, are a major global burden. One type of cancer that is primary cause of death from cancer in women in many low- and middle-income nations. The Beyond cervical cancer, other HPV-related cancers are also part of the burden of HPV-associated diseases. genital warts. Initiatives to expand access to screening and treatment for HPV and boost vaccination coverage. In order to lessen the worldwide burden of diseases linked to HPV, services are essential. **[21,16,18,31]**

The most common viruses in the world, HPV-16 and HPV-18, are mostly to blame for HPV- associated cancers. Cancers of the cervical, anal, vaginal, vulvar, penile, and oropharyngeal regions frequently contain them. **[32,17,33,34] Some** of the highest incidence rates of cervical cancer worldwide are found in Sub-Saharan Africa, where HPV-16 and the most common type is HPV-18. Additional high-risk varieties, like HPV-31, Additionally, HPV-35 and HPV-45 are frequently detected. **[32,17,33,34]** A meta-analysis of the genotype distribution and global prevalence of human papillomavirus DNA in normal cytology and cervical cancer. **[35]**

3 . HUMAN PAPILLOMAVIRUS ASSOCIATED CERVICAL LESION: PATHOGENESIS

Infection with the human papillomavirus (HPV) is very common in women who are of reproductive age. **[36]** HPV is divided into high-risk and low-risk varieties according to its pathogenicity. Types 16, 18, 31, 33, 35, 39, 45, 52, 56, 58, 59, 66, and 68 are classified as high-risk HPVs (HR-HPVs). **[37]** Most HPV infections don't cause any symptoms and go away on their own in 12 to 24 months. A tiny percentage of infections, nevertheless, either continue or develop into preneoplastic lesions, which eventually lead to cancer. **[38]** About 70% of HPV-related cervical cancers are linked to HPV16 and 18, the two most common carcinogenic HPV types. **[38]**

3.1. HPV and it's pathogenesis

The basal layer of the stratified squamous epithelium is the target of HPV. Following its entry into the host cell, it starts both differentiation-induced and initial replication, which eventually leads to the viral particles' assembly and release inside the upper epithelial cells. Treating HPV infection requires an understanding of the virus' life cycle and the relevant host factors.

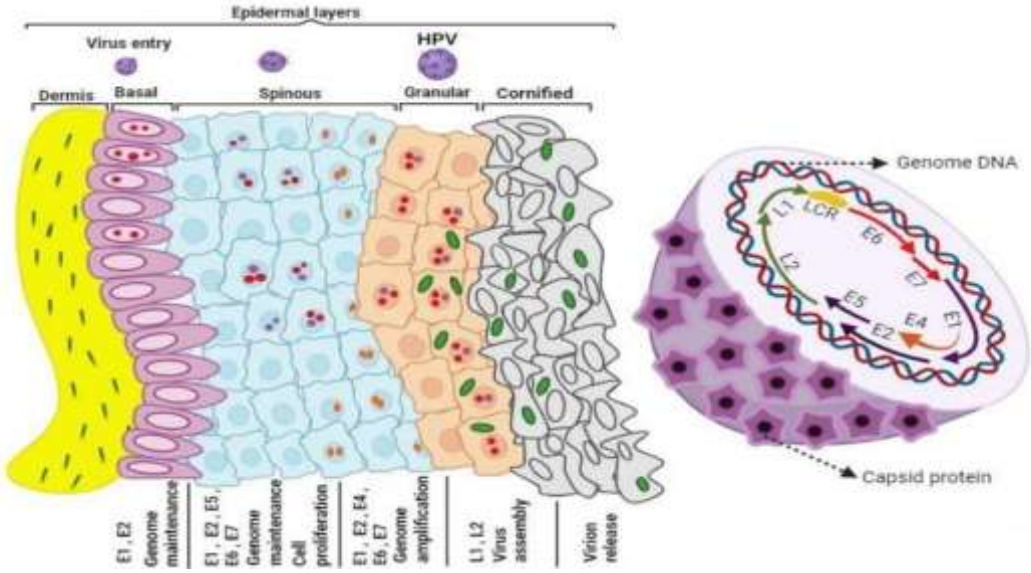

FIG 1. Life cycle of human papillomavirus. HPV entry to the basal cells, once it enters into the cells, HPV initiates its genome replication, which is mainly dependent on the E1 and E2 proteins; the expression of E6 and E7 contributes to promote host cell replication and prevent apoptosis

The HPV life cycle begins when cells In the stratified squamous epithelium's basal layer become infected. This happens when minor injuries cause the epithelial barrier to be disrupted. Whereas the differentiated cells in the upper layer have left the cell cycle, the basal cells in the normal epithelium are the only cells that are still growing. **[31]** The virus passes through cellular barriers, such as the nuclear envelope and plasma membrane, during the early stages of infection. We call this process virus entry. Using the L1 major capsid protein, HPV16 attaches itself to heparan sulfate proteoglycans (HSPGs) on the surface of epithelial cells and the basement membrane (BM) to start the interaction.In addition to interactions between the virus and secondary entry receptor molecules, such as integrin complexes, growth factor receptors, tetraspanin family members (CD63, CD9, and CD151), and the phospholipid binding protein annexin, a sequence of signaling processes follows HPV entry. **[24]**

The virus can finish its life cycle thanks to this process, which takes place in the upper epithelial layers. As a result, benign or malignant proliferative lesions of the cervix may develop. in the Golgi until cell cycle progression into mitosis, at which point viral transcription and replication take place at promyelocytic leukemia nuclear bodies, where the nuclear membrane's disintegration makes it easier for viral DNA to accumulate. **[29]** The viral oncoproteins E1 and E2 are essential for the start of replication. **[22]** As a DNA binding factor, E2 attaches itself to the palindromic DNA sequences in the LCR that encircle the viral replication origin. The recruitment of the viral helicase E1 is facilitated by this interaction, which starts the viral genome's replication. **[25]** However, E1 doesn't seem to be necessary for the first replication. **[26]** The only two virus-encoded proteins needed for DNA replication are E1 and E2. In terms of the virus's genome replication mechanism, the HPV genome replicates in both directions during the early stages of infection, which is crucial for preserving genome integrity. The Werner helicase has the ability to control this replication process. **[27]** The virus genome begins to replicate through break-induced replication (BIR) as the viral genomes oligomerize.

Under stressful circumstances, BIR is triggered to fix double-strand breaks and collapsed classical replication forks. **[38]** By causing a significant number of DNA breaks, HPV oncoproteins activate the ATR and ATM pathways. **[39]** Additionally, they enlist DNA damage factors like pATM and pCh2**[30]** to facilitate the replication of the viral genome. Additionally, by causing double-strand DNA breaks, topoisomerase 2β aids in this crucial process. **[31,32,33]**

The production of HPV16 late L2 mRNAs is the consequence of HPV late gene expression caused by enhanced read-through at the early HPV16 polyadenylation signal into the late region of the HPV16 genome. **[36]** The expression of L1 and L2 follows the activation of late promoters, which ultimately results in the full formation of virions. The virus can finish its life cycle thanks to this process, which takes place in the upper epithelial layers. As a result, benign or malignant proliferative lesions of the cervix may develop.

4 . ROLE OF MICROBIOTA DYSBIOSIS IN HPV AND COINFECTION IN VIRUSES: -

Cervical squamous cell carcinoma, cervical intraepithelial neoplasia, and a number of other benign and malignant clinical manifestations are primarily caused by the human papillomavirus (HPV). There are 396 distinct subtypes of HPVs, a family of circular double-stranded DNA viruses, known to exist. **[14]** Invasive cervical cancers are commonly linked to genital HPVs, which are classified into high- and low-risk types. **[15]** Since integrated HPV DNA is found in practically all cervical cancer biopsies,

high-risk HPVs (HR-HPVs) are the primary cause of cervical carcinogenesis. The transformation, immortalization, and malignancy of cervical cancer are influenced by major HPV oncogenic proteins, especially E6 and E7. **[16,17]**

4.1 Mechanism of vaginal flora imbalance;

Lactobacillus, which is frequently thought of as the first line of defense against pathogenic agents, is the dominant microbial genus group present in healthy vaginal bacterial communities in women of childbearing age. In contrast to most body sites, a diverse range of microbial communities is currently regarded as a sign of good health. **[68]** Ravelet was the first to use bacterial 16S RNA sequencing technology to determine the makeup of the vaginal microbiota. The component of a prokaryotic ribosome's 30S small subunit is 16S RNA **[14].** Although 16S rRNA gene sequencing has limited phylogenetic power at the species level and poor discriminatory power for certain genera, it is extremely helpful for classifying bacteria**. [76].**Because this part of the gene evolved slowly, the genes that code for it are known as 16S rRNA genes and are used to reconstruct phylogenies. Based on whether a specific Lactobacillus species was present or absent, they classified the vaginal microbiota into five community state types (CSTs): I, II, III, IV, and V. L. crispatus, L. gassier, L. iners, and L. jessenii are the microbiota associated with CST I, II, III, and V, respectively. The depletion of Lactobacillus species and the presence of strictly anaerobic species like Gardnerella, Megasphera, Sneathia, and Prevotella make CSTI V heterogeneous. According to longitudinal studies, the vagina showed better longitudinal stability than other mucosal sites and the diversity and abundance of microbes within subjects varied significantly over time, both within and among subjects. **[29],[20],[21],[22][24,25]**

4.2 Co-infection of HPV with HIV

HIV is the causative agent and a member of the retroviridae family regarding AIDS, or acquired immunodeficiency syndrome.**[37]** HIV exhibits a variety of cell types, such as monocytes, dendritic cells, and epithelial cells, but its main objective is the reduction of CD4+ T lymphocytes via various methods. **[28,29]** A powerful correlation between the risk and genital HPV infection was found of contracting HIV **[30]** While the majority of HPV infections will occur spontaneously, be resolved, but their high rates will continue to exist, resulting in heightened vulnerability to anogenital dysplasia, particularly in individuals infected with HIV. Co-infection between HIV and HPV is prevalent among HIV positive individuals (PLWH). **[21,22,23,24]** The co-occurrence of HIV and HPV revealed that the most prevalent AIDS-defining disease is cervical cancer in females**[25].**

5. VACCINATION;

The cancers of the cervix, vulva, vagina, penis, anus, rectum, and oropharynx are among those linked to the human papillomavirus (HPV) **[36].** Nearly all of the evidence supporting preventative vaccination against incident type-specific HPV infection is found in cervical disease, as the cervix is the site of over 80% of all HPV associated cancers **[87]**. Gardasil9, which replaced the first approved vaccine, Gardasil, is not inferior to Cervarix, a competing HPV vaccine for cervical cancer, in terms of overall prevention of CIN 3 disease **[38]**. In this review, we address the potential for cancer prevention of all three vaccines.

5.1 Comparison of the immunogenicity of three doses of HPV vaccine

Head to head trials of three doses of Cervarix vs Gardasil in women **[9]** and in 12–15 years old adolescents [96] are complete. Seropositivity for anti-HPV16 titers after 5 years is high for both Cervarix and Gardasil, but the actual induced GMTs measured by pseudovirion based neutralization assay (PBNA) are significantly lower for Gardasil than Cervarix; the decrease in titers might affect the long term duration of protection. Gardasil has significantly lower seropositivity retention and GMTs for anti-HPV18 titers than Cervarix. Cervarix also exhibited significantly greater serum binding antibody responses for both HPV 16/18 than Gardasil **[6,7,8]**.

In three doses, Gardasil9 exhibits the same decline in GMTs and loss of seropositivity for HPV18 as Gardasil **[9]**. After 24 months, detectable levels of antiHPV18 titers were lost in nearly 20% of Gardasil9 recipients. Over 10% of women who received Gardasil had no detectable anti-HPV18 titers after 1.5 years, over 20% lost detectable titers after 3 years, and nearly 35% lost detectable titers after 5 years **[10]**. After 24 months, detectable anti-HPV45 (an alpha 7 phylogenetically related type to HPV 18) titers were lost in nearly 15% of Gardasil9 recipients. Compared to the minimal loss observed among Gardasil9 recipients for anti-HPV16 titers, the loss of antibodies to these two HPV types is substantially greater and may have consequences for the length of protection. The anti-HPV16 decay pattern was followed over a 24-month period by the seropositivity and GMTs linked.

6. DIAGNOSIS

6.1 Cytological screening: - Cytological screening, such as the Papanicolaou stain (Pap smear), colposcopy, or visual inspection analysis, has been the main method for detecting precancerous and cancerous lesions resulting from HPV infections. **-Cytology or Pap smear** :-It functions as a routine CC screening and is used to identify abnormal cervical epithelial cells that may indicate cervical carcinoma or precancerous lesions. Death and the incidence of CC have significantly decreased as a result of Pap smears **[8].** Increased coverage and the implementation of successful Pap-based screening programs have been credited with this decline

[9]. However, the Pap smear's main clinical drawbacks are its low specificity, low sensitivity, poor repeatability, and yearly or triennial testing schedule **[10,11]**.

6.2 Visual inspection test with acetic acid (VIA)

It works well in place of cytology. Because the Pap screening method involves several steps, it is necessary to have a cytopathology laboratory with skilled professionals to detect cancer. This allows for prompt treatment, if needed. To finish the VIA, the cervix is treated with this 3–5% acetic acid solution for one to two minutes. After that, the cervix is checked for a whitened appearance, which could be a sign of underlying disease. According to studies, cervical cancer mortality can be decreased by 35% and incidence by 25% with early diagnosis using VIA **[12]**. VIA has not been extensively used in mass screening programs despite having a higher sensitivity, most likely because of its higher false-positive rates **[13].**

6.3Colposcopy

It serves as a diagnostic bridge between low-magnification microscopy and visual inspection. This method improves diagnostic accuracy, particularly for asymptomatic early-stage cervical cancer, by accurately locating subtle lesions that are invisible to the naked eye, identifying them, and making tissue sampling easier for histopathological analysis. Patient adherence is high because the examination is inexpensive, staff training is simple, and the procedure is painless and non-invasive. On the other hand, it is linked to low specificity and high sensitivity **[14]**.

6.4 Thin prep cytologic test (TCT)

For cervical lesions, it is a thin-layer liquid-based cytological screening technique. Another noteworthy accomplishment was the FDA's approval of liquid-based cytology, which offered a homogeneous distribution of a monolayer of cells that was mostly free of obscuring substances **[13]**. With a higher rate of abnormal cervical cell detection and improved smear quality, it outperforms the Pap smear test, achieving an effectiveness of over 95%. It lowers the associated mortality rate by facilitating cervical cancer's early prevention, detection, and treatment. This test is suitable for routine gynecological examinations because of its convenient and non-invasive features **[15]**.

7. TREATMENT*;*

The main curative treatment options for cervical cancer are surgery, chemoradiation, and a combination of these, depending on the stage of the cancer at diagnosis **[29]**. No treatment option is excluded because of HPV infection or the presence of a cancer subtype (Squamous cell carcinoma (SCC), adenocarcinoma (AC), or adenosquamous carcinoma (ASC)) **[129]**. In order to describe clinical management and the most recent developments in treatment, three groups were identified in relation to Fe deration staging:

1Cervical cancer in its early stages (FIGO IA-IIA)

2.FIGO IIB–IVA, or locally advanced cervical cancer (LACC), which spreads to the side wall of the pelvis or nearby organs

3.Cervical cancer that has returned or spread (FIGO IVB, any T, any N, M+) [129,130,131].

As suitable substitute options for specific patients, the NCCN also suggests platinum-containing combination regimens such as cisplatin/paclitaxel (category -1), carboplatin/paclitaxel (category--1), topotecan/paclitaxel/bevacizumab (category 1), topotecan/paclitaxel, and cisplatin/topotecan **[19]**.

The most recent recommendations of **[29]** numerous scientific societies also include new treatment options. It is now a category 1 preferred treatment for patients with PD-L1 (CPS ≥1) tumor expression because of the KEYNOTE-826 study, which demonstrated the effectiveness of pembrolizumab in combination with chemotherapy (with or without bevacizumab) with clinically significant improvements in OS. **[31, 32, 33, 29, 30**]. A new first-line treatment option is suggested by another open-label, randomized trial. By comparing the anti-PD-L1, atezolizumab, and paclitaxel– platinum plus bevacizumab regimens, BEATcc (ENGOT-cx10/GEICO 68C/JGOG1084/GOG-3030) demonstrated that atezolizumab added to a standard bevacizumab plus platinum regimen significantly improves progression-free and overall survival **[34]**. Unfortunately, progression-free survival was only about 3 to 6 months in cases of progression following first-line chemotherapy **[35]**.

Depending on the features of the tumors, second-line treatment options for recurrent or metastatic cervical cancer include: 1. chemotherapy (docetaxel, gemcitabine, fluorouracil, pemetrexed, topotecan, vinorelbine, irinotecan, albumin-bound paclitaxel, and paclitaxel), Bevacizumab, Pembrolizumab, Nivolumab for tumors that are PD-L1 positive **[29]**.

CONCLUSION

A common sexually transmitted infection that can have major health consequences is HPV.It is caused by different HPV strains, with high-risk strains being closely linked to the emergence of specific cancers, especially those of the cervical region. Genital disorders and other benign conditions are caused by low-risk types. warts. A key component of treating HPV infection is prevention. HPV vaccination is very successful. in avoiding infections of the most prevalent, high-risk kinds, and ought to be given prior to

start having sex. Safe sexual behaviors, like using condoms frequently and reducing the number. Moreover, sexual partners contribute to lowering the risk of transmission. Finding and treating precancerous lesions or detecting them early on requires routine screening. early-stage cancer. Programs for cervical screening are crucial, but they are especially crucial for women. to increase knowledge about HPV and motivate men and women to get the right medical care. The general public Access to immunization and screening programs, as well as education and awareness, should be the main goals of health initiatives. By putting into practice all-encompassing tactics that include immunization, safe sexual behavior, and early detection, we can enhance general sexual health and drastically lower the burden of diseases linked to HPV. It is important to remember that although this information gives a general picture of papillomaviruses, the specifics and as research advances, scientific knowledge of HPV keeps changing.

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