Review Article

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Human Papillomavirus: It's Characteristics, Pathogenesis, Transmission, Immunity, and it's Role in Cervical Cancer: A Mini Review

Ameer Mezher Hadi[1]*, Yasir Haider Al-Mawlah[2], Lubna Abdulazeem Majeed[3] and Wissam Hamid Al-Janabi[4]

[1,2,3]*DNA research center, University of Babylon, Hilla , Babylon state, Nader Street , 51001, Iraq.*

[4]*Department of Dentisy /Al-Zahrawi University College, Karbala, Iraq.*

***Corresponding Author**
Ameer Mezher Hadi, DNA research center, University of Babylon, Hilla, Babylon state, Nader Street, 51001, Iraq.

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Abstract

Human papillomaviruses (HPVs) have the ability to cause clinical disease in the epithelium of the skin and mucous membranes. It also possesses oncogene genes capable of transforming normal cells into cancerous cells in the oral and anal mucosa, and in various skin locations, these viruses infect almost all tissues, such as dermal-oriented epithelial, mucosal, and lining tissues. The symptoms of the human papilloma virus are sometimes mild and not apparent, while some other infections are of moderate or severe as well as some infection may lead to the transformation of normal cells into tumor cells, as is the case in some subtypes of this virus. Basic knowledge of the pathology and the ability of some microorganisms to cause disease is important for understanding the clinical presentation of the disease and how it is diagnosed and treated. In this review, we decided to discuss some important aspects of HPV, including the general characteristics of the virus, its life cycle, pathogenesis, epidemiology, immunity, and vaccination.

Keywords: HPV, Epidemiology, Cancer, Vaccination, Immunity

1. Introduction

Human papilloma virus belongs to the family of small double-stranded DNA viruses that infect epithelial tissues, where there are more than 200 species belonging to this family genetically distinguished that are capable of infecting and causing disease for human and animal, such as visible, genital warts and skin scales. So, there are 40 types of these viruses that infect the mucus membranes lining the uterus and can cause cancerous transformation in the surrounding cells, resulting cervical cancer [1]. These viruses are naked and have an icosahedral shape consisting of 72 capsules with a diameter of about 50 nm. Despite their large numbers and wide spread, they only infect mucous membranes and dry epithelium (skin) and enter the body through the mouth and genitals. The infection appears. In the form of either benign lesions (warts or papillomas), or the infection may develop into cancerous tumors [2]. The genome of human papilloma virus is consist of eight protein-coding genes and to forming three region early (E), late (L) and upstream regulatory regions [3]. This virus is distinguished by its ability to transform normal cells into tumor cells, causing cervical, anal, and vaginal and vulvar cancer, as it is considered one of the most sexually transmitted types of viruses [4]. Moreover, this virus was diagnosed in several cases of patients with penile cancer, and studies indicated that among the 100 types of human papillomavirus there are at least 40 types capable of infecting genital tract [5]. Among the most important types associated with cancers of the reproductive system are the two types, HPV16 and HPV18, which are associated with a large percentage of up to 50% of cervical cancer, in addition to being associated with other types of cancers of the reproductive system compared to other types of the virus [6].

The virus enters the target cells by binding the L1 protein to the cellular receptors, after which it is transmitted into the cell by the process of endocytosis of the virion [7]. After that the virus moves into the cell through the vector vesicles reaching to cytoplasm, then the viral protein L1 separates from the genome, and becomes the role of the second viral protein, L2, which contributes to the exit of the virus from the endosome (the vector vesicle), finally the virion continues to complete its path to the nucleus through the microtubules and start copying the early E1 and E2 proteins [8]. The HPV life cycle divided into three stages: initiation, recurrence, and vegetative or productive amplification [9]. The first stage of the virus life cycle begins with viral replication (genome transcription), followed by the entry of the virus into the nucleus, where it can directly merge with the nucleus to start viral replication, or it can be latent inside the nucleus until the appropriate conditions are available. The early viral proteins E1, E2 and E4 contributing to replication of viral genome, while E6 and E7 prevent apoptosis and increasing

proliferation of host cell proliferation, E2 have the controlling on the expression of E6 and E7, so Loss of E2 controlling function leads to promote the E6 and E7 viral oncogenes [10]. After the initial stage, this phase consists of constant number of viral genomes then establishing a chronic infection. Finally, the last step involves vegetative or productive viral replication, with the subsequent production of progeny virions [11]. At this time the oncolytic viral proteins E6 and E7 expressed at relatively low levels in differentiated cells play a key role by inactivating tumor suppressor proteins (eg, p53, retinoblastoma protein (pRb)) and activating signal transduction, to ensure infected cells remain active and progress. To the S stage. Moreover, vegetative amplification, besides being associated with an increase in HPV genome copy numbers, is also followed by the expression of the structural proteins L1 and L2 (Figure 1) [12].

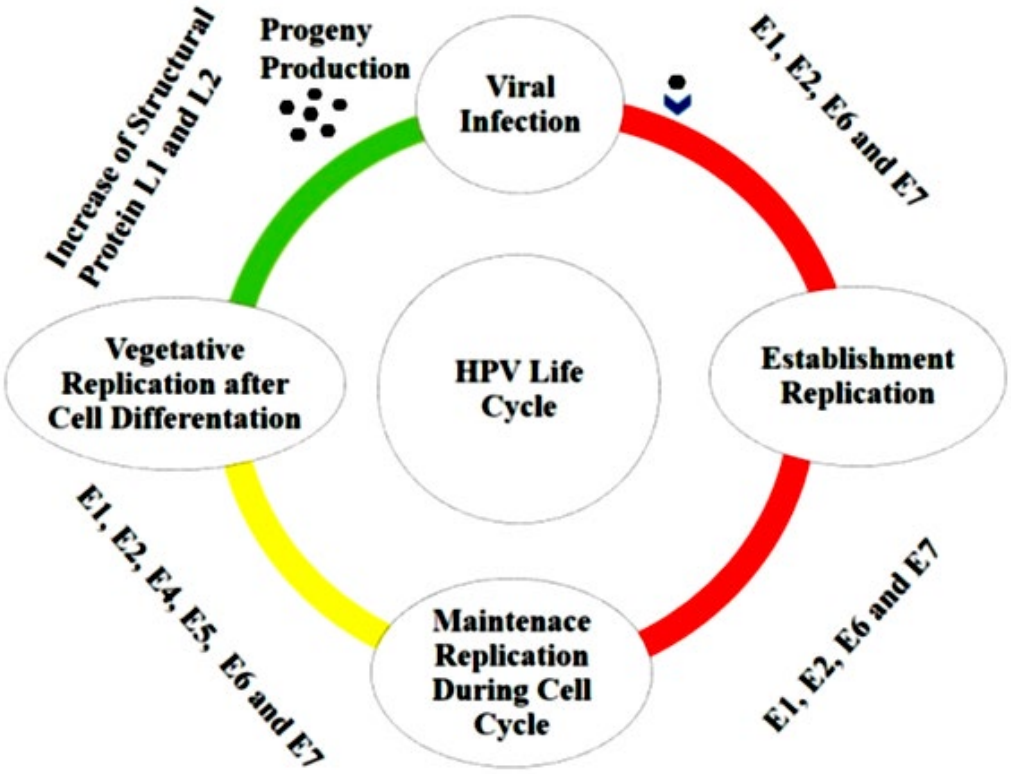

Figure 1: HPV Life Cycle. The First Step of the Replication Cycle of HPV, Called Establishment Replication, Replication, Consists of Maintaining a Constant Number of Episomal Copies [13].

1.1 Transmission

The human papillomavirus is transmitted directly through contact between the skin and mucous membranes, where sexual contact is one of the most important ways of transmission of the virus, and there are other ways of transmission such as those that occur between the mother and the child or at the time of birth. Also, there are other ways of transmitting the virus through fomites, surgical materials, clothing, and objects. The development of the infection depends on the transmission of the virus as a whole, not just fragments of DNA. Many studies have indicated that the virus is latently present in sexually active individuals, especially women, as it infects more than 80% of women of childbearing age [1].

HPV infections are believed to occur following wounding of epithelium and subsequent infectious virion access to basal epithelial cells and basement membrane components of the epithelium [14]. Enhanced infection following wounding has been confirmed experimentally in preclinical models [15]. HPV associated lesions are then maintained via persistence of viral-infected basal cells and the lesions increase in mass via replication of infected cells coupled with epithelial differentiation. Vertical maturation of infected keratinocytes completes the virus life cycle culminating in virion assembly in the upper layers of the wart. Natural transmission of cutaneous infections likely involves physical contact of the upper keratinized wart with normal skin generating microabrasions allowing virus-containing squames to be shed into the wounded site. Environmental contact between virus-laden shed squames and skin surface wounds are also a likely transmission mechanism. Virion release from the squames may include a combination of keratin filament disassembly events involving viral E4 proteins and host/microbial proteases with subsequent release of the cell-free virions into the wounded site. Mucosal infections are also believed to occur following mechanical wounding during sexual intercourse for vaginal and anal infections [16].

Cell culture experiments have demonstrated that virions can bind to cellular filopodia and subsequently be retro-transported significant distances suggesting possible cell-to-cell or cell-to-ECM (extracellular matrix) transfer that would bypass the need for direct wounding [17]. Other viruses use a similar strategy of

cell-cell transfer and epithelial basement membrane interactions [18]. The transition zone sites are particularly vulnerable to persistent HPV infections that can lead to malignant progression [19]. A mechanism to describe the selectivity and exclusivity of entry of HPV virions into these unique sites is not easy to reconcile with the general concept of transmission via site specific mechanical damage during sexual intercourse [20].

1.2 Pathogenicity

Human papillomaviruses (HPVs) are associated with benign lesions known as warts and several cancer types including cancer of the cervix, penis, anus and oral cavity. HPVs are classified by their oncogenic potential and are divided into high-risk oncogenic HPVs and low-risk HPVs. Tissue tropism is used as another means of classifying the virus, and HPVs are divided into types that infect mucosal or cutaneous tissues. Several risk factors have been identified that elevate an individual's likelihood of becoming infected with HPV including cigarette smoking, a large number of lifetime sexual partners and immunosuppression. Most HPV infections are cleared naturally, although persistent infection with oncogenic HPV types can lead to the cancers mentioned above. HPV has employed several mechanisms to avoid detection by the host immune system [21].

Papillomavirus is an oncogenic virus which infects mucosal and cutaneous epithelia where it induces benign hyperproliferative lesions. Infections by high risk human papillomaviruses (HPVs) have been implicated as causative agents in a variety of cancers such as anogenital, and head and neck cancers. HPVs appear to have evolved mechanisms resulting in escape from host immune surveillance and delay of resolution of infection. The HPV E5 oncoprotein is one of the possible effectors that allows the virus to escape from host immune system through the downregulation of surface classical major histocompatibility complex class I (MHC I) and not the nonclassical MHC I. Lack of classical MHC I in infected cells expressing E5 would allow evasion of cytotoxic T lymphocytes (CTLs) killing and thus establishment and persistence of viral infection [22].

1.3 Epidemiology

There are approximately 218 types of HPV have been isolated and identified as causing infections in humans , about 45 of them infect the genital tract, while the others will cause skin disease [23]. The Alpha HPVs produce clinically visible lesions on mucous membranes and skin, while beta and gamma HPVs are mainly responsible for persistent subclinical skin lesions secondary to infections acquired early in childhood .The infection occurs predominantly via direct contact, although skin lesions can be transmitted indirectly, via contaminated surfaces.8Microtraumas expose the basal layer keratinocytes and facilitate contagion [24]. Cutaneous warts (CWs) related to non-sexually transmit-ted HPV types have completely different epidemiological characteristics and are mainly caused by types 1, 2, 4, 27 and 57 [25]. Although these are the most prevalent types in several studies, the proportion of individuals affected by each of them is quite variable. Some authors speculate that the differences are due to socio-geographical variations. The most frequently involved are types 6 and 11, present in about 80% of oral lesions and more than 90% of genital lesions, in addition the risk factors include number of partners and age at first sexual intercourse, immunosuppression (including HIV) and the presence of other STIs, such as herpes simplex [26]. The relationship with smoking and the use of oral contraceptives remains controversial. Contagion can occur through any form of sexual contact, even without penetration. The incidence of anal infection is high among men who have sex with men (MSM) [27]. Lesions in men appear to be less persistent than in women. The peak incidence of infection occurs about 10 years after searches, usually between 24 and 30 years of age for both sexes. Although the prevalence decreases with age, studies show a second late peak of incidence in women in the fifth decade [28]. The episodes of clinical manifestation have a mean duration of two and a half months. For each of these, a mean of three medical consultations are held 16. In the an genital region, HPV especially types 16 and 18 is involved in the pathogenesis of malignant tumors, with involvement in practically 100% of cervical cancer cases, 85% of anal tumors, and 50% of penile and vulvar tumors [29].

Oral infection with human papilloma virus is rather low, ranging between 0-20%, and some studies indicated that infection for some immunocompromised people developed into Oropharyngeal squamous cell carcinoma (SCC), 36% while infection with this virus may decrease depending on the person's immunity. The use of drugs that decrease immunity or what is called immunosuppression is a risk factor that increases the spread of many latent viruses, including the human papilloma virus, and the temporary immune changes of pregnant women may increase infection rates when compared to healthy women [30].

1.4 Risk factors for HPV infection

There are many risk factors associated with infection with the human papilloma virus, and among these factors is the increase in sexual activity during adolescence, as well as other external factors such as smoking, which is considered. It is a catalyst and an inhibitor of the innate and adaptive immune system leading to the infection of malignant tumors, which is considered one of the most important risk factors that increase the infection with latent viruses that begin to become active. The body may also be exposed to transmission of the virus through the mouth or direct sexual contact [31]. There are 7 types of viruses classified as having the ability to cause tumors, according to the International Agency for Research on Cancer (IARC), which are HPV (types: 16, 18), human immunodeficiency virus 1 (HIV 1), hepatitis C virus (HCV), hepatitis B virus (HBV), Ebstein Barr virus (EBV), human herpes virus 8 (HHV 8), and Human T lympho trophic virus 1 (HTLV 1) [32]. Studies indicate that about 15-20% of cancers are attributed to viruses, but only a small cases are fatal, as there are 15 genotypes out of 30 that spread between the mucous membrane of the genital mucosa of human papillomavirus, which is a main causes of cervical cancer [33]. The stage of cervical cancer divided onto four main stages: Acquisition of the human papillomavirus, persistence (vs. clearance); progression to precancerous lesions and Invasive carcinoma [34].

1.5 Routes for HPV Transmission

The route of HPV transmission is primarily through skin to skin or skin to mucosa contact. Sexual transmission is the most documented, but there have been studies suggesting non sexual ways [35]. The horizontal transmission of HPV includes fomites, fingers, and mouth, skin contact (other than sexual). These possible routes have been largely discussed in various studies. Contaminated equipment in gynecological examination rooms has been an interesting topic of evaluation in HPV infection routes. We know about HPVs that they are very steady viruses, repellant to heat, and drying [they show 30% infectivity after seven days of dehydration. The viruses are apt to live for days on surfaces, clothing, frequently used gynecological equipment, and fomites [36]. The Vertical transmission from mother to newborn is another HPV transmittal route. Several studies have emphasized the possibility of infection through the amni¬otic fluid, or the placenta, or via contact with maternal genital mucosa during natural birth. The possibility of vertical HPV infection was discussed as early as 1950, in a study on infantile anogenital warts, papillomatosis [37].

The Waterborne transmittal of HPV has never been proven; still, HPV DNA has been identified in water habitats. In 2008, a study in United States concerning the variety of viruses in raw sewage uncovered for the first time 2/12 HPVs in sewage samples, but not in treated wastewater. Bibby and Peccia identified in 2013 HPV in sewage sludge [38]. They also discovered oncogenic papillomavirus: 16, 18 and 53 suggesting a waterborne route of infection, as was first proposed 40 years ago. Epitheliotropic viruses, as demonstrated by these studies, can be found in sewage. It might be the result of scrubbing the skin and mucous membranes, but it can also be due to urine or feces pollution [31].

1.6 HPV and Local Immunity

The fate of the HPV virus infection of the mucosa is determined by its ability to hide itself and survive and the inability of the local cells to catch and neutralize the viral antigens. The balance between these conditions defines the virus clearance, persistence or cancerization [39]. The effective evasion of all levels of innate immune recognition seems to be the hallmark of HPV infections. HPV globally down-regulates the innate immune signaling pathways in the infected Keratinocytes; pro-inflammatory cytokines, particularly the type I interferon's, are not released, and the signals for Langerhans cell activation and migration and consecutively for the recruitment of stromal DCs are diminished or abolished [40]. Keratinocytes (Kcs) targeted by HPVs are considered as nonprofessional antigenpresenting cells (APCs), defined as "immune sentinels", because of the various cytokines produced in response to innate immune sensor signaling [41]. Potentially, HPV PAMPs are the L1 and L2 capsid proteins and the double DNA genome [42]. TLRs are particularly important in establishing the evolution of lesions because they have the role to guide the individual's acquired immunity in order to neutralize viral HPV infection. The activation of TLRs on Kcs leads to the production of type I and interferons (IFNs) and enhances the cytotoxic response of Th1 lymphocytes [43]. A reduced expression of TLRs indicates the progression of the disease, while their increased expression is suggestive of the regression of the pathology [44]. Except for TLR7 and TLR8, the others are found in Kcs. TLR9 hosted in the cytosolic endosomal compartment of Kcs, neutrophils, plasmacytoid dendritic cells (pDCs), B and Th1/Th2 lymphocytes, fibroblasts and endothelial cells is able to recognize PAMPs that have already passed the cell membrane, such as viral double-stranded DNA [45]. HPV can avoid immune recognition by downregulating TLR9 through E6 and E7 proteins; in low-risk HPV genital infection, TLR9 repression does not occur. TLR7 and TLR9 signaling can induce not only inflammatory cytokines secretion but also type I IFNs, including IFN α and β , in addition the effectiveness of TLRs activation during HPV evolution who demonstrated that RNA expression of 1–3 and 6–9 TLRs was increased in cytological samples from patients with healed lesions [46]. Their study conducted on cervical tissue and blood samples from HPV+ and HPV- patients evaluated the expression levels of genes involved in innate immune responses and cell adhesion. HPV-infected patients expressed higher levels of TLR9 and lower levels of PRR that recognize RNA (TLR3, TLR7 and MDA5/IFIH1). The authors concluded that HPV infection leads to changes in the innate antiviral immune responses: it increases the levels of DNA recognition receptors, and it decreases the expression of TLRs that recognize RNAs [47]. The natural life cycle of the HPV virus is entirely intraepithelial, and the infection does not produce local inflammation, cellular apoptosis or cytolysis, viremia after virus release with a successful getaway of innate immune recognition and consecutively the activation of adaptative immune reaction. Viral regression is associated with the successful priming of an adaptative immune response after antigen takeover by the APCs [48].

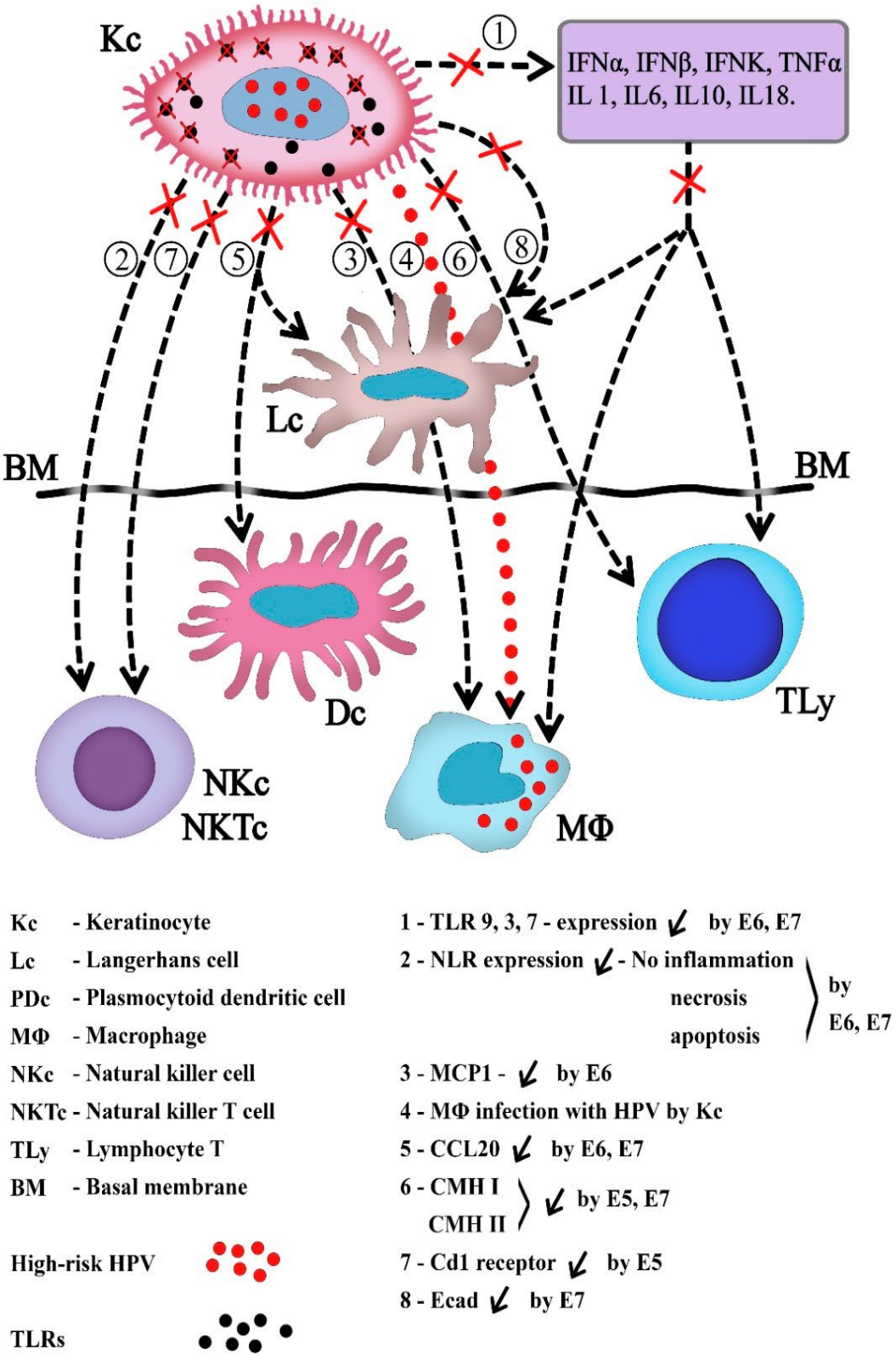

Figure 2: The important role of infected keratinocyte in the immune response suppressing [49].

1.7 Human Papilloma virus and Cancer

Viruses are considered one of the types that cause cancerous transformation in some types of cancers, the most important of which is the human papillomavirus, which has been scientifically proven to be the main cause of cervical cancer, especially types 16 and 18. These genotypes belong to the alpha-type of Papillomaviridae family [49]. Studies also indicated that the two types HPV 16 (alpha-9) and HPV 18 (alpha-7) are a major cause of cervical cancer. Since 1995. While other types HPV 31 and HPV 33 (alpha-9), may cause cancer in the genital tract, Furthermore, all alpha species are capable of causing cervical cancer cases in almost all parts of the world [50].

The types in the high-risk clade are listed below. Given the existence of some HPV types that are very carcinogenic, notably HPV 16 and HPV 18, determining which less common and weaker types are also carcinogenic becomes, in epidemiology, an issue of confounding. The alpha genus types share a common route of transmission, and multiple infections are present in a large minority of women, both concurrently and sequentially. None of the traditional approaches to control confounding is entirely successful. Because HPV 16 causes over 50% of cases of cervical cancer, logistic regression and similar approaches will parsimoniously attribute to HPV 16, cases associated with both HPV 16, and a less important type [51]. HPV 18 is the second most important cervical carcinogen, responsible for approximately 15% of cervical cancer of all histological types combined (and a higher fraction of adenocarcinomas). If a type co-occurs with either HPV 16 or HPV 18, its association with cervical cancer might be confounded by either of these powerful carcinogens. For types causing only a very small fraction of cervical cancer, confounding by any of the more important types is possible [52]. The main epidemiological criterion used for the classification of an HPV type as a carcinogen, i.e. finding the HPV genotype as a single infection in a cervical scrape or biopsy specimen in a woman with cancer, might sometimes be too lax, and prone to error. Colposcopic biopsies and cytology specimens can be misdirected and fail to obtain the critical cells, whereas the contamination of scrapes and biopsies from lower-grade lesions that often surround cancers can lead to the detection of types other than the causal one [53]. The most clearly carcinogenic genotypes, HPV 16 and HPV 18 in particular, are more common among cervical squamous carcinomas than cytologically normal women or even in low-grade squamous intraepithelial lesions. HPV 18 is especially common in adenocarcinomas, as are other members of the alpha-7 clade of which HPV 18 is a member, lending additional support to the importance of genetic similarity in terms of the carcinogenicity of different HPV types [54]. Almost all types of HPV in the high-risk clade – except for HPV 16 and HPV 18 – are (relatively) more common in low-grade lesions. Including HPV 16 and HPV 18, eight HPV types (alpha-7, HPV types 18 and 45; alpha-9, and HPV types 16, 31, 33, 35, 52, and 58) are the most common types found in cancers in both the Catalan Institute of Oncology (ICO) study and the IARC meta-analysis in all regions of the world providing data. These types are all much more common in cancer case specimens than in controls, providing sufficient epidemiological evidence of carcinogenicity [55].

1.8 HPV vaccination

Viral vaccines are considered one of the most important medication against viruses, as they are among the most complex microorganisms compared to bacteria. For human papilloma virus, there are two main vaccines that have proven effective against it, one of which is bivalent and contains antigens of entry proteins (VLP) is effective against types HPV 16 and 18, and the other type is quadrivalent that contains antigens of entry proteins for each of the types 6, 11, 16 and 18, as both types have the ability to prevent the entry of the virus into the target cells and cause disease, so they are a prophylactic vaccines to protect against infection taken before infection or at its beginning not for treatment people who are already infected [56]. These two vaccines were also used as an alternative treatment for some types of cancer, such as adenocarcinoma and cervical cancer, as both vaccines proved effective against about 90% of women with cervical cancer, especially among women between the ages of 15 and 26 years who were not previously diagnosed with papillomavirus. The effectiveness of the vaccine varies depending on the age of the infected and the location and duration of the infection [57]. In addition, trials of the quadrivalent HPV vaccine have shown close to 100% efficacy against certain vulvar and vaginal lesions against types 16 or 18, and against genital warts caused by the virus [58]. Studies have shown that the use of the dual and quadrivalent HPV vaccines protects against infection for a period of 5 to 6 years, and it also prevents cancer of the cervix, genital and non-genital organs associated with this virus [59].

2. Conclusion

This review provided some information about HPV such as Transmission, epidemiology, pathogenesis, high risk serotypes of HPV, HPV vaccination, HPV and cancer and more information that explains the composition of the virus, its more dangerous types that may cause cancer, and how to treat it using vaccines, Therefore, in this review, we tried to focusing on this virus pathogenicity, transmission, and some virus genes that closely that is capable of infecting many places in the body depending on the tropism affinity for cell receptors such as genital warts and some types may develop to be oncogenic proteins.

References

1. Alba, A., Cararach, M., & Rodríguez-Cerdeira, C. (2009). The human papillomavirus (HPV) in human pathology: description, pathogenesis, oncogenic role, epidemiology and detection techniques. The Open Dermatology Journal, 3(1).
2. Meites, E., Szilagyi, P. G., Chesson, H. W., Unger, E. R., Romero, J. R., et al. (2019). Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. American Journal of Transplantation, 19(11), 3202-3206.
3. Ding, D. C., Chiang, M. H., Lai, H. C., Hsiung, C. A., Hsieh, C. Y., et al. (2009). Methylation of the long control region of HPV16 is related to the severity of cervical neoplasia. European Journal of Obstetrics & Gynecology and Reproductive Biology, 147(2), 215-220.
4. Dillner, J., Krogh, G. V., Horenblas, S., & Meijer, C. J.

(2000). Etiology of squamous cell carcinoma of the penis. Scandinavian Journal of Urology and Nephrology, 34(205), 189-193.
5. Bosch, F. X., & de Sanjosé, S. (2007). The epidemiology of human papillomavirus infection and cervical cancer. Disease markers, 23(4), 213-227.
6. Ferreira, A. R., Ramalho, A. C., Marques, M., & Ribeiro, D. (2020). The interplay between antiviral signalling and carcinogenesis in human papillomavirus infections. Cancers, 12(3), 646.
7. Cosper, P. F., Bradley, S., Luo, Q., & Kimple, R. J. (2021, October). Biology of HPV mediated carcinogenesis and tumor progression. In Seminars in Radiation Oncology (Vol. 31, No. 4, pp. 265-273). WB Saunders.
8. Lugović-Mihić, L., Cvitanović, H., Djaković, I., Kuna, M., & Šešerko, A. (2021). The influence of psychological stress on HPV infection manifestations and carcinogenesis. Cell Physiol Biochem, 55(S2), 71-88.
9. Maglennon, G. A., McIntosh, P., & Doorbar, J. (2011). Persistence of viral DNA in the epithelial basal layer suggests a model for papillomavirus latency following immune regression. Virology, 414(2), 153-163.
10. Colpani, V., Soares Falcetta, F., Bacelo Bidinotto, A., Kops, N. L., Falavigna, M., et al. (2020). Prevalence of human papillomavirus (HPV) in Brazil: A systematic review and meta-analysis. PLoS One, 15(2), e0229154.
11. Reusser, N. M., Downing, C., Guidry, J., & Tyring, S. K. (2015). HPV carcinomas in immunocompromised patients. Journal of clinical medicine, 4(2), 260-281.
12. De Oliveira, C. M., Fregnani, J. H. T., & Villa, L. L. (2019). HPV vaccine: updates and highlights. Acta cytologica, 63(2), 159-168.
13. Soleymaninejadian, E., Zelini, P., Cassaniti, I., Baldanti, F., Dominoni, M., Get al. (2022). Immunological Aspects of Human Papilloma Virus-Related Cancers Always Says,"I Am like a Box of Complexity, You Never Know What You Are Gonna Get". Vaccines, 10(5), 731.
14. Doorbar, J., Quint, W., Banks, L., Bravo, I. G., Stoler, M., Bet al. (2012). The biology and life-cycle of human papillomaviruses. Vaccine, 30, F55-F70.
15. Cladel, N. M., Hu, J., Balogh, K., Mejia, A., & Christensen, N. D. (2008). Wounding prior to challenge substantially improves infectivity of cottontail rabbit papillomavirus and allows for standardization of infection. Journal of virological methods, 148(1-2), 34-39.
16. Doorbar, J. (2013). The E4 protein; structure, function and patterns of expression. Virology, 445(1-2), 80-98.
17. Schelhaas, M., Ewers, H., Rajamäki, M. L., Day, P. M., Schiller, J. T., et al. (2008). Human papillomavirus type 16 entry: retrograde cell surface transport along actin-rich protrusions. PLoS pathogens, 4(9), e1000148.
18. Smith, J. L., Lidke, D. S., & Ozbun, M. A. (2008). Virus activated filopodia promote human papillomavirus type 31 uptake from the extracellular matrix. Virology, 381(1), 16-21.
19. Mcnairn, A. J., & Guasch, G. (2011). Epithelial transition zones: merging microenvironments, niches, and cellular transformation. European Journal of Dermatology, 21(2), 21-28.
20. Mirkovic, J., Howitt, B. E., Roncarati, P., Demoulin, S., Suarez-Carmona, M., et al. (2015). Carcinogenic HPV infection in the cervical squamo-columnar junction. The Journal of pathology, 236(3), 265-271.
21. Brendle, S. A., Bywaters, S. M., & Christensen, N. D. (2014). Pathogenesis of infection by human papillomavirus. Human Papillomavirus, 45, 47-57.
22. Ashrafi, G. H., & Salman, N. A. (2016). Pathogenesis of human papillomavirus–immunological responses to HPV infection. Human Papillomavirus-Research in a Global Perspective, 13, 243-53.
23. Sichero, L., & Nunes, E. M. (2018). Epidemiology and biology of cutaneous human papillomavirus. Clinics, 73.
24. Egawa, N., Egawa, K., Griffin, H., & Doorbar, J. (2015). Human papillomaviruses; epithelial tropisms, and the development of neoplasia. Viruses, 7(7), 3863-3890.
25. De Koning, M. N. C., Quint, K. D., Bruggink, S. C., Gussekloo, J., Bouwes Bavinck, J. N., et al. (2015). High prevalence of cutaneous warts in elementary school children and the ubiquitous presence of wart-associated human papillomavirus on clinically normal skin. British Journal of Dermatology, 172(1), 196-201.
26. Wendland, E. M., Villa, L. L., Unger, E. R., Domingues, C. M., & Benzaken, A. S. (2020). Prevalence of HPV infection among sexually active adolescents and young adults in Brazil: the POP-Brazil study. Scientific reports, 10(1), 4920.
27. Sichero, L., Giuliano, A. R., & Villa, L. L. (2019). Human papillomavirus and genital disease in men: what we have learned from the HIM study. Acta cytologica, 63(2), 109-117.
28. Marra, F., Ogilvie, G., Colley, L., Kliewer, E., & Marra, C. A. (2009). Epidemiology and costs associated with genital warts in Canada. Sexually transmitted infections, 85(2), 111-115.
29. Salcedo, M. M., Damin, A. P., Agnes, G., Pessini, S. A., Beitune, P. E., et al. (2015). Prevalence of human papillomavirus infection in pregnant versus non-pregnant women in Brazil. Archives of gynecology and obstetrics, 292, 1273-1278.
30. Mehedintu, C., Bratila, E., Cirstoiu, M., Petca, A., Brinduse, L. A., et al. (2019). Evaluation of effectiveness and tolerability of boric acid in the treatment of vaginal infection with Candida Species. Rev Chim, 70, 2375-2378.
31. Fratini, M., Di Bonito, P., & La Rosa, G. (2014). Oncogenic papillomavirus and polyomavirus in water environments: is there a potential for waterborne transmission?. Food and environmental virology, 6, 1-12.
32. Sasagawa, T., Takagi, H., & Makinoda, S. (2012). Immune responses against human papillomavirus (HPV) infection and evasion of host defense in cervical cancer. Journal of Infection and Chemotherapy, 18(6), 807-815.
33. Doorbar, J., Quint, W., Banks, L., Bravo, I. G., Stoler, M., et al. (2012). The biology and life-cycle of human papillomaviruses. Vaccine, 30, F55-F70.
34. Nestle, F. O., Di Meglio, P., Qin, J. Z., & Nickoloff, B. J. (2009). Skin immune sentinels in health and disease. Nature Reviews Immunology, 9(10), 679-691.

35. Hibma, M. H. (2012). Suppl 2: the immune response to papillomavirus during infection persistence and regression. The open virology journal, 6, 241.
36. Stanley, M. A. (2012). Epithelial cell responses to infection with human papillomavirus. Clinical microbiology reviews, 25(2), 215-222.
37. Vega, M. M., & de Andres Martin, A. (2009). The significance of toll-like receptors in human diseases. Allergologia et immunopathologia, 37(5), 252-263.
38. McClure, R., & Massari, P. (2014). TLR-dependent human mucosal epithelial cell responses to microbial pathogens. Frontiers in immunology, 5, 386.
39. Daud, I. I., Scott, M. E., Ma, Y., Shiboski, S., Farhat, S., et al. (2011). Association between toll-like receptor expression and human papillomavirus type 16 persistence. International journal of cancer, 128(4), 879-886.
40. Britto, A. M. A., Goes, L. R., Sivro, A., Policarpo, C., Meirelles, Â. R., et al. (2020). HPV induces changes in innate immune and adhesion molecule markers in cervical mucosa with potential impact on HIV infection. Frontiers in Immunology, 11, 2078.
41. Hibma, M. H. (2012). Suppl 2: the immune response to papillomavirus during infection persistence and regression. The open virology journal, 6, 241.
42. Rose, J. B., & Jiménez-Cisneros, B. (2019). Global Water Pathogen Project. East Lansing, MI: Michigan State Univ.
43. Chesson, H. W., Ekwueme, D. U., Saraiya, M., Dunne, E. F., & Markowitz, L. E. (2011). The cost-effectiveness of male HPV vaccination in the United States. Vaccine, 29(46), 8443-8450.
44. Castle, P. E., & Maza, M. (2016). Prophylactic HPV vaccination: past, present, and future. Epidemiology & Infection, 144(3), 449-468.
45. Petca, A., Borislavschi, A., Zvanca, M. E., Petca, R. C., Sandru, F., et al. (2020). Non-sexual HPV transmission and role of vaccination for a better future. Experimental and therapeutic medicine, 20(6), 1-1.
46. Gallay, C., Miranda, E., Schaefer, S., Catarino, R., Jacot-Guillarmod, M., et al. (2016). Human papillomavirus (HPV) contamination of gynaecological equipment. Sexually transmitted infections, 92(1), 19-23.
47. Hong, Y., Li, S. Q., Hu, Y. L., & Wang, Z. Q. (2013). Survey of human papillomavirus types and their vertical transmission in pregnant women. BMC infectious diseases, 13(1), 1-7.
48. Bibby, K., & Peccia, J. (2013). Identification of viral pathogen diversity in sewage sludge by metagenome analysis. Environmental science & technology, 47(4), 1945-1951.
49. Andrei, E. C., Baniță, I. M., Munteanu, M. C., Busuioc, C. J., Mateescu, G. O., et al. (2022). Oral Papillomatosis: Its Relation with Human Papilloma Virus Infection and Local Immunity—An Update. Medicina, 58(8), 1103.
50. Ault, K. A. (2007). Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. The Lancet, 369(9576), 1861-1868.
51. Garland, S. M., Hernandez-Avila, M., Wheeler, C. M., Perez, G., Harper, D. M., et al. (2007). Females United to Unilaterally Reduce Endo/Ectocervical Disease II (2007) Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med, 356(19), 1928-1943.
52. Bosch, F. X., Burchell, A. N., Schiffman, M., Giuliano, A. R., de Sanjose, S., et al. (2008). Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine, 26, K1-K16.
53. Smith, J. S., Lindsay, L., Hoots, B., Keys, J., Franceschi, S., et al. (2007). Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. International journal of cancer, 121(3), 621-632.
54. De Sanjosé, S., Diaz, M., Castellsagué, X., Clifford, G., Bruni, L., et al. (2007). Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. The Lancet infectious diseases, 7(7), 453-459.
55. Wheeler, C. M., Hunt, W. C., Schiffman, M., & Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. (2006). Human papillomavirus genotypes and the cumulative 2-year risk of cervical precancer. The Journal of infectious diseases, 194(9), 1291-1299..
56. Kreimer, A. R., Sampson, J. N., Porras, C., Schiller, J. T., Kemp, T., et al. (2020). Evaluation of durability of a single dose of the bivalent HPV vaccine: the CVT trial. JNCI: Journal of the National Cancer Institute, 112(10), 1038-1046.
57. Porras, C., Tsang, S. H., Herrero, R., Guillén, D., Darragh, T. M., et al. (2020). Efficacy of the bivalent HPV vaccine against HPV 16/18-associated precancer: long-term follow-up results from the Costa Rica Vaccine Trial. The Lancet Oncology, 21(12), 1643-1652.
58. Scheller, N. M., Pasternak, B., Mølgaard-Nielsen, D., Svanström, H., & Hviid, A. (2017). Quadrivalent HPV vaccination and the risk of adverse pregnancy outcomes. New England journal of medicine, 376(13), 1223-1233.
59. Gee, J., Weinbaum, C., Sukumaran, L., & Markowitz, L. E. (2016). Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. Human vaccines & immunotherapeutics, 12(6), 1406-1417.