

Human Papilloma Virus: A Comprehensive Review

Shreya Veggalam¹, Venkataramana Kandi^{2*}, Srikar Reddy Vummenthala³

¹Third Year MBBS Student at Prathima Institute of Medical Sciences

²Department of Microbiology Prathima Institute of Medical Sciences

³Final Year MBBS Student at Government Medical College Nalgonda

*Corresponding author: ramana20021@gmail.com

Received December 05, 2023; Revised January 08, 2024; Accepted January 15, 2024

Abstract Human Papillomavirus (HPV) is among several Deoxyribonucleic acid (DNA) viruses that can infect humans. HPV is a tumorigenic virus associated with carcinoma of the cervix in females. Additionally, HPV was found to be involved in the development of oropharyngeal and anogenital cancers. Cervical cancer is the second most predominant cancer resulting in death among women worldwide. Despite the availability of an approved vaccine, there is little awareness about the vaccine that could be administered to prevent HPV-associated cancers. HPV has been causing trouble in the lives of millions of women globally. The majority of HPV-associated cancers remain unrecognized due to the lack of specific symptoms. Additionally, women who are infected at an early age develop symptoms after decades, thereby complicating the treatment and contributing to the worsening of disease outcomes. HPV appears in several hundreds of serotypes with some of them being primarily responsible for most of the disease-causing complications including cancer. It is high time for the Indian government and other administrations, especially those belonging to developing and underdeveloped countries, throughout the world to consider the implementation of the HPV vaccination. Besides, it is extremely important to enforce preventive screening of women for cervical cancer at regular intervals since early diagnosis enables initiation of treatment and minimizes morbidity and mortality. In this review, we comprehensively discuss the epidemiology, pathogenicity, complications, diagnosis, management, and prevention of HPV-associated diseases including cancer.

Keywords: Human Papillomavirus (HPV), cervical cancer, women, vaccination, preventive screening, cancer, carcinoma, HPV vaccination, epidemiology, pathogenesis

Cite This Article: Shreya Veggalam, Venkataramana Kandi, and Srikar Reddy Vummenthala, "Human Papilloma Virus: A Comprehensive Review." *American Journal of Infectious Diseases and Microbiology*, vol. 12, no. 1 (2024): 9-15. doi: 10.12691/ajidm-12-1-2.

1. Introduction

Infection with Human Papillomavirus (HPV) results in sexually transmitted diseases [1]. HPV is a small double-stranded Deoxyribonucleic acid (DNA), and non-enveloped virus belonging to the family of Papillomaviridae. The papillomaviruses are further classified into various genera that include Alpha, Beta, Gamma, Delta, Epsilon, Zeta, Eta, Theta, Iota, Kappa, Lambda, Mu, Nu, Xi, Omikron, and Pi-type papillomaviruses [2]. A vast majority of adults get exposed to this virus during their initial years of sexually active life. Additionally, a majority of HPV infections resolve without any complications. However, some HPV infections can result in diseases including cancer, especially among women. HPV infections can be of two types including infections following low-risk (LR) and high-risk (HR) exposures. The low-risk HPV infections result in the development of warty lesions in the anogenital regions and oral cavity. Alternatively, the HR infections result in cancers [3]. Although any individual can get exposed to the virus at any point of time in life, the most vulnerable population to getting HPV infection are

sex workers. HPV-associated oropharyngeal and anogenital cancers are very common among men, and women predominantly develop cervical cancer. There are over 200 HPV genotypes wherein LR types are responsible for asymptomatic infections and mild diseases [1]. Infections with HR HPV types result in cancers. The prevalence of HPV is notably higher among women and cervical cancer is the most common cancer caused by the virus. The virus also infects the male population. In males, HPV infections may result in genital warts, oropharyngeal cancers, anogenital cancers, and plantar warts [4]. HPV is one of the most important reasons for microbial infection-related cancers and five percent of cancers all over the world are predominantly caused by HPV. Among the hundreds of HPV serotypes, approximately 80% of cervical cancer cases are caused by HPV 16 serotype [4,5]. Being a sexually transmitted disease, HPV spreads along with Human Immunodeficiency Virus (HIV). Additionally, HPV infections among HIV-infected individuals result in rapid disease progression and the development of cancer [6].

HPV infection-related cancers have been noted to be the most common ones in developing countries [7]. The awareness about HPV infection among females is very poor in India due to a lack of publicity on the potential

complications including the development of cervical cancer [8]. Despite HPV being a cause of cervical cancer, the available literature suggests other factors like multiparity, early sexual activity in life, use of hormonal contraceptives, and tobacco consumption among others could also be associated with the development of HPV infection-related cancers [9,10]. In this review, we comprehensively discuss the epidemiology, pathogenicity, complications, diagnosis, management, and prevention of HPV-associated diseases including cancer.

2. Review

2.1. Epidemiology

HPV is one of the most prevalent viruses throughout the world and it accounts for more than 90% of cervical cancers [11]. In 2018, 91% of global HPV-related cancers in women were cervical cancers [12]. More than 25% of women including both healthy and unhealthy populations were identified as HPV carriers [11]. India accounts for one-third of the global burden of cervical cancer [13,14]. The incidence of HPV viral infection among the general population is very high. The highest rates of HPV infection are found in women of reproductive age under 25 years. The HR HPV types are 16, 18, 52, 31, and 58. The LR HPV types like 6 and 11 can cause genital warts [15,16]. The HR HPV types have a greater potential to cause carcinogenesis than the other types discovered. Most commonly, sexually active men and women would encounter the virus at any point in their lives. The infection mainly sets in during early adulthood. It is estimated that more than 10% of the population between ages 15 to 25 years has an active infection of HPV. About 90% of HPV resolves on its own within two years provided the immunity of the individual is good [17].

Since the virus remains in a person's body for a long period without manifestations, they can be potential carriers of the disease and transmit HPV to others. In the United States, 27,000 cases of HPV-related cervical cancer deaths are reported to occur every year. According to WHO, about 84 % of HPV cases present as cervical cancers among women. More than 500,000 new cervical cancer cases are being diagnosed each year globally. This indicates that HPV infection is a major health issue and needs large-scale interventions to stop the spread and prevent the disease [18]. In India, the age-related incidence and mortality rate of HPV was reported as 14.7 and 9.2 per 100,000 people, respectively [19]. India is among the most populated countries and a disease like HPV can easily spread among people. Nearly 90% of HPV infection-related deaths in 2018 occurred in low- and middle-income countries [20].

The World Health Organization (WHO) proposed a strategy named Global Strategy for Cervical Cancer Elimination. This aims to eliminate HPV and its complications by implementing various measures that include wide range coverage of vaccination, providing better screening to women, and initiating appropriate treatment to minimize the complications [21].

3. Pathogenesis

The infection of HPV occurs via the shredding of mucosa over the cervix. The layers of the mucosa above the basement membrane are sloughed off following HPV infection. Due to this, the basement membrane surface proteins like the Heparan Sulphate Proteoglycans (HSP) get exposed to the virus [22]. The capsid proteins like the L1 proteins recognize the HSP proteins on the cells of the basement membrane. The capsid proteins bind to HSPs on the surface of host cells. This triggers a conformational change in the cells of the basement membrane. The virus enters the cell and the viral genome replicates in the basal keratinocytes [22]. The virus replicates in the host cell producing daughter viruses. Along with the dividing host cells the virus also spreads along the basement membrane infecting the other cells using the host cells' resources. The virus replication does not kill the host cells as noticed in the lytic cycle of replication as observed in some other viruses. The assembly of the viral particles replicated in the host cells occurs in the upper layers of the epithelium. The squamous layer is then shed off leading to the spread of the virus.

Mechanisms behind HPV infection and cancer

The HPV initially causes epithelial abrasion following primary infection that generally occurs through sexual contact. Later, the basement membrane is denuded or exposed allowing the virus to bind to the cells. HPV binds to the HSPs on the surface of basal keratinocytes through the L1 capsid proteins present on the capsid of the virus. This brings about conformational changes in the capsid proteins which will lead to the exposure of a minor subunit protein L2 and the entry of the virus into the host cell. The HPV genome replicates in the host cell, producing oncoproteins like E1, E2, E4, E5, E6, and E7. Each of these proteins function uniquely wherein the E1 protein authorizes the replication of virus DNA, E2 enforces controlled viral RNA splicing shifts from early to late polyadenylation sites, and E6 induces proteasomal degradation of Protein 53 (p53), blocks its activity and other pro-apoptotic factors, and promotes telomerase activity. The E7 protein overcomes restriction points of the cell cycle which allows the proliferation of the virus to occur without causing cell death. The HPV escapes the immune response since the replication occurs in the upper layer of keratinocytes, where there is less access to immunity. The newly synthesized viruses infect the neighboring keratinocytes, and the process continues. Among the LR-type HPV, the oncoproteins including E6 and E7 are not manufactured, and therefore, such strains of HPV cause mild dysplasia of the epithelium of the cervix and do not have the potential to cause cancer. However, the HR-type HPV synthesizes E6 and E7 proteins that potentially possess tumorigenic abilities and infection with such strains can lead to disease progression and the development of cancer [23,24,25,26]. A diagrammatic representation of HPV pathogenesis is depicted in Figure 1.

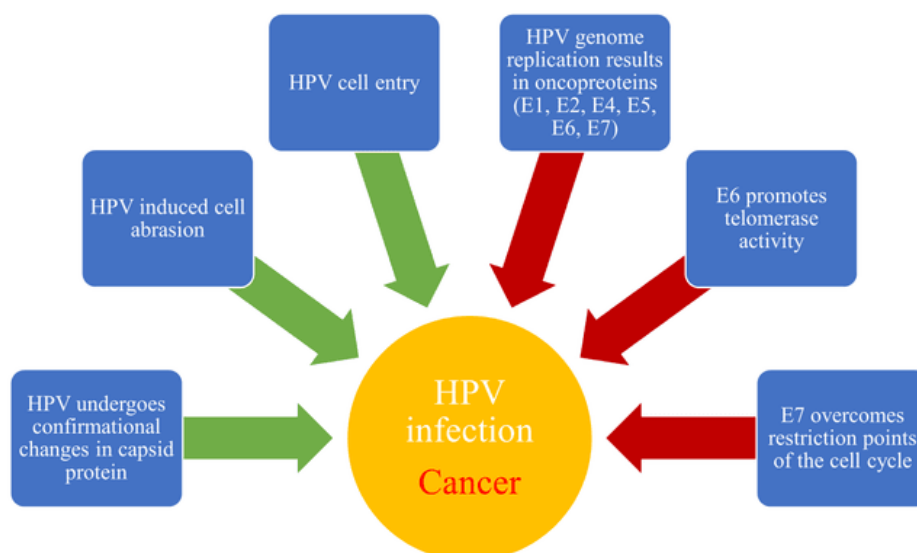


Figure 1. Mechanisms of Human Papilloma Virus pathogenesis resulting in cancer

4. Complications

The main symptoms of the disease are post-coital vaginal bleeding, pelvic pain, and sometimes pain during sex. The vaccines are developed with the HPV capsid proteins, which act as the antigens. Following the vaccination, which is administered intramuscularly, immunologic responses are generated, thereby activating the immune system and producing the antibodies.

About 10 % of women with an active HPV infection with the HR types are prone to develop cervical cancer throughout their lives. The severity of the infection lies in the symptoms it causes like bleeding per vagina irregularly, irrespective of the menstrual cycle. Pain in the lower abdomen and irregular bleeding are the most commonly reported symptoms. HPV causes cervical cancers and pre-cancerous lesions related to the vulva, anus, oropharynx, tonsils, and plantar warts, and wart-like lesions mainly on the body's mucosal surfaces. Some studies reveal a correlation between anal cancers and HPV infection along with HIV co-infection [27]. Usually, most of the people infected with HPV do not develop serious complications but the infection may result in cancerous changes when the immunity of the individual is compromised. Studies reveal that most women infected with HPV do not even know that they got infected by the virus since the infection can be asymptomatic [28]. When the infection is superimposed with conditions like Acquired Immunodeficiency Syndrome (AIDS), the complications could be severe [29].

Approximately, it takes around 15-20 years to develop cervical cancer in women infected with HPV [21,30]. Among immunocompromised individuals, the duration from infection to the development of cancer is less. Most of the cancers are diagnosed at a later stage of the disease due to the unavailability of timely screening or due to a lack of awareness of the infection. Such cases have a lesser survival rate as the disease progresses further wherein the initiation of treatment becomes too late for better outcomes [31]. Cervical cancers are graded based on the CIN (cervical intraepithelial neoplasia), and most of the cases are diagnosed at the CIN+3 stage due to so

many factors, some of which have been discussed in the earlier paragraphs [32]. Not all HPV infections are oncogenic, and most lesions like plantar warts are non-oncogenic and subside without any medical support/treatment.

Among males, the infection can be asymptomatic and resolve on its own, but some cases may result in complications like genital warts, plantar warts, oropharyngeal cancers, etc. HPV infection generally subsides on its own within two years of infection among immunocompetent individuals. The complications set in only when the infected person is immunologically deficient/compromised [33].

5. Management

There is no cure for HPV infections. However, a few antiviral medications available targeting HPV are known to produce little effect on the virus [34]. The infection of HPV results in warts or benign growths of abnormal tissue on the body's mucosal/skin surfaces in both men and women. In women, cervical cancer is the most frequent sequelae. The treatment plan includes surgical resection of the tumor. Treatment can change depending on the clinical presentation of the patient, the extent of disease spread, the stage of the tumor, etc. Radiotherapy, cryotherapy, laser therapy, and chemotherapy can be part of the treatment modalities [35]. The management, sometimes, depends solely on surgical excision of the potential tumor [36]. However, there can be chances of recurrence in the future. In developed countries, the pap (Papanicolaou test) screening technique proved unsatisfactory. Nevertheless, in India, routine screening of women for cervical cancer is carried out via pap smear. Additionally, this process appears to be cumbersome and requires huge manpower [9].

6. Screening

Proper screening of warts or cancerous lesions can be done either by tissue biopsy or molecular conformation regarding HPV infection. In the case of cervical lesions, a

pap smear is preferred as a screening test, which can be confirmed by molecular diagnostic tests like Polymerase Chain Reaction (PCR). A pap smear screening test is useful for early detection, diagnosis, and to get a better insight into the patient's condition, and for starting an appropriate treatment modality and predicting the outcome of HPV infection [7,37]. After confirmation by laboratory investigations, the lesions are surgically excised and removed appropriately depending on the dissemination/spread of cancer. For a developing nation like India, a pap smear and HPV DNA testing are suggested as the diagnostic approach towards HPV detection [38,39]. There is a need to educate the general population regarding the benefits of regular screening for HPV infection [40,41].

7. Prevention

Since HPV is most commonly transmitted through sexual routes, discouraging sexual intercourse with multiple partners can decrease the risk of infection. Employing barrier methods during sex like using condoms can help reduce the risk but not completely protect people from getting exposed to the virus. Condoms aid in contraception but can't prevent infection as the genitals are not fully covered. The barrier methods provide protection only to a lesser extent as the infection can also be transmitted by exposed mucosal surfaces where the condoms do not essentially provide coverage.

Because cervical cancers are caused by HPV infections, vaccines against the virus can be a huge defense against infection. Several vaccines available in the market specifically target the HR types of HPV like 16,18 etc [22]. Only six vaccines are certified by the World Health Organization (WHO) and these are marketed and are ready for use among the general population [30]. Vaccines are primarily manufactured based on the capsid proteins of the virus including the L1 capsid proteins [42]. Because there is a high incidence of HR-type HPV infections

among people, vaccines targeted against them can provide good protection. The vaccines are effective in preventing the complications of the disease. The recommended age for vaccination is 15 to 25 years because at this age most females begin their sexual lives. The recommended vaccine dosage for women is two doses pre-puberty or around puberty age (11-12 years). HPV vaccines are not indicated for girls above the pubertal age or those who have already indulged in sexual activities [15].

The Ministry of Health in India has taken up HPV infection as a challenge and is creating awareness programs to educate people within the country regarding the availability and implementation of vaccination [43]. Merging the HPV vaccination with the ongoing immunization schedule is important at this point [44]. Medical colleges should include HPV vaccination in the curriculum of MBBS courses so that students get awareness regarding the disease and its complications [45].

HPV vaccination may be ineffective in individuals who cross the age of 25 years or after they become sexually active in their course of life. Education regarding vaccination, its effectiveness, strategies, and proper implementation methods for healthcare workers (HCWs) is important. This is because HCWs should be able to educate the need for vaccination to all the women [7]. Vaccinating women should be considered as a better strategy by the governments to control and prevent the disease. Additionally, vaccinating men can be helpful to prevent non-cervical cancer-related complications including lesions, and decrease the burden of the disease in the population as men can act as potential carriers [46]. There are different types of vaccines available against HPV infections including bivalent, quadrivalent, and nine-valent vaccines. A majority of these vaccines target cancer-causing serotypes of HPV. Additionally, all the vaccines available appear to have moderate levels of efficacy and produce mild adverse events following vaccination [12] [47,48,49,50,51]. The details of the currently available six different types of HPV vaccines approved for human use and their details can be found in Table 1.

Table 1. Details of the currently available Human Papillomavirus vaccines

Name of the vaccine	Vaccine type	Name of the manufacturer	Serotypes covered	Indications	Efficacy	Adverse effects
Gardasil®	Recombinant-quadrivalent	Merck Sharp & Dohme B.V., Netherlands MSD pharmaceuticals, Mumbai, India	6,11,16,18	Intramuscular, 9-14 years males and females, two doses (0, 6-12 months); 15-45 years males and females, three doses (0, 1-2, 6 months)	99%	Injection-site pain, swelling, erythema, and headache in females and injection site pain, swelling, and erythema
Gardasil-9	Recombinant-9 valent	Merck & Co., Inc., Rahway, NJ, USA	6, 11, 16, 18, 31, 33, 45, 52, and 58	Intramuscular, 9-14 years males and females, two doses (0, 6-12 months); 15-45 years males and females, three doses (0, 1-2, 6 months)	99%	Injection-site pain, swelling, erythema, and headache in females and injection site pain, swelling, and erythema
Cervavac®	Recombinant-quadrivalent	Serum Institute of India	6,11,16,18	Intramuscular, 9-14 years males and females, two doses (0, 6-12 months); 15-45 years males and females, three doses (0, 1, 6 months)	90%	Injection site pain, headache, nausea, dizziness, fever
Cervarix®	Recombinant-bivalent	GlaxoSmithKline Biologicals	16,18	Intramuscular, males and females, three doses (0, 1-2, 6 months)	75-85%	Pain, redness, and swelling at the injection site, fatigue, headache, myalgia, gastrointestinal symptoms,

Name of the vaccine	Vaccine type	Name of the manufacturer	Serotypes covered	Indications	Efficacy	Adverse effects
						and arthralgia
Cecolin®	Recombinant-bivalent	Xiamen Innovax Biotech Co. Ltd., China	16, 18	Intramuscular, 9-45 years, three doses (0, 1, 6 months)	97.3%	Injection site pain, fatigue, cough, fever
Walrinvax®	Recombinant-bivalent	Walvax, China	16, 18	Intramuscular-deltoid, 9-14 years, two doses (0, 6 months), >14 years, three doses (0, 1, 6 months)	78.6%	Injection site pain and erythema, and fever

8. Factors Influencing HPV Vaccination

It is a fact that HPV-associated diseases including cancers are not curable but are vaccine-preventable. This suggests that vaccines can prevent the incidence of the disease. Therefore, extensive vaccination drives targeting prepuberty teenage girls and boys can be taken up so that they don't grow up to become carriers of the disease and do not suffer from the complications of infections. Governments must ensure people do not unnecessarily suffer from vaccine-preventable diseases. Moreover, the lack of fundamental statistics regarding the infection burden due to poor government interventions is a major setback that needs to be urgently addressed [52].

The high cost of manufacturing the vaccine can lead pharmaceutical companies to raise the costs of the vaccines to the public. The expensive vaccines are not affordable by a majority of the population in a setting like India and other poor and developing countries where the cost of vaccines becomes a massive disadvantage [9,53]. According to 2022 estimates by the World Bank, India's rural population is about 64.13% [54]. Moreover, the rural population tends to suffer from sexually transmitted infections due to illiteracy, ignorance, unprotected intercourse/sex, multiparity, etc. In countries that fall under the low-income group or if the majority of the population is not able to afford the vaccine, interventions have to be made by the government, non-government organizations (NGOs), and other organizations to make sure the vaccine is given to the public at a lower/affordable cost.

Though the disease manifests in women at a late period of life in the form of cervical cancer, it must be understood that it is often caused by a virus that enters the body at a very young age. So, getting vaccinated even before the encounter with the virus would be the most effective prevention method. In India with a population of 1.4 billion people, a majority of them being illiterate, HPV can spread easily.

Some studies reveal that parents are unwilling to vaccinate their children against HPV as they are not sure of its efficacy and are worried about the complications of the vaccines as they are newly discovered [55]. Mothers could face difficulties in educating their young girls regarding unprotected sexual intercourse with boys and the importance of getting vaccinated. This is because the age of vaccinating the girls is about prepubertal age wherein they are not mature enough to understand the problem [56]. Usually, girls around that age are not aware of proper sexual behaviors and about sexually transmitted infections (STIs). There is a stigma that these vaccines are ineffective or there would be complications following

vaccination. Proper awareness drives all around the world educating people regarding the importance of HPV vaccination would help in overcoming the stigma associated with the vaccination [57].

There is very little awareness among healthcare professionals regarding the HPV vaccination despite its efficacy being high in preventing disease complications and cancerous lesions [58,59]. Some studies reveal that less than half of the female population is aware of pap smear and HPV virus and about 75% of the females are showing a willingness to get vaccinated against HPV [60]. There is a need to educate the HCWs first alongside creating awareness among the general population. The govt of India's National Health Mission includes a project named ARSH (Adolescent Reproductive and Sexual Health), which targets the adolescent population to bring awareness about their changing bodies, sexual activities, and awareness of STIs and preventive vaccinations [61,62].

9. Conclusions

Cervical cancer is the second most common cancer after breast cancer among women. HPV infection predisposes women to cervical cancer. Since there is no specific pharmacotherapeutic agent developed yet for the treatment of HPV infections, vaccination remains the only strategic intervention to prevent the infection and related consequences including cancer. Additionally, HPV infection could go unnoticed for several long years before resulting in cancer. The government of India and other administrations throughout the world are advised to include HPV vaccination in their national immunization schedules. Moreover, vaccination should be made mandatory for all girls and boys before they reach puberty. Since the HPV vaccines pass through various clinical trials before being approved for marketing, the public should be adequately educated about the safety and efficacy of the vaccines. Additionally, people should be advised to avoid the social stigma associated with vaccination among women. It is essential to devise a global strategy to eliminate the burden of HPV-associated cancers which can save the lives of millions of people.

References

- [1] Wikipedia contributors. (2023, July 10). Human papillomavirus infection. In *Wikipedia, The Free Encyclopedia*. Retrieved 04:51, August 28, 2023, from https://en.wikipedia.org/w/index.php?title=Human_papillomavirus_infection&oldid=1164603394.
- [2] HPV and cancer. (2023). <https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-and-cancer>

Last Accessed: August 10, 2023

- [3] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Human Papillomaviruses. Lyon (FR): International Agency for Research on Cancer; 2007. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 90.) 1, Human Papillomavirus (HPV) Infection. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK321770/>.
- [4] Chaturvedi AK. Beyond cervical cancer: burden of other HPV-related cancers among men and women. *J Adolesc Health*. 2010 Apr; 46(4 Suppl): S20-6.
- [5] Sankaranarayanan R, Bhatla N, Gravitt PE, Basu P, Esmay PO, Ashrafunnessa KS, Ariyaratne Y, Shah A, Nene BM. Human papillomavirus infection and cervical cancer prevention in India, Bangladesh, Sri Lanka and Nepal. *Vaccine*. 2008 Aug 19; 26 Suppl 12: M43-52.
- [6] Arora R, Pandhi D, Mishra K, Bhattacharya SN, Yhome VA. Anal cytology and p16 immunostaining for screening anal intraepithelial neoplasia in HIV-positive and HIV-negative men who have sex with men: a cross-sectional study. *Int J STD AIDS*. 2014 Sep; 25(10): 726-33.
- [7] Fontham ETH, Wolf AMD, Church TR, Etzioni R, Flowers CR, Herzig A, Guerra CE, Oeffinger KC, Shih YT, Walter LC, Kim JJ, Andrews KS, DeSantis CE, Fedewa SA, Manassaram-Baptiste D, Saslow D, Wender RC, Smith RA. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020 Sep; 70(5): 321-346.
- [8] Shetty S, Shetty V, Badiger S, Shetty AK. An exploratory study of undergraduate healthcare student perspectives regarding human papillomavirus and vaccine intent in India. *Women's Health*. 2021; 17.
- [9] Kaarthigeyan K. Cervical cancer in India and HPV vaccination. *Indian J Med Paediatr Oncol*. 2012 Jan; 33(1): 7-12.
- [10] Sreedevi A, Javed R, Dinesh A. Epidemiology of cervical cancer with special focus on India. *Int J Womens Health*. 2015 Apr 16; 7: 405-14.
- [11] Kombe Kombe AJ, Li B, Zahid A, Mengist HM, Bounda GA, Zhou Y, Jin T. Epidemiology and Burden of Human Papillomavirus and Related Diseases, Molecular Pathogenesis, and Vaccine Evaluation. *Front Public Health*. 2021 Jan 20; 8: 552028.
- [12] Human papillomavirus vaccines: WHO position paper, December 2022. <https://www.who.int/publications/i/item/who-wer9750-645-672> Last Accessed: August 14, 2023.
- [13] Aoki ES, Yin R, Li K, Bhatla N, Singhal S, Ocviyanti D, Saika K, Suh M, Kim M, Termrungruanglert W. National screening programs for cervical cancer in Asian countries. *J Gynecol Oncol*. 2020 May; 31(3): e55.
- [14] Holroyd TA, Yan SD, Srivastava V, et al. Designing a Pro-Equity HPV Vaccine Delivery Program for Girls Who Have Dropped Out of School: Community Perspectives From Uttar Pradesh, India. *Health Promot Pract*. 2022 Nov; 23(6): 1039-1049.
- [15] National Cancer Institute. Human Papillomavirus (HPV) Vaccines. (2021). <https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet> Last accessed: August 28, 2023.
- [16] de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol*. 2010 Nov; 11(11): 1048-56.
- [17] <https://www.who.int/news-room/fact-sheets/detail/cervical-cancer#:~:text=HPV%20and%20cervical%20cancer&text=More%20than%2090%25%20of%20the,be%20attributed%20to%20HPV%20infection.>
- [18] McGraw SL, Ferrante JM. Update on prevention and screening of cervical cancer. *World J Clin Oncol*. 2014 Oct 10; 5(4): 744-52.
- [19] Singh M, Jha RP, Shri N, Bhattacharyya K, Patel P, Dhamnetiya D. Secular trends in incidence and mortality of cervical cancer in India and its states, 1990-2019: data from the Global Burden of Disease 2019 Study. *BMC Cancer*. 2022 Feb 7; 22(1): 149.
- [20] <https://www.who.int/initiatives/cervical-cancer-elimination-initiative>.
- [21] WHO: Cervical cancer. (2022). <https://www.who.int/news-room/fact-sheets/detail/cervical-cancer#:~:text=HPV%20and%20cervical%20cancer&text=More%20than%2090%25%20of%20the,be%20attributed%20to%20HPV%20infection.> Last accessed: August 28, 2023.
- [22] Roden RBS, Stern PL. Opportunities and challenges for human papillomavirus vaccination in cancer. *Nat Rev Cancer*. 2018 Apr; 18(4): 240-254.
- [23] Lehoux M, D'Abramo CM, Archambault J. Molecular mechanisms of human papillomavirus-induced carcinogenesis. *Public Health Genomics*. 2009; 12(5-6): 268-80.
- [24] Groves IJ, Coleman N. Pathogenesis of human papillomavirus-associated mucosal disease. *J Pathol*. 2015 Mar; 235(4): 527-38.
- [25] Ashique, S., Hussain, A., Fatima, N. et al. HPV pathogenesis, various types of vaccines, safety concern, prophylactic and therapeutic applications to control cervical cancer, and future perspective. *VirusDis*. 34, 172–190 (2023).
- [26] Bordignon V, Di Domenico EG, Trento E, D'Agosto G, Cavallo I, Pontone M, Pimpinelli F, Mariani L, Ensoli F. How Human Papillomavirus Replication and Immune Evasion Strategies Take Advantage of the Host DNA Damage Repair Machinery. *Viruses*. 2017 Dec 19; 9(12): 390.
- [27] Lin C, Franceschi S, Clifford GM. Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis. *Lancet Infect Dis*. 2018 Feb; 18(2): 198-206.
- [28] Ramavath, K.K., Olyai, R. Knowledge and Awareness of HPV Infection and Vaccination Among Urban Adolescents in India: A Cross-Sectional Study. *J Obstet Gynecol India* 63, 399–404 (2013).
- [29] Stelzle D, Tanaka LF, Lee KK, et al. Estimates of the global burden of cervical cancer associated with HIV. *Lancet Glob Health*. 2021 Feb; 9(2): e161-e169.
- [30] Valentine K, Vanden Broeck D, Benoy I, Truyens M, Bogers J. Cytology at the Time of HPV: Some Things to Think about when Discussing HPV. *Acta Cytol*. 2016; 60(6): 527-533.
- [31] Khanna D, Khargekar N, Budukh A. Knowledge, attitude, and practice about cervical cancer and its screening among community healthcare workers of Varanasi district, Uttar Pradesh, India. *J Family Med Prim Care*. 2019 May; 8(5): 1715-1719.
- [32] Demarco M, Hyun N, Carter-Pokras O, Raine-Bennett TR, Cheung L, Chen X, Hammer A, Campos N, Kinney W, Gage JC, Befano B, Perkins RB, He X, Dallal C, Chen J, Poitras N, Mayrand MH, Coutlee F, Burk RD, Lorey T, Castle PE, Wentzensen N, Schiffman M. A study of type-specific HPV natural history and implications for contemporary cervical cancer screening programs. *EClinicalMedicine*. 2020 Apr 25; 22: 100293.
- [33] Gamboa-Hoil SI. Human papillomavirus in men. *Rev Int Androl*. 2023 Jan-Mar; 21(1): 100325.
- [34] Stern PL, van der Burg SH, Hampson IN, Broker TR, Fiander A, Lacey CJ, Kitchener HC, Einstein MH. Therapy of human papillomavirus-related disease. *Vaccine*. 2012 Nov 20; 30 Suppl 5(0 5): F71-82.
- [35] <https://www.webmd.com/sexual-conditions/hpv-genital-warts/hpv-treatment-is-there-hpv-cure>.
- [36] Stern PL, van der Burg SH, Hampson IN, Broker TR, Fiander A, Lacey CJ, Kitchener HC, Einstein MH. Therapy of human papillomavirus-related disease. *Vaccine*. 2012 Nov 20; 30 Suppl 5(0 5): F71-82.
- [37] Schiffman M, Mirabello L, Egemen D, et al. The combined finding of HPV 16, 18, or 45 and cytologic Atypical Glandular Cells (AGC) indicates a greatly elevated risk of in situ and invasive cervical adenocarcinoma. *Gynecol Oncol*. 2023 Jul; 174: 253-261.
- [38] Srivastava AN, Misra JS, Srivastava S, Das BC, Gupta S. Cervical cancer screening in rural India: Status & current concepts. *Indian J Med Res*. 2018 Dec; 148(6): 687-696.
- [39] Bruni L, Saura-Lázaro A, Montoliu A, et al. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010-2019. *Prev Med*. 2021 Mar; 144: 106399.
- [40] Watson M, Benard V, King J, Crawford A, Saraiya M. National assessment of HPV and Pap tests: Changes in cervical cancer screening, National Health Interview Survey. *Prev Med*. 2017 Jul; 100: 243-247.
- [41] Saraiya M, Steben M, Watson M, Markowitz L. Evolution of cervical cancer screening and prevention in United States and Canada: implications for public health practitioners and clinicians. *Prev Med*. 2013 Nov; 57(5): 426-33.
- [42] Plotzker RE, Vaidya A, Pokharel U, Stier EA. Sexually Transmitted Human Papillomavirus: Update in Epidemiology, Prevention, and Management. *Infect Dis Clin North Am*. 2023 Jun; 37(2): 289-310.
- [43] Burki TK. India rolls out HPV vaccination. *Lancet Oncol*. 2023 Apr; 24(4): e147.

- [44] Jacob M, Mawar N, Menezes L. Assessing the Environment for Introduction of Human Papillomavirus Vaccine in India. *The Open Vaccine Journal*, 2010, 3: 96-107.
- [45] Kamath A, Yadav A, Baghel J, Mundle S. Level of Awareness About HPV Infection and Vaccine Among the Medical Students: A Comprehensive Review from India. *Indian J Gynecol Oncology* 19, 61 (2021).
- [46] Elbasha EH, Dasbach EJ. Impact of vaccinating boys and men against HPV in the United States. *Vaccine*. 2010 Oct 4; 28(42): 6858-67.
- [47] Administering HPV Vaccine. (2021). [https://www.cdc.gov/vaccines/vpd/hpv/hcp/administration.html#:~:text=A%20two%2Ddose%20series%20\(0,years%2C%20and%20for%20immunocompromised%20persons](https://www.cdc.gov/vaccines/vpd/hpv/hcp/administration.html#:~:text=A%20two%2Ddose%20series%20(0,years%2C%20and%20for%20immunocompromised%20persons). Last Accessed: August 14, 2023.
- [48] Cervarix: <https://www.fda.gov/media/78013/download> Last Accessed: August 14, 2023.
- [49] CERVAVAC®. <https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadSmPC/qHPV%20-%20SmPC%202022.pdf> Last Accessed: August 14, 2023.
- [50] Chu K, Bi ZF, Huang WJ, Li YF, Zhang L, Yang CL, Jiang HM, Zang X, Chen Q, Liu DL, Pan HX, Huang Y, Zheng FZ, Zhang QF, Sun G, Su YY, Huang SJ, Pan HR, Wu T, Hu YM, Zhang J, Zhu FC, Xia NS. Safety and immunogenicity of an *Escherichia coli*-produced 9-valent human papillomavirus L1 virus-like particle vaccine (types 6/11/16/18/31/33/45/52/58) in healthy adults: an open-label, dose-escalation phase 1 clinical trial. *Lancet Reg Health West Pac*. 2023 Mar 13; 34: 100731.
- [51] Li M, Zhao C, Zhao Y, Li J, Wei L. Immunogenicity, efficacy, and safety of human papillomavirus vaccine: Data from China. *Front Immunol*. 2023 Mar 13; 14: 1112750.
- [52] Krokidi E, Rao AP, Ambrosino E and Thomas PPM. The impact of health education interventions on HPV vaccination uptake, awareness, and acceptance among people under 30 years old in India: a literature review with systematic search. *Front. Reprod. Health* 2023; 5: 1151179.
- [53] Balaji M, Panwar A, Kudva MA, Ballal NV, Keluskar V. Awareness and Knowledge Among Dental and Medical Undergraduate Students Regarding Human Papilloma Virus and Its Available Preventive Measures. *Ann Glob Health*. 2020 Nov 25; 86(1): 150.
- [54] Rural population (% of total population). (2023). <https://data.worldbank.org/indicator/SP.RUR.TOTL.ZS>. Last accessed: August 28, 2023.
- [55] Waller J, Marlow LA, Wardle J. Mothers' attitudes towards preventing cervical cancer through human papillomavirus vaccination: a qualitative study. *Cancer Epidemiol Biomarkers Prev*. 2006 Jul; 15(7): 1257-61.
- [56] Herman R, McNutt LA, Mehta M, Salmon DA, Bednarczyk RA, Shaw J. Vaccination perspectives among adolescents and their desired role in the decision-making process. *Hum Vaccin Immunother*. 2019; 15(7-8): 1752-1759.
- [57] Thanasis I, Lavranos G, Gkogkou P, Paraskevis D. The Effect of Health Education on Adolescents' Awareness of HPV Infections and Attitudes towards HPV Vaccination in Greece. *Int J Environ Res Public Health*. 2022 Jan 3; 19(1): 503.
- [58] Saha A, Chaudhury AN, Bhowmik P, Chatterjee R. Awareness of cervical cancer among female students of premier colleges in Kolkata, India. *Asian Pac J Cancer Prev*. 2010; 11(4): 1085-90. PMID: 21133629.
- [59] Rani U, Darabaner E, Seserman M, Bednarczyk RA, Shaw J. Public Education Interventions and Uptake of Human Papillomavirus Vaccine: A Systematic Review. *J Public Health Manag Pract*. 2022 Jan-Feb 01; 28(1): E307-E315.
- [60] Doshi D, Srikanth Reddy B, Karunakar P, Deshpande K. HPV, cervical cancer and pap test related knowledge among a sample of female dental students in India. *Asian Pacific J Cancer Prev*. (2015) 16(13): 5415–20.
- [61] ARSH (ADOLESCENT REPRODUCTIVE AND SEXUAL HEALTH). (2021). <https://nhm.gujarat.gov.in/arsh1.htm>. Last accessed: August 28, 2023.
- [62] Buskwofie A, David-West G, Clare CA. A Review of Cervical Cancer: Incidence and Disparities. *J Natl Med Assoc*. 2020 Apr; 112(2): 229-232.



© The Author(s) 2024. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).