NARRATIVE

Exploring The Potential of Human Papilloma Virus: An Overview

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ABSTRACT

Human papillomavirus (HPV) infection is the most frequent viral sexually transmitted infection in the world. HPV is currently the most prevalent infection responsible for female cancers, with more than 90% of cervical cancers - the fourth deadliest malignancy in women- having been diagnosed. Additionally, genital and upper aerodigestive tract malignancies, as well as cutaneous and anogenital warts, are also linked to HPV infection. Cervical screening programs that are organized have the potential to be more effective than opportunistic screening programs. Nonetheless, screening programs have consistently been linked to lower cervical cancer incidence and mortality. Over the last 40 years, developed countries have achieved such a reduction in cervical cancer incidence and mortality. This is largely because of organized cytological screening and immunization programs. In women with no indication of previous or current HPV infection, HPV vaccinations are very efficient at preventing infection and illnesses caused by vaccine-specific genotypes. Despite the effective implementation of the HPV vaccination program in many nations around the world, challenges with HPV prevention and treatment of linked diseases will persist in developing and poor countries. This review provides an insight into various aspects of HPV infection.

Keywords: Human Papillomavirus (HPV), Sexually Transmitted Disease, Epidemiology, Cervical Cancer, HPV vaccination

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INTRODUCTION

Human papillomavirus (HPV) infection is a common and typically temporary infection that has lately received public attention as a result of advances in vaccine protection and modifications in cancer-screening recommendations.[1] HPV is the causative agent of many dermatological and sexually transmitted illnesses.[2] The most prevalent sexually transmitted disease is HPV infection, which is usually healed by the immune system. Worldwide, both men and women have a 50% chance of being infected at least once in their lives.[3] Although most HPV infections resolve on their own, chronic HPV infection is closely linked to an increased risk of cervical cancer and genital warts. The recently authorized quadrivalent HPV vaccine (types 6, 11, 16, and 18) targets the HPV strains that cause roughly 70% of cervical malignancies and 90% of genital warts.[4] HPV is a virus that can be transferred sexually, and high-risk HPV DNA has been discovered in 99.7% of cervical cancer specimens.[5] Cervical cancer is predicted to impact 500 000 women each year, with 80% of those affected living in underdeveloped nations. HPV infection in the vaginal tract causes nearly all cervical cancer cases. Regular gynecological screening and treatment of precancerous lesions is particularly successful in avoiding squamous cervical cancer (the most prevalent kind), but has had less influence on adeno carcinoma and is challenging to execute in low-resource settings.[6] 90% of HPV infections resolve or become inactive within 12 to 24 months of virus exposure. However, high-risk HPV infections persist, increasing the chance of cervical cancer progression.[7]

General characteristics

HPV is a DNA virus with two strands that belongs to the Papovaviridae family. There are about 200 HPV kinds recognized, with more than 40 strains colonizing the genital canal.[8] HPV is a small, double-stranded DNA virus that is responsible for anogenital and cutaneous warts, and high-risk HPVs (HRHPVs) are responsible for oropharyngeal (oral, tonsil, and throat areas) cancers and anogenital cancers such as cervical, anal, vulvar, vaginal, and penile cancers.[9,10] Cervical cancer (CC), the third most common cancer in women,[11] is an HPV-related disease with the highest-burden since it is the second leading cause of death in women after breast cancer.[12] The papillomavirus genome is made up of three parts and is made up of tiny double-stranded and highly conserved DNA with an approximate size of 8000 base pairs. This tiny DNA molecule's molecular biology is complicated. Six early proteins, three regulatory proteins (E1, E2, and E4), and three oncoproteins (E5, E6, and E7) are encoded in 4000 base pairs (bp) and are involved in viral replication and cell transformation. Another 3000 bp stretch of DNA encodes two structural proteins L1 and L2 that make up the viral capsid. A long control region (LCR) expressed in a 1000 bp area controls viral DNA replication and transcriptional regulatory elements.[13] There are up to 225 types of HPV divided into 5 groups (α, ß, γ, μ, and ν).[14] The exact classification of each group is shown in Figure 1. The accumulation of multiple lineage-defining genetic variants in these locations during viral evolution can result in HPV-type speciation. HPV families, relatedness, and phylogeny can be determined by sequence changes such as single-nucleotide polymorphisms or genetic mutations within the L1, LCR, E6, and E7 areas. HPV type is defined as a difference of more than 10% in the DNA sequence of the L1 gene between two genomes. The difference between 2% and 10%, on the other hand, determines the HPV subtypes. Furthermore, the variations are entities that account for less than 2% of the differences between HPV genomes. According to current research, 60 of the 160 HPV varieties are related to mucosal epithelia and are classified as the Alphapapillomavirus genus (alpha-PV).[15]

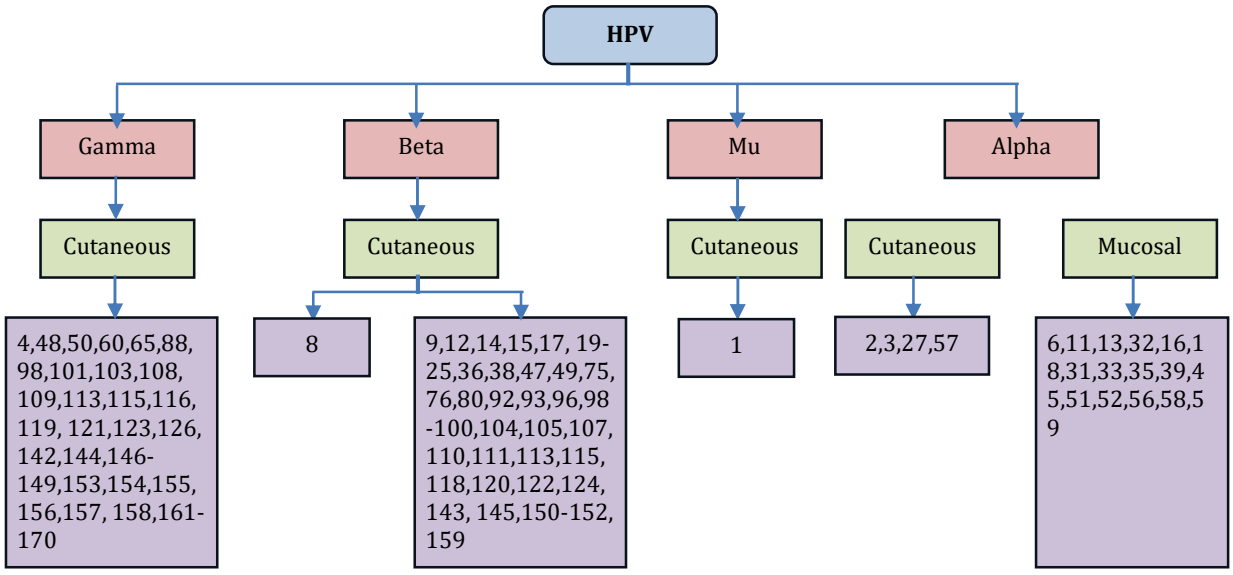

Figure: 1 Classification of HPV

Furthermore, alpha-PV is divided into nine groups: alpha-5 (HPV23, 51, 69, and 82), alpha-6 (HPV30, 53, 56, and 66), alpha-7 (HPV18, 39, 45, 59, 68, 70, 85, and 97), and alpha-9 (HPV16, 31, 33, 35, 52, 58, and 67), all of which are oncogenic high-risk varieties.[16] However, the genus Betapapillomavirus and Gammapapillomavirus have not yet been thoroughly studied.[17] According to the Papillomavirus Nomenclature Committee, each HPV type can be classified into evolutionary lineages based on geographic distribution, pathogenicity, transcriptional regulation, and immunological response.[18] The Alpha-9 HPV16 has been subdivided into four evolutionary lineages: A, B, C, and D. Phylogeny A is further subdivided into four sublineages: A1, A2, A3, and A4. Sublineages A1, A2, and A3 contain European HPV DNA sequences, whereas A4 has Asian sequences isolated worldwide. Lineage B is divided into two sublineages, B1 and B2, which contain the African HPV sequences. Lineage C is also known as African sequences. Lineage D is divided into three sublineages: D1, D2, and D3, which include Asian-American and North-American sequences. Despite their evolutionary similarity, HPV intratympanic molecular variations can be differentiated depending on their carcinogenic potential. Several research studies have found that HPV16 lineage D is more tumorigenic than the other lineages.[19]

HPV and cancers

Human papillomaviruses are DNA viruses that infect skin and mucosal cells. There is international cooperation. There is agreement that "high-risk" genotypes, such as 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66, can lead to cervical cancer and are linked to other mucosal anogenital and head and neck malignancies. Infections with other genotypes, referred to as "low-risk," can result in benign or low-grade cervical tissue alterations, as well as genital warts (condyloma acuminata), which are growths on the cervix, vagina, vulva, and anus in women and the penis, scrotum, or anus in males. They also induce epithelial growths on children's and adults' vocal cords (juvenile respiratory papillomatosis or recurrent respiratory papillomatosis), which necessitate surgical intervention.[20] Most HPV cervix infections are asymptomatic, and more than 90% of diagnosed infections are eradicated within a year.[21] The extent of protection and durability of immunity following spontaneous infection are unknown. After a natural infection, only 50-60% of women produce serum antibodies against HPV.[22] Early HPV infections may be accompanied by minor epithelial alterations detectable through screening utilizing virological and/or cytological techniques, allowing for early therapy. Squamous intraepithelial lesions (SIL) of low or high grade can be detected by cytology of cervical smears, depending on how much of the cervical epithelium is affected and how aberrant the cells seem. Cervical intraepithelial neoplasia (CIN) is a term used to describe abnormal cells in the cervix detected by histological examination of cervical biopsies; grades ranging from 1 to 3 are used to describe the proportion of the thickness of the cervical epithelium composed of abnormal cells seen in the histology section. In CIN 3, aberrant cells cover more than two-thirds of the cervical epithelium. There are similar gradings for vaginal (VaIN 1-3) and vulvar (VIN 1-3) lesions. As the viral infection progresses, it integrates into human DNA, potentially leading to cancer precursors such as moderate or severe cervical intra-epithelial neoplasia (CIN 2, CIN 3, or adenocarcinoma in situ (AIS), which are frequently classed together as CIN 2/3 or AIS). If left untreated, they have a significant risk of developing cancer.[23]

Epidemiology of HPV infection

In India, around 77,348 cervical cancer deaths occur each year (estimations for 2020). Cervical cancer is the second largest cause of cancer deaths among women in India.[24]The Cervical cancer mortality in India are shown in Table.1. Cervical cancer is the second major cause of cancer death in Indian women aged 15 to 44 years. Cervical cancer is the fourth most frequent disease in women worldwide, with a projected 604,127 new cases and 341,831 deaths in 2020. Cervical cancer mortality rates are significantly lower than incidence rates, with a mortality-to-incidence ratio of 57% (GLOBOCAN 2020). Squamous cell carcinoma is the most common type of cancer, followed by adenocarcinomas.[25] Much research on the proportion of cervical cancer, high- and low-grade squamous intraepithelial lesions (HSIL and LSIL) caused by different HPV genotypes have been conducted worldwide, but there are notable gaps in Central Asia, Africa, and Eastern Europe. The same eight HPV genotypes were the most common in each location, with the possible exception of Europe. These kinds are responsible for a substantially smaller fraction of all HPV infections and low-grade cervical lesions. According to a recent meta-analysis of HPV type distribution among women with LSIL, the most prevalent types were HPV 16 (26%), 31 (12%), 51 (11%), 53 (10%), 56 (10%), 52 (9%), 18 (9%), 66 (9%), and 58 (8%). Many other HPV kinds were also discovered, and multiple infections were common.[26] Genital HPV infection is generally transmitted by genital skin-to-skin contact, which occurs most often but not always during sexual intercourse.[27] HPV infection can develop at any age and has been recorded in young children who are otherwise healthy.[28] Age-standardized HPV prevalence varied more than tenfold amongst populations in a cross-sectional survey of over 20,000 women aged 15 to 74 years without cervical lesions. In many nations, there is an inverse link between age and HPV prevalence, but in some of the poorest communities surveyed, HPV prevalence was high across all age categories. Cross-sectional and cohort studies in several countries revealed a U-shaped curve with a first peak in women under 30 years old and a second high in women aged 55-64 years.[29] A recent meta-analysis of HIV-infected women discovered that over 40% of individuals with no cervical cytological abnormalities had HPV infection. In HIV-infected women, concur-

rent infection with various HPV genotypes is more common than in HIV-negative women. HIV-infected men and women are more likely to develop HPV-related anal cancer.[30]

Table 1: Cervical cancer mortality in India

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

HPV infections are common around the world; however, the prevalence and type distribution vary. The age-specific prevalence of HPV differs between young and old women. According to a comprehensive meta-analysis of the global prevalence of cervical HPV infection among women without cervical lesions, over 12% of females globally are positive for HPV DNA.[31] Much research has been conducted worldwide on the epidemiology of HPV infection and the carcinogenic qualities of various HPV genotypes.[32] One multinational study discovered that 10.4% of patients with normal cytology had either high- or low-risk HPV strains. Women in less developed countries and those under the age of 25 have a higher prevalence, ranging from 15 to 45%.[33] Sub-Saharan Africa (24%), Eastern Europe (21.4%), and Latin America (16.1%) had the highest HPV prevalence, while Northern America (4.7%) and Western Asia (1.7%) had the lowest. HPV type 16 was the most prevalent virus worldwide, accounting for 32.3% of all infections in Southern Asia, 28.9% in Southern Europe, 24.4% in Western Europe, 24.3% in Northern America, and 12% in Africa.[34] According to the Extended Middle East and North Africa (EMENA) study, the Middle East has lower HPV incidence rates than the rest of the world. In Qatar, for example, HPV prevalence in the general population of women with normal or abnormal cytology was recently reported to be 6.1%.[35] HPV16 (18.4%) and HPV18 (9.22%) were the most common forms discovered, followed by HPV types 33, 51, and 52 (almost 5% each).[36]

Africans had a greater frequency of HPV infection than Europeans, with 26.3% in Nigeria, 47.9% in Guinea, 41% in South Africa, and 38.8-42.3% in Kenya. The possibly high prevalence of HPV among women in Sub-Saharan African countries is more prominent due to high HIV exposure in the country, and cervical cancer may become epidemic if cervical cancer knowledge is not increased and barriers to early screening services remain.[37] Some researchers have discovered regional disparities in the frequency of squamous cell carcinoma associated with HPV infection. A meta-analysis of 85 studies involving 10,058 women with cervical cancer found that HPV16 prevalence was highest in squamous cell carcinoma, ranging from 46% in Asia to 63% in North America. HPV18 was the second most common kind, identified in 10-14% of squamous cell carcinoma specimens. The prevalence of adenocarcinoma among all invasive cervical malignancies remains high. It varies between 4% in Africa and 32% in North America. High-risk HPV type 18 was shown to be prominent in adenocarcinoma patients, with a frequency ranging from 37% to 41%. The next most prevalent HPV types are type 16 and type 45, which were detected in 26-36% and 5-7% of samples, respectively.[38] According to a meta-analysis of 133 studies and 14,595 women, the combination of HPV16 and 18 causes 74-77% of squamous cell carcinoma in Europe and North America and 65-70% in Africa, Asia, and South/Central America. While findings from meta-analyses are constrained by their reliance on the HPV DNA testing methodologies used in each investigation, several studies involving large cohorts of patients have verified the presence of the same HPV types in invasive cervical cancer specimens.[39]

Transmission of HPV

HPV is most commonly transmitted by direct skin-to-skin or skin-to-mucosa contact.[40] The most prevalent form of transmission is sexual activity (including vaginal, anal, or oral intercourse) with someone who has an active HPV infection.[41] Furthermore, non-sexual horizontal transmission of HPV occurs by skin, oral, or fomite contact, which is less common.[42] Some risk factors for cervical cancer are related to its sexually transmitted nature, such as sexual intercourse from a young age and having multiple sexual partners.[43]

Pathogenesis of HPV

Cervical cancerogenesis is a complex mechanism of uncontrolled cell proliferation that might include HPV gene integration as well as other cellular alterations and epigenetic variables. As the HPV infection progresses, the DNA might change due to cellular and environmental factors, resulting in viral DNA integration and operation with the host DNA synthesis machinery. As a result, viruses can evade cellular and immunological defense mechanisms while encouraging cell growth and preventing cellular apoptosis.[44] The oncogenic potential of HPV16 is dependent on viral transcriptional factor modulation. The HPV16 genome can be displayed as an unintegrated tiny DNA molecule, commonly known as an episome, at the start of a viral infection, resulting in benign and

precancerous cervix lesions. However, HPV16 can integrate its genome into the host genome, which can result in the development of cervical cancer and cervical intraepithelial neoplasia grade III.[45] The carcinogenic process is aided by viral genome integration in conjunction with dysregulation of the E2 protein, which is a regulator of the oncoprotein. These processes result in the overexpression of E6 and E7 proteins, which contribute to viral carcinogenesis by changing the cellular apoptotic pathway.[46]

Overexpression of E6 and E7 alone will not lead to cancerogenesis since additional genetic and epigenetic variables must also be created. Various forms of HPV have been linked to cancer - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 types.[47] HPV16 is the most dangerous HPV type, accounting for 50% of all cervical malignancies.[48] E6 and E7 viral genes are shown to be retained and integrated into the host genome and expressed in HPV16-positive cells, while E6/E7 overexpression may be absent in some HPV16-infected cells. Furthermore, E6/E7 overexpression is detected in cells infected with different HPV strains.[49] E6 and E7 are tiny proteins of 150 and 100 amino acids, respectively, that have no known enzymatic activity but can alter host cell activity by attaching to cellular proteins. For example, E6 interacts with E6-associated binding protein (E6AP), a ubiquitin ligase, causing a structural change in E6 that allows it to bind to p53, the cell cycle control tumor suppressor protein, to create a trimeric complex E6/E6AP/p53.This binding causes p53 degradation, which results in cell growth. E7, on the other hand, binds to pRb, inactivating and degrading it. Both the low-risk and high-risk E7 proteins have been demonstrated to degrade pRB family members such as p107 (RBL1) and p130 (RBL2).[50] E2F, a transcription factor, is downregulated by pRb. As E7 deactivates pRb, E2F is activated and cell proliferation genes are triggered. Furthermore, E6 and E7 have been found to form complexes with hundreds of different proteins in the host cell, and it will be intriguing to learn more about the activities and outcomes of these complexes. It is important to note that the transforming and carcinogenic features of E6 and E7 involve alternative cancer pathways that do not need p53 or Prb.[51] E7 has also been reported to interact with histone deacetylases (HDAC1-3-), which increases E2F activation, which is linked to differentiation and viral replication.

miRNA is critical in the posttranscriptional regulation of host gene expression. According to recent research, HPV E6, E7, and E5 oncoproteins modulate the host miRNA profile. Several miRNAs, including miR-21, miR-143, and miR-9, are overexpressed in HPV-associated cervical cancer cells, targeting CCL20 (chemokine (C-C) motif ligand) and encouraging migration of HPV16-positive malignant cells. Overexpression of other miRNAs, such as miR-203, however, limits HPV multiplication. +us, in HPV-infected cancer cells, miR-203 is inhibited by HPV E7 gene upregulation, resulting in viral multiplication. MiRNA expression can be deregulated primarily as a result of the epigenetic methylation of miRNA promoters.[52] E6 from tumorigenic HPV strains contains a PDZ binding motif (PBM) at the C terminus, which allows E6 to attach to a variety of proteins that contain the PDZ site. E6 interaction with these proteins results in their deactivation and destruction. Potential tumor suppressors such as Dlg,[53] MAGI-1,[54] and Scribble are examples of such proteins.[55] The epigenetic control of viral and host gene expression, which involves changes in DNA methylation, histone modifications, and noncoding RNA profile, plays a crucial role in carcinogenesis. Cervical carcinogenesis is tightly linked to persistent HPV infection, which can further impact both the host genome and the methylation process of the viral genome.

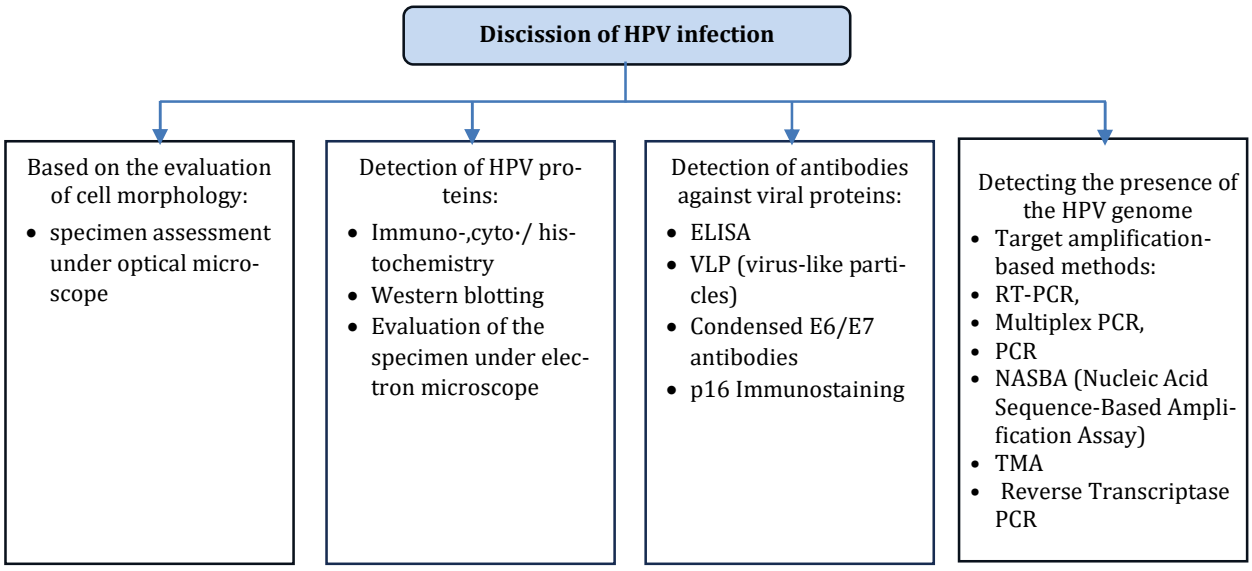

Figure: 2 Diagnostic methods for detection of HPV infection

It has been proposed that increased methylation of CpG dinucleotides inside the E2 binding site (E2BS) on the host genome can alter the interaction of many components, resulting in aberrant cell differentiation and disease development. As a result, the viral regulatory protein E2's binding affinity to E2BS is reduced, resulting in E6 and E7 overexpression and additional epigenetic suppression of tumor suppressor genes. According to certain research, CpG area methylation can be utilized as a biomarker for cervical cancer screening.[56]

Detection of HPV infection

To account for differential biomarkers and histological variations, various detection approaches are utilized to diagnose HPV. Figure 2 provides the most commonly used detection methods for HPV identification in clinical samples. Previously, summarized molecular detection approaches and screening tools for distinct HPV-driven cancer types.[57] High levels of p16 and wild-type p53 in HPV-associated OPSCC (HPV+OPSCC) indicate HPV infection. p16 immunostaining (related to HPV-16) can be utilized to identify HPV-implicated malignancies. This is especially important in OPSCC, which can be caused by HPV or occur on its own. HPV-negative OPSCC (HPV-OPSCC) is distinguished by p53 mutations and low p16 expression due to deletion, mutation, or hypermethylation. In HPV +OPSCC, p16 overexpression can also be caused by non-HPV-related mechanisms. As a result, p16 staining is frequently used in concert with other techniques to accurately diagnose HPV+OPSCC.[58]

Treatment of HPV

HPV-related disease management and therapy are greatly reliant on HPV types, available therapies, and disease progression. External genital warts caused by non-oncogenic HPVs are treated with Podophyllotoxin (an antimitotic drug that destroys warts).[59] Excisional treatment with local anaesthesia, cryosurgery (freezing), electrosurgery also known as a cone biopsy or conization, or loop electrosurgical excision process (LEEP) are all indicated for the treatment of cervical precancerous lesions caused by oncogenic HPVs. [60] Current cervical cancer therapies include adjuvant or neoadjuvant chemotherapy with radiation, as well as complete or radical hysterectomy. Chemotherapy has been shown to be effective in the treatment of cervical cancer, from localized to advanced and metastatic. Women with distant metastatic and recurring illnesses have historically received cisplatin-based chemotherapy.[61] Despite significant recurrence rates (25-40%), definitive radiation therapy with concurrent cisplatin-based chemotherapy (CRT) is regarded the gold standard in invasive cervical cancer.[62] Furthermore, new research and analyses have revealed that combining several chemotherapy medicines, such as vinorelbine, paclitaxel, pemetrexed, ifosfamide, irinotecan, topotecan, capecitabine, and S-1, increases the chances of treatment and can be administered based on the patient's situation. [63] A hysterectomy is a type of surgery that removes the uterus. Among the several types of hysterectomy, radical hysterectomy, which removes the uterus together with the parametrium (i.e., the round, broad, cardinal, and uterosacral ligaments) and the top one-third to one-half of the vagina, has been proven to be preferable. [64] Several studies have recently been published that look into the effect of combining checkpoint inhibitors with conventional therapies. Immune checkpoint mechanisms such cytotoxic lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) cause an immunosuppressive response, resulting in decreased T-cell activity. Multiple monoclonal antibodies (mAb) have been developed and FDA-approved for targeting the PD-1 axis in cervical cancer, including ipilimumab, pembrolizumab, and nivolumab.[65]

HPV vaccine

Statistical data from recent years demonstrate that using HPV vaccines to prevent infection and sickness caused by specific HPV genotypes is quite successful. Vaccination programs have been undertaken with great effectiveness in several nations throughout the world.[66] The FDA authorized the first HPV vaccination in June 2006. In the United States, three HPV vaccines are approved for use: bivalent (Cervarix), quadrivalent (Gardasil), and 9-valent (Gardasil 9) are shown in Table 2.[67] Gardasil® (Merck & Co., Inc., Whitehouse Station, NJ) is a preventive quadrivalent vaccination produced from noninfectious viruslike particles (VLPs) that are administered as a series of three injections over 6 months (at 0, 2, and 6 months). The vaccine targets the four HPV strains that are responsible for 70% of cervical cancer, AIS, CIN 3, VIN 2/3, and VAIN 2/3 cases, 50% of CIN 2 cases, 35% to 50% of all CIN 1, VIN 1, and VAIN 1 cases, and 90% of genital warts.[68] Cervarix (a bivalent vaccine against HPV16 and HPV18), Gardasil (a tetravalent against HPV6, 11, 16, and 18), and Gardasil 9 (9-valent vaccine against HPV6, 11, 16, 18, 31, 33, 45, 52, and 58) are the three commercially available preventive vaccines. They are non-infectious subunit vaccines that contain viral-like particles (VLP) generated from the recombinant production of the HPV L1 main capsid protein in yeast (Gardasil) and insect cells (Cervarix). The vaccine is administered via intramuscular injection in three doses of a prime/boost series over 6 months. Early research indicates that a single dose can reduce infection and is effective in preventing the recurrence of infection and premalignant neoplasia.[69] One month following the third dose of the HPV vaccine, over 100% of women aged 15-26 years in each vaccine trial exhibit detectable antibodies to each HPV genotype, with levels 10-104 times higher than in spontaneous infections.[70] Antibody levels obtained following vaccination are inversely related to age. The antibody responses to both the recombinant hepatitis B vaccination and the quadrivalent HPV vaccine were similar whether delivered at the same or different visits.

The concurrent use of quadrivalent and bivalent vaccines with other vaccines typically administered to adolescents, such as combined diphtheria, tetanus, and pertussis vaccine (Tdap) and meningococcal conjugate vaccine, is being studied. The vaccinations have not yet been tested in people with HIV, severe malnutrition, or concurrent malaria or helminth infection. The endpoint of CIN 2/3 OR AIS has been universally acknowledged as a surrogate for cervical cancer that may be researched feasibly and ethically among women for vaccine licensure. Bridging studies are undertaken in children or young teens by comparing antibody responses in younger people with those in women who will also have data on the clinical endpoint of CIN 2/3 or AIS.[71]

Table 2: HPV Vaccines Approved by the FDA

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

In addition to the efficacy of the quadrivalent vaccine against the HPV subtypes for which it is designed, recent analysis of data from phase III trials revealed that the vaccine also provides cross-protection against other viral subtypes not included in the vaccine. This discovery is not surprising given that the HPV virus family shares numerous proteins. The quadrivalent vaccine had a 27% efficacy against CIN 1 to 3 or AIS due to 10 oncogenic nonvaccine HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) in the trial population of HPV-naive women, and a 38% efficacy against CIN 2/3 and AIS due to the same 10 HPV strains.[72] These findings are the first to show a significant reduction in cervical lesions caused by ten nonvaccine HPV strains, which cause approximately 20% of cervical malignancies worldwide. This cross-reactivity may offer additional protection to young women who receive quadrivalent immunization. The quadrivalent vaccine's duration of protection has currently been established for up to 5 years, but its duration beyond that is unknown. Immunogenicity tests have revealed that antibody levels peak after the third dose, then fall by 1 log over the next 18 months before leveling out. For the approximately 5 years of follow-up analysis currently available, antibody levels are maintained at or above the level seen with natural infection, and sustained efficacy of the quadrivalent vaccine against CIN and persistent infection has been demonstrated in follow-up analysis for the same duration of time.[68] While preliminary studies demonstrate an increase in antibody titers following a challenge dose administered 5 years after the original immunization, it is currently unknown if a booster dose will be required. Follow-up research is currently being conducted to determine the longevity of protection for at least 14 years after vaccination. Although the quadrivalent vaccine's efficacy has not been tested in children under the age of 16, immunogenicity data from HPV trials show that immunologic responses among 9- to 15-year-old girls at 1-month post-dose 3 were not inferior to anti-HPV responses in 16- to 26-year-old adolescents and young adults. Thus, the efficiency of the quadrivalent vaccine in this age range is extrapolated based on equivalent or stronger immunogenic responses among 9- to 15-year-old girls.[73] The bivalent CervarixTM (GlaxoSmithKline, Philadelphia, PA) HPV vaccine is now awaiting FDA approval. The bivalent vaccine is an L1 VLP vaccine against HPV 16 and 18, and it is also administered in three shots (0, 1, and 6 months). The bivalent vaccine phase III trials involved 18,644 women aged 15 to 25, with 9258 receiving the immunization. As with the quadrivalent vaccine trials, the key outcomes were CIN 2+ lesions (CIN 2, CIN 3, AIS, and invasive cancer) in women who were HPV-negative at enrollment and completed the immunization regimen. The bivalent vaccine had a combined efficacy of 90.4% against HPV 16 and 18-associated CIN 2+ lesions, with 93.3% efficacy against HPV 16-related lesions and 83.3% efficacy against HPV 18-related lesions. The bivalent vaccine, like the quadrivalent vaccine, shows indications of modest cross-reactivity against other HPV strains. HPV 45 (59.9% efficacy) and HPV 31 (36.1% efficacy) provided six-month protection against persistent infection, while 12-month protection against 12 combined non-16 or 18 HPV types was 27.1%. Because the bivalent vaccine exclusively targets HPV 16 and 18, it is not intended to protect against genital warts.[74]

Cervarix was approved in 2007, however, the FDA delayed approval and requested additional information from the producer. There is a question over whether the vaccine will be included in the normal vaccination schedule and whether it will be offered to girls as young as 9 years old. It should also be made available to girls and women aged 13 to 26 who have not finished their vaccine series. Similar guidelines are supported by the American College of Obstetricians and Gynaecologists, the Society for Adolescent Medicine, and the American Academy of Family Physicians. It is our job as gynecologists to vaccinate all women aged 9 to 26 who have not yet finished the immunization series. Patients often tolerate the HPV vaccine well. Clinical trials were conducted in the United States in 2008.[75] The bivalent vaccination is now accessible in Europe and has recently received approval in Australia. Only with government leadership and the execution of sustained and successful screening and immunization programs in underdeveloped countries may cervical cancer incidence and death be reduced.

Future Prospects

HPV vaccinations reduced HPV infection and HPV-related illnesses considerably. Better protection against HPV infections and fewer HPV-related cancer cases are expected when vaccine coverage improves and pan-gender immunization programs are implemented. To do this, educational initiatives emphasizing the dangers of HPV and the benefits of vaccines are critical, particularly in low- and middle-income countries. Reduced adverse effects from various adjuvants or vaccine formulations will aid in the acceptance and provision of immunizations at a young age. Another critical issue is that HPV kinds not covered by immunizations continue to be prevalent among young females.[76] Next-generation HPV vaccines should prioritize high-valent vaccines with wide protection. Furthermore, investigations or clinical trials are required to assess the impact of HPV vaccination on all HPV-related malignancies. Therapeutic vaccines for cancer therapies are extremely important and have a bright future in battling HPV infection and related disorders from Prevention to Clearance.

Conclusion

HPV infection plays a vital role in common dermatologic and sexually transmitted diseases, as well as some of the world's most common and severe cancers. The importance of immunizations in preventing the consequences of this prevalent virus cannot be overstated. Due to the absence of HPV screening and little public knowledge of the issue, there is a high incidence of cervical cancer with a sizable fatality rate. Understanding the prevalence and type distribution of HPV could help the vaccination program be implemented successfully. To increase awareness of this public health issue, educational health promotion projects for the general public should be made available. In developing nations with a high incidence and mortality of cervical cancer, the government should establish and fund the HPV screening program in addition to the vaccination program. More research linking HPV etiology to various types of cancer and disorders, in addition to cervical cancer, will contribute to the value, usefulness, and potential of HPV vaccination.

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