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HPV REVEALED: COMPREHENSIVE REVIEW ON PREVENTION, IMPACT, AND GLOBAL HEALTH STRATEGIES

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Abstract

The most common viral infection worldwide is human papillomavirus, or HPV. HPV is the cause of cervical cancer in women, accounting for more than 90% of cases of cervical cancer, one of the most common cancers in women. Additionally, HPV is associated with skin and anogenital infections, as well as genital and upper respiratory tract cancers. Cervical screening is generally more successful than periodic screening and continues to reduce cervical cancer incidence and mortality. Developing countries have reduced cervical cancer cases and deaths over the past four years thanks to coordinated cytology screening and vaccination. For women who are not infected with HPV or are not currently infected with HPV, the vaccine is effective in preventing infection and disease caused by the virus. Many countries have implemented HPV vaccination programs, but significant barriers to HPV prevention and treatment remain in low-income areas. This review explores several topics related to HPV infection.

Keywords: Human Papillomavirus (HPV) Cervical Cancer HPV Vaccination Cytological Screening Genital Warts.

INTRODUCTION

Human papillomavirus (HPV) infection is a common and mostly transient condition that has garnered public attention due to recent advancements in immunization and modifications to cancer screening standards (1).HPV is the cause of numerous STDs as well as dermatological disorders (2).It is the most common STD worldwide, and the immune system typically treats it. Globally, men are 50% more likely than women to experience it at least once in their lifetime (3). Even while most HPV infections go away on their own, persistent infections are significantly associated with an elevated risk of genital warts and cervical cancer. The recently authorized quadrivalent HPV vaccination targets types 6, 11, 16, and 18, with the goal of eliminating the HPV strains that cause approximately 90% of genital warts and 70% of cervical malignancies (4). In 99.7% of instances of cervical cancer, high-risk DNA from the sexually transmitted virus HPV has been discovered (5).It is projected that 500,000 women will be impacted by cervical cancer year, with 80 percent of cases occurring in underdeveloped countries. Nearly all occurrences of cervical cancer are caused by an HPV infection in the vaginal tract. Regular gynecological screenings and treatment of precancerous lesions can largely prevent the most frequent kind of Cervix cancer, Squamous. These procedures, however, are difficult to implement in low-resource settings and have little effect on adeno carcinoma (6). Approximately 90% of HPV infections either go away or go dormant within 12 to 24 months of exposure (7).

General Characteristics

Double-stranded DNA viruses belong to the family Papilloviridae, which includes human papillomavirus (HPV) of approximately 200 viruses, more than 40 types of HPV have been found in cervical cancer (8). Anogenital and skin warts are caused by HPV, and anogenital cancers such as cancer of the cervix, anus, anus, genitals, and prostate, as well as cancers in the oropharyngeal area (mouth, tonsils, and throat) are associated with a high risk of HPV. (9, 10). Cervical cancer (CC), the second most common cancer in women after cervical cancer, is associated with HPV (11, 12). It is also the third most common cancer in women. Each of the three parts that make up the HPV genome is an 8000 base pair long, double-stranded, conserved DNA molecule. This DNA molecule encodes six early proteins, three regulatory proteins (E1, E2, and E4), and three oncoproteins (E5, E6) in a 4000 base pair (bp) region involved in viral replication and cellular transformation and E7. The two structures that make up the viral capsid, L1 and L2, are encoded in separate 3000 bp regions. Transcription and viral DNA replication are controlled by a long regulatory region (LCR) that is approximately 1000 bp long (13). There are 225 different types of HPV divided into five groups: Î±, Î±, Î³, Î³, and Î³ (14). Figure 1 shows how each group is divided. Accumulation of organisms during evolution.

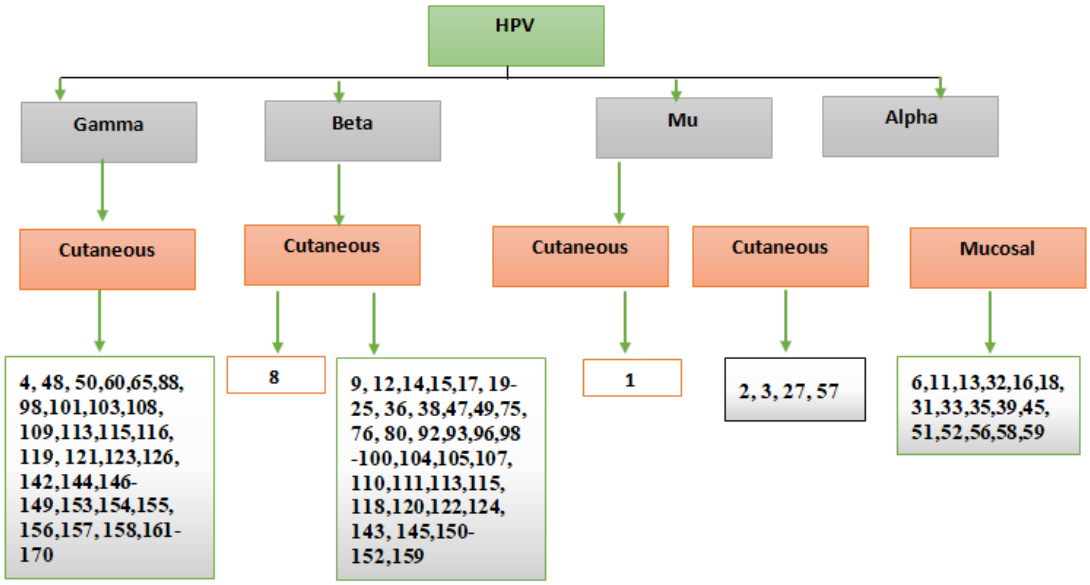

Figure: 1 Classification of HPV (77)

HPV and Cancer

Human papillomaviruses (HPV) are DNA viruses that can infect mucosal cells in addition to the skin(15). A number of globally acknowledged "high-risk" genotypes, specifically 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66, have been associated with anogenital and head and neck cancers as well as mucosal cancers(16,17). On the other hand, infections brought on by "low-risk" genotypes can cause genital warts (condyloma acuminate) (18), which appear as growths on the male penis, scrotum, oranus, as well as the female cervix, vagina, vulva, and anus (19,20). More than 90% of instances of cervical HPV infections resolve within a year after diagnosis, and most have no symptoms at all (21). The duration and efficacy of immunity following a natural

infection are still unknown.Only 50–60% of women produce serum antibodies against HPV following infection (22). The small epithelial abnormalities that early HPV infections might produce, which can be detected by virological and/or cytological screening, may allow for early intervention. The squamous intraepithelial lesions (SIL) of various grades identified in the cytology of cervical smears represent the amount and abnormalities of cervical epithelial cells.Histological analysis of cervical epithelial biopsy results in the diagnosis of cervical intraepithelial neoplasia (CIN). Depending on the proportion of aberrant cells in the cervical epithelium, CIN is ranked 1 through 3. The cervical epithelium in CIN3 is more than two thirds covered in aberrant cells.Similar techniques are used to grade vaginal (VaIN 1-3) and vulvar (VIN 1-3) Lesions.

Epidemiology of HPV Infection:

Estimates state that 77,348 Indians lost their lives to cervical cancer in 2020.Cervical cancer is the most common cause of cancer-related deaths among Indian women (23,24). According to GLOBOCAN 2020, cervical cancer ranks fourth among all malignancies that affect women worldwide, resulting in 341,831 deaths and an anticipated 604,127 new cases. With a death-to-incidence ratio of 57%, cervical cancer mortality rates are notably lower than incidence rates. Squamous cell carcinoma is the most prevalent kind of cervical cancer, followed by adenocarcinomas (25). Many studies worldwide have been done on the distribution of high- and low-grade squamous intraepithelial lesions (HSIL and LSIL) caused by various HPV genotypes. However, there are still large gaps in data in regions like as Africa, Central Asia, and Eastern Europe. Despite these variations, it has been repeatedly noted that women with LSIL had a higher likelihood of carrying particular HPV genotypes, primarily HPV 16, 31, 51, 53, 56, 52, 18, 66, and 58 (26). Multiple HPV infections of different types are also common.Genital contact with the skin common means of genital HPV infection transmission, though not necessarily during intercourse (27). HPV can infect people at any age, and infections have been documented in young toddlers who are otherwise healthy (28). Age and HPV prevalence are adversely associated in some places, while age and age-standardized HPV prevalence varies significantly among groups. Still, though.

Table 1: Cervical cancer mortality in India(77)

INDICATOR	INDIA	SOUTHERN ASIA	WORLD
The annual number of deaths	77,348	89,307	341,831
Uncertainty intervals of mortality cancer cases [95% UI]	[74,246-80,580]	[619-1,095]	[324,231-360,386]
Crude mortality rate	11.7	9.5	8.84
Age-standardized mortality rate	11.4	9.75	7.25
Cumulative risk (%) at 75 years old	1.3	1.12	0.82

Prevalence of HPV Globally

HPV infection is common, but its prevalence and distribution varies (29). According to a meta-analysis of cervical HPV infection in women without cervical cancer, more than 12% of women worldwide tested positive for HPV DNA (30, 31). There are many studies examining the oncogenic potential of different HPV genotypes and the epidemiology of HPV infection (32). The prevalence of HPV in underdeveloped countries and in women under 25 years of age varies between 15% and 45% (33). The highest prevalence of HPV is seen in sub-Saharan Africa

(24%), Eastern Europe (21%) and Latin America (16% to 1%). The lowest rates were reported in North America (4 percent of individuals, 7%) and Western Asia (1 percent of individuals, 7%) (34). Type 16, the most common HPV type worldwide, accounts for 32.3% of infections in South Asia, 28.9% in Southern Europe, 24.4% in Western Europe, and 24.3% in It constitutes 12% in North America and 12% in Africa. According to the Middle East and North Africa Extension Study (EMENA), HPV prevalence is low in the Middle East. Qatar reported the incidence as 6% in women with normal or abnormal cytology (35). This region hosts HPV16 (18, 4%), HPV18 (9, 22%), HPV33, 51 and 52 (about 5%) and other HPV types (36). The high prevalence of HIV infection in sub-Saharan African countries is associated with the high prevalence of HPV; If early diagnosis and awareness are poor, it may lead to cervical cancer (37, 38). The result varies in different regions.

Transmission of HPV:

HPV mostly spreads by indirect skin-to-skin or skin-to-mucosa contact (39,40). The most typical way that the virus spreads is through sexual contact with an infected person, whether through vaginal, anal, or oral means (41). Non-sexual horizontal transmission through oral, cutaneous, or fomite contact is less likely (42,43).Cervix cancer is linked to risk factors such as multiple sexual partners and early sexual activity since it is a sexually transmitted disease (43).

Pathogenesis of HPV

The intricate process of cervical carcinogenesis, which is impacted by a number of cellular and epigenetic variables in addition to the integration of the HPV gene, is characterized by unchecked cell proliferation.The viral DNA, which integrates into the host genome and interacts with the machinery responsible for host DNA synthesis, is altered by cellular and environmental variables as the HPV infection develops.By integrating itself, the virus can evade the immune system and the body's defenses, speeding up cell proliferation and stopping apoptosis (44). For example, the potential for HPV16 to cause cancer is dependent on changes to the transcription factors that the virus uses. The HPV16 genome initially manifests as an episome, or non-integrated DNA molecule, in benign and precancerous cervical lesions.

However, HPV16 has the ability to integrate its genome into the host genome, which is a critical process linked to the development of cervical cancer and high-grade cervical intraepithelial neoplasia (CIN III) (45).A component of this carcinogenic process is the disruption of the E2 protein, which controls the viral oncoproteins E6 and E7. Dysregulated E6 and E7 lead to overexpression, which alters cellular apoptotic pathways and promotes the growth of viral carcinogenesis (46).

Role of E6 and E7 in HPV Carcinogenesis

Overexpression of E6 and E7 is not sufficient for carcinogenesis; other genetic and epigenetic variables are also needed.Among those linked to cancer include HPV types16,18,31,33,35,39,45,51,52,56,58,59,68,73, and 82 (47).Given that HPV16 is the cause of 50% of cervical malignancies, it is quite risky (48). The degree of E6/E7 overexpression varies depending on the HPV strain and the infected cells, but the HPV16 E6 and E7 genes integrate into the host genome and are expressed (49). Small proteins called E6 and E7, which have 150 and 100 amino acids, respectively, can bind to cellular proteins and alter the host cell's normal functioning even though they

lack any enzymatic activity. For instance, E6 links to E6-associated protein (E6AP), a ubiquitin ligase, to create the trimeric complex E6/E6AP/p53, which facilitates E6's interaction with tumor suppressor protein p53.

This complex leads to p53 degradation, which promotes cell division (50). When E7 binds to pRb, it inactivates and degrades it, activating E2F, a transcription factor that activates genes involved in the cell cycle (50). Moreover, E6 and E7 interact with a wide range of host cell proteins to regulate different biological pathways.Notably, through its interactions with histone deacetylases (HDAC1-3), E7 increases E2F activation, which is linked to differentiation and viral replication (51-54).Moreover, E6, E7, and E5 oncoproteins influence host microRNA profiles through post-transcriptional control of gene expression. Certain miRNAs, such as miR-21 and miR-143, have been overexpressed in cervical malignancies linked to HPV.

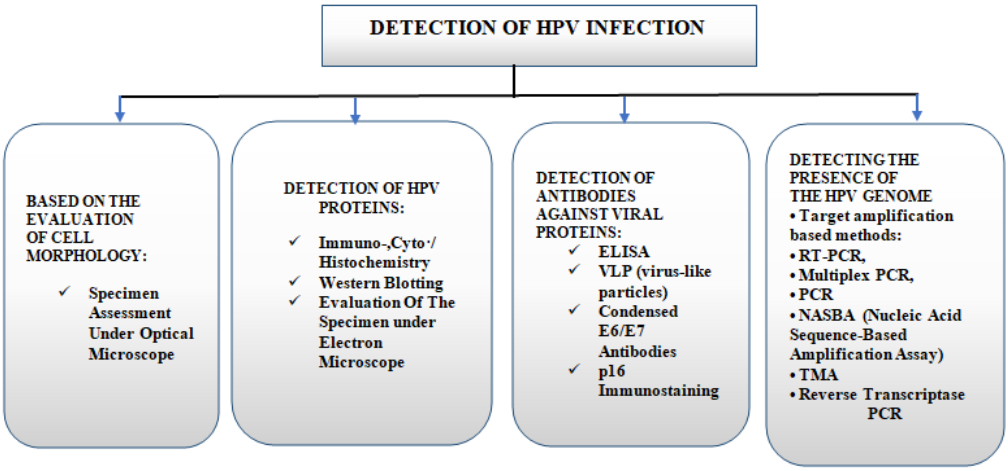

Figure: 2 Diagnostic methods for detection of HPV infection(77)

Methylation and HPV Integration in Carcinogenesis:

Increased methylation of CpG dinucleotides inside the E2 binding site (E2BS) on the host genome might cause abnormal cell differentiation and disease progression by interfering with interactions with multiple components(55). The viral regulatory protein E2 has a decreased binding affinity to E2BS as a result of this altered methylation, which encourages the overexpression of E6 and E7 as well as increased epigenetic repression of tumor suppressor genes.According to studies, the CpG methylation in this region may serve as a biomarker for cervical cancer screening (56).

Detection of HPV Infection

Many detection methods are employed to diagnose HPV, accounting for differential biomarkers and histopathological differences. Figure 2 displays the typical methods used to identify HPV in clinical samples. A list of screening tools and molecular detection techniques for different malignancies connected to HPV has been supplied (57). In HPV-associated oropharyngeal squamous cell carcinoma (HPV+OPSCC), high levels of wild-type p53 and p16 are suggestive of HPV infection. Cancers associated with HPV are detected by immunostaining for p16, a protein linked to HPV-16.This aids in distinguishing HPV-related cancers from non-related cancers. OPSCC, which frequently displays low p16 expression and p53 alterations, is caused by hypermethylation, mutations, or deletions (58).

Treatment of HPV-Related Diseases

The type of HPV, available therapies, and illness stage all influence how these diseases are treated.Podocyllotoxin is an antimitotic drug used to treat genital warts caused by non-cancerous HPVs (59). Precancerous cervical lesions produced by oncogenic HPVs are treated with excisional techniques such as cryosurgery, electrosurgery, cone biopsy (conization), or loop electrosurgical excision procedure (LEEP) (60). The modern therapies for cervical cancer include radiation therapy, chemotherapy alone, and radical hysterectomy. Chemotherapy is helpful in all stages, including metastatic and advanced illness, particularly regimens based on cisplatin (61). Definitive radiation therapy in conjunction with concurrent cisplatin-based chemotherapy (CRT) is considered the standard of care for invasive cervical cancer, despite notable recurrence rates of 25–40 percent (62, 63). Recent studies have looked into combination therapies that use multiple chemotherapeutic drugs to increase treatment efficacy based on patient-specific characteristics (64). Radical hysterectomy, which entails removing the uterus and parametrium, is another effective surgical option (65). Checkpoint inhibitors may be used in addition to conventional therapies, according to more recent research. Monoclonal antibodies that target the PD-1 axis, such as ipilimumab, pembrolizumab, and nivolumab, show potential in the therapy of cervical cancer by reversing immune suppression processes (66).

HPV Vaccine:

Current statistics show that the HPV vaccine is effective in preventing diseases caused by certain types of HPV (70). Vaccination has proven to be successful worldwide (66). In June 2006, the FDA approved the first HPV vaccine. Three HPV vaccines are approved for use in the United States: quadrivalent Gardasil, nonnavalent Gardasil 9, and bivalent Cervarix (67). Merck & Co. He produced GardasilÂ®. Inch. It contains non-viral virus-like particles (VLPs) and is a quadrivalent antibody produced at Whitehouse Station in New Jersey. Three doses are given over six months (0, 2 and 6 months). Anal intraepithelial neoplasia (AIS), cervical intraepithelial neoplasia grade 3 (CIN 3), vulvar intraepithelial neoplasia grade 2/3 (VIN 2/3), and genital intraepithelial neoplasia grade 2/3 (VAIN), as well as 50% of CIN 2 cases, 35-50% of all CIN 1, VIN 1 and VAIN 1 cases and 90% of genital warts are the target of the vaccine (68). HPV6, 11, 16 and 18 are targeted by the quadrivalent vaccine Gardasil, while HPV16 and HPV18 are targeted by the bivalent vaccine Cervarix. The ninevalent Gardasil 9 vaccine targets HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58 (69). These nonviral vaccines contain virus-like particles (VLPs) derived from the recombinant HPV L1 capsid expressed in yeast (Gardasil) and worms (Cervarix). Administration is done via intramuscular injection. Among women without HPV infection at the start of the study, the vaccine was 27% effective against AIS caused by CIN 1 to 3 or 10 non-vaccine oncogenic HPV types (31, 33, 35, 39, br>
 45, 51, 52, 56, 58 and 59) are based on current analysis of phase III data simulation(71). It also showed 38% effectiveness against 10 HPV types that cause CIN 2/3 and AIS. These results are important because they show that the non-vaccine HPV vaccine, which causes about 20% of cervical cancers worldwide, reduces oral cancer in children (73, 73). This combination may provide better protection for young women who receive the quadrivalent vaccine. Vaccines have been shown to be effective against CIN and recurrent infection for up to five years, with the vaccine peaking after the third dose and still effective five years later. It is not clear whether additional doses are

needed, but preliminary studies suggest that there are more antibodies after the trial dose given five years after the injection (74, 75). Studies are ongoing to find out how long protection lasts 14 years after vaccination. Vaccination has not proven to be particularly effective in children under the age of sixteen (76).

Table 2: HPV Vaccines Approved by the FDA(77)

TYPE OF VACCINE	TYPE OF HPV
Cervarix (Bivalent HPV vaccine)	HPV 16 and 18
Gardasil (Quadrivalent HPV vaccine)	HPV 6, 11 (genital warts), 16, and 18
Gardasil 9 (9-valent HPV vaccine)	HPV 6, 11 (genital warts), 16, 18, 31, 33, 45, 52, and 58

Future Prospectus

As vaccination coverage increases, especially through inclusive, gender-neutral immunization programs, the future of HPV immunizations offers enormous promise for dramatically lowering HPV infections and related disorders. The main components of this endeavor include educational programs designed to increase knowledge of the risks associated with HPV infections and the significant advantages of vaccination, particularly in resource-constrained areas like low- and middle-income nations. Enhancing public acceptance and guaranteeing the broad availability of vaccines will depend critically on improving vaccine safety profiles, which include lowering adverse effects from vaccine adjuvants and formulations. This is especially important when immunizations are given in adolescence or early adulthood.

It is imperative that future research and efforts to create vaccinations concentrate on addressing the issues posed by HPV kinds that are not currently covered by current vaccines, especially among young women.It is anticipated that next-generation HPV vaccinations would provide more comprehensive protection by utilizing sophisticated formulations to target many high-risk HPV strains. To fully evaluate the long-term effect of HPV vaccine on preventing all HPV-related malignancies, ongoing research and clinical studies are essential. Furthermore, therapeutic vaccinations are a significant development in the industry since they may provide therapy options that go beyond prevention to actively treat and eradicate pre-existing HPV infections and related illnesses.

CONCLUSION

Sexually transmitted infections, common dermatological problems, and some of the most common and serious malignancies in the world are all associated with HPV infection. It is impossible to overestimate the importance of immunizations in halting the development of this prevalent illness.Cervical cancer still has high fatality rates even in the absence of comprehensive HPV screening and little public awareness. For vaccination programs to be implemented successfully, it is imperative to comprehend the prevalence and distribution of HPV types. It is essential to launch educational programs to increase public awareness of this pressing public health concern. Governments should prioritize and appropriately fund initiatives for HPV screening and vaccination in nations with high rates of cervical cancer incidence and mortality. Increased investigation into the relationship between HPV infection and a number of malignancies and other illnesses, including cervical cancer, will improve the benefits, effectiveness, and potential of HPV vaccination. This continuous study is essential to improving our knowledge and tactics for fully treating diseases linked to HPV.

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