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REVIEW ARTICLE

Increasing Awareness of Papillomaviruses and Their Association with Human Diseases

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Abstract: The papillomavirus family is known to be responsible for a quarter of virus-related cancers worldwide. High-risk types are the causative agents of anogenital, cervical and various cancers of the mouth, throat, intestines, vagina, penis and anus. Cervical cancer and various other malignancies induced by papillomaviruses are a global health problem, and the growing prevalence of these diseases indicates the need to increase awareness of this viral family. In this review, published articles during 2001-2020 were searched using keywords such as Papillomavirus, Cervical Cancer and Papilloma Vaccine. Our review represents the results of the association of high-risk HPV serotypes with many malignancies in human. Furthermore, issues such as HPV vaccination, cervical cancer screening, and other preventive programs worldwide are discussed.

Keywords: cervical cancer; Papillomavirus; papilloma vaccine

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1. Introduction

Papilloma viruses are small circular double-stranded DNA viruses. According to the latest International Committee on Taxonomy of Viruses classification in 2019, papilloma viruses are in the realm of Monodnaviria, Shotokuvirae kingdom, Cossaviricota phylum, Papovaviricetes class, Zurhausenvirals genus, Papillomaviridae family with two first and second papilomavirinae subfamilies with 53 genera and 133 species. Human papilloma virus (HPV) is divided into five groups: alpha, beta, gamma, mupa, and juvenile. Most alpha-papillomaviruses infect mucosal surfaces in the genital and non-genital organs and are also called "mucosal-genital". These viruses have a strong tendency to infect basal keratinocyte cells on the surface of the skin and mucous membranes (1).

Until the 19th century, genital warts were known as syphilis or gonorrhea. The viral nature of these warts became known in the early 1990s after examining cells isolated from these lesions. The nature of the animal papilloma virus was also identified in 1930 by Richard Shop (2). Historically, papilloma viruses, along with polyoma viruses, were known as papova viruses, but after examining the genomic sequence and replication mechanisms, each was finally introduced as an independent family in 2000. To date, more than 200 papilloma virus genotypes have been identified, only a limited number of which are associated with cancer, and based on this association, they are divided into high-risk and low-risk types (3). Clinical manifestations in low-risk types may range from completely asymptomatic to changes in the form of papillomas and benign warts. In contrast, high-risk types of HPV have been identified as causative agents of anogenital, cervical, and various cancers of the mouth, throat, intestines, vagina, penis, and anus (4, 5).

According to the latest classification of the International Center for Cancer Studies (IARC), 20 types of papilloma viruses fall into group one, which includes high-risk or carcinogenic infectious agents for humans. These 20 types include types 16, 18, 31, 33, 34, 35, 39, 42, 44,45, 51, 52, 56, 58, 59, 66, 68, 70, 73 and 82. Types 16 and 18 are more common and are responsible for about 70% of cervical cancers worldwide, and type 16 alone is responsible for about 60% of oropharyngeal cancers worldwide. Stability of high-risk types is a key step in the transformation of natural epithelium into precancer-

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ous and cancerous lesions (6-9). Due to the growing trend of this disease in different age and sex groups and the development of various programs in the prevention and treatment of diseases this study was conducted in developed and developing countries to raise awareness about papilloma viruses and their association with human diseases.

This review aimed to raise awareness of papilloma viruses and their relationship with human diseases and cancers by searching the databases of Google Scholar, ISI, PubMed, Google search engine and a comprehensive review of published articles in this field in order to review articles related to this study were used to search for papillomavirus, cervical cancer and papilloma vaccine to raise awareness of papilloma viruses and their risks for humans and prevention methods. We included articles that matched the search terms. Articles that were less relevant to the topic or provided incomplete data were excluded from the study. Ultimately, 80 articles were used.

1.1. Genome structure and function of papillomavirus proteins

Papilloma viruses are 60 nanometers in diameter and have a genome of about 8,000 bp. These viruses are uncoated and have an icosahedral capsid. The genome of papilloma viruses consists of three functional regions: Early region E (functional region), the secondary genes region or L region (Late region), the controlling region, and the coding LCR region or UR (upper regulation) region. The early region includes E6, E5, E4, E2, E1 and E7, which are involved in viral replication and carcinogenicity. The late region encodes the structural proteins L1 and L2 for the viral capsid. The regulatory region or Long control region includes the original primary promoter called p97 and the DNA replication regulatory sequences. Table 1 shows the proteins and their function in human papilloma viruses.

1.2. Papilloma virus replication cycle

The life cycle of this virus depends on the differentiation of epithelial cells. Because papilloma viruses do not encode DNA polymerase and other required factors themselves, their replication is highly dependent on the host cell. Binding of the virus with L1 to its specific receptors, heparan sulfate proteoglycans (HSPGs) and a number of secondary cellular receptors, including integrins, tetraspanins, growth factor receptors, and anxin A2, causes the virus to enter the cell. HSPGs alter the structure of L2 Cyclophylline B, a cell surface chaperone in the luminal membrane, helps establish a cutoff site for furin convertase at the N-terminal L2 by cleaving this region and separating 12 amino acids from the end of the L1 protein. It can bind to its secondary receptors and be transmitted to the endosome through endocytosis.

Low pH in the endosome space leads to the opening of the capsid and the virus enters the cell by the mechanism of endocytosis through clathrin. The virus genome enters the nucleus and remains as a small circular chromosome in the nucleus. Many chronic viruses retain their DNA by integrating into the host genome, but HPVs retain their genome as extrachromosomal episomes that attach to the host DNA. The primary genes of the virus are transcribed, leading to the amplification phase and the proliferation of 50 to 400 copies of DNA per cell. This phase of genome amplification is called "plasmid proliferation". After that, the viral genome multiplies almost once with each cell division, and the viral genome divides evenly among the daughter cells.

To ensure that the viral genome is not lost during cell division, there is a binding mechanism between viral DNA and host mitotic chromosomes that is mediated through some cellular mediators and viral proteins such as E2. When stem cells differentiate into stable keratinocytes, we see an explosion of viral DNA replication, known as the "vegetative proliferation" phase, which eventually leads to a production phase with the production of thousands of viral copies in the infected cell. This is followed by late gene expression and virus assembly. The viral particles then accumulate in the nucleus and are released on the surface of the lesion after cell death. The presence of cellular factors is essential for viral replication (11-13). Figure 1 shows papilloma virus infection of the cervix with organized expression of viral proteins following keratinocyte differentiation (14).

2. Methods

International databases such as PubMed, Web of Sciences, and Scopus were searched using various keywords such as Human Papilloma Virus, Cervical cancer, HPV, and Papilloma Virus within January 2001 until December 2020. Inclusion criteria was defined as any study investigating the relationship of HPV with human cancers, those assessing vaccine effectiveness or efficacy, and those related to the dormant course of HPV infection. Amongst which, articles assessing non-human hosts, and those investigating other serotypes of HPV other than high-risk ones were excluded. Screening of the extracted articles were performed by two independent virologist experts with a medical background.

3. Results

3.1. The natural course of infection with the papilloma virus

Most HPV infections are transient and asymptomatic and do not cause clinical problems, so most sexually active people may develop and recover from an HPV infection without ever realizing it. The virus does not have the effect of ping pong, meaning that a couple in a relationship does not in-

fect each other frequently. After a person comes in contact with a genotype of HPV and clears it, the person is likely to become immune to that particular genotype, so re-infection can occur with a new type of HPV in a new contact. The average infection time with a new genotype is approximately 9.8 months in men and women.

Common viral types in the genitals can be found in asexual areas such as hands, nails and underwear, but the presence of the virus in these areas is an efficient mode of transmission of the virus has not yet been proven (15, 16). Low-risk types 6 and 11 are responsible for benign lesions that occur in the head, neck, and face. These lesions may spread to the lips, lungs, trachea, nose, and oral cavity, hoarse voice and rare diseases of oral epithelial hyperplasia (Heck). Epidermodysplasia verruciformis is a chronic genetic skin infection associated with the EVER1 and EVER2 genes that causes flat warts. Papilloma virus types 5, 8, 9, 12, 14, 15, 17, 19, 25, 36, 38, 47 and 50 along with genetic mutations are the causes of this disease (17, 18).

3.2. Pathogenicity of papilloma viruses

The papilloma virus family is responsible for a quarter of all cancers associated with the virus and about 4.5% (640,000 cases) of cancer worldwide (19). One of the hypotheses regarding the pathogenicity of papilloma virus is related to its integration into the human genome. Studies show that integration with the human genome, in addition to possibly being associated with virus stability in the body, can also play a role in the process of viral DNA methylation. Study on HPV16 in the human genome fusion mode shows that the viral genome in this state can be affected by methylation in human genes adjacent to the fusion point and activate or inactivate some of its genes by the spontaneous methylation mechanism. For example, methylation in the L1 gene sequence can act against the host defense mechanism and play a role in the development of infection. On the other hand, methylation in the region related to E2 gene suppresses E2 expression and thus reduces the expression of E6/E7 oncogenes (20, 21).

3.3. Pathogenicity in men

According to the statistics, genital infections with papillomavirus are more common in men than women, but these infections rarely persist. Few studies have been performed on papilloma virus infection in men anatomically, however, infection is most common in the penis and least common in the urethra. Especially in men it is increasing rapidly. More than 70% of the approximately 12,000 cases of oropharyngeal cancer diagnosed each year are due to HPV, and approximately 90% of HPV-positive cases are due to HPV16 and the rest are due to other types of papilloma. The prevalence of these cancers is higher in men than in women (22). Regarding anal infections, most studies have been performed on HIV-positive as well as gay men. These studies have shown a high prevalence of HPV infection. Overall, HPV anal infections have been reported in 58.8% of gay men, 30.7% of women, and 14.2% of heterosexual men (8). Oral HPV infections are less common and more common in men. The statistics in this regard are very variable because the reports are influenced by sampling methods and the population studied. A study in the United States reported an average prevalence of 10.1% in men and 3.6% in women (23).

3.4. Genital warts

Genital warts are a common in papilloma virus infections, especially low-risk genotypes 11 and 6. These two types are responsible for about 90% of genital warts. Although epidermal manifestations such as warts or candidiasis occur in only 1% of cases of low-risk types, in the case of lesions, the average time of infection and genital warts in men is 11-12 months and in women 5-6 months (24).

3.5. Papilloma virus and carcinogenic mechanisms

Cancer is the result of abnormal cell proliferation. In cancer cells, a variety of mutagens, oncogenic viruses, and replication errors, genetic alterations, and alterations in DNA methylation may disrupt cell cycle regulation, as well as effect on proto-oncogenes and tumor suppressors genes (25). Environment including UV and X-rays, chemical agents such as mutagens and carcinogens, and infectious agents such as bacteria and viruses can lead to the development of cancer. High-risk papilloma viruses, such as HPV 16 and 18 are associated with human cancer because they encode the two transforming proteins E6 and E7 (26, 27). After breast cancer, the prevalence and morbidity and mortality of cervical cancer has the second place in developing countries and is the third leading cause of cancer death among women (28). Intraepithelial neoplasia of the cervix (CIN), which is a primary event in cervical cancer, is classified into three categories in terms of histological severity: CIN I, CIN II, CIN III (29). Genes cause cell deformation and cancer. HPV E7 protein can bind to the retinoblastoma suppressor tumor (RB, a member of the P130 protein family (RBL2) and increase its protease-mediated degradation (30). In addition, HPV E7 can bind to the MuvB nucleus complex associated with BMYB and FOXM1 and activate gene expression in the G2 and M phases of the cell cycle. Thus, HPV-16 E7 acts by inhibiting cell cycle exit and increases mitotic proliferation (31). Induced cervical cancers in transgenic mice expressing HPV-16 E7 require continuous expression of E7 to preserve the tumor, even in the presence of E6, persistent expression of E7 is required for survival of cervical cancers and most precancerous lesions (32). Protein E6, along with protein E7, stabilizes

epithelial cells and increases the expression of human TERT (reverse telomere transcriptase) protein (33). The main activity of E6 protein, is the destruction of p53 protein through ubiquitination. The binding of E6 to p53 and its ubiquitination to E6- (AP) is dependent on cellular E6 protein. P53 is a transcription factor that stimulates the expression of genes involved in cell cycle arrest and apoptosis, such as p21. Inhibition of translocation and degradation by p53 by E6 prevents the activation or suppression of gene transcription by P53. E6 can also increase the regulation of cell telomerase complex activity. This enzyme stores telomeric DNA at the ends of chromosomes, and the lack of telomerase enzyme causes the telomeres to gradually shorten with each cell division. Telomere shortening controls the number of cell divisions (34). Overall, HPV is responsible for about 96% of cervical cancers, 93% of anal cancers, 64% of vaginal cancers, 51% of vulvar cancers, 36% of penile cancers, and 63% of oropharyngeal cancers (35).

3.6. Cervical cancer

Cervical cancer is found among many women around the world. More than 90% of cervical cancers are caused by high-risk HPV genotypes and 70% are genotypes 16 and 18 (36-38). Cervical cancer is one of the most common cancers in women worldwide and one of the leading causes of cancer death in developing countries (39). The cervix is the area below the uterus that connects the uterus to the vagina. The cervix has two parts and is covered with two types of cells. The part near the uterus or endocervix is covered with glandular cells. The part that is closest to the vagina, called the exocervix, is covered with squamous cells. These two types of cells are connected in an area called the conversion area. Most cervical cancers occur in this area. Normal cells first transform into precancerous lesions. Several terms are used in connection with precancerous lesions in this area: cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesion (SIL), and dysplasia. It usually takes several years for cancerous lesions to turn into cancer. According to studies, HPV was diagnosed in about 74.8% of low-grade cervical lesions (including LSIL and CIN1) and 88.9% of high-grade cervical lesions (including HSIL and CIN2 / CIN3). The likelihood of the virus increasing with the severity of the lesions increases. Among these, HPV16 genotype has been identified in 3.19% of low-grade lesions and 1.45% of high-grade lesions (25) (figure 2).

3.7. Risk factors for cervical cancer

Having high-risk types of HPV, early onset of sexual activity (less than 16 years old) since the T-zone in the cervix has not yet reached full maturity and is more vulnerable to HPV infection, a large number of sexual partners (more than 4), receiving immunosuppressive therapies (such as corticosteroids), malnutrition and strictly restricted diets, prolonged smoking, oral contraceptives, high birth rates, multiple births, chronic vaginal inflammation to other sexually transmitted diseases (Chlamydia, Mycoplasma, HSV, Haemophilus ducreyi, Trichomonas vaginalis, etc.) are important risk factors for cervical cancer. However, not performing routine screening for cervical cancer is still the most important risk factor (8, 11, 40). Asexual routes of transmission, such as transmission from mother to fetus through the birth canal or medical devices (such as vaginal ultrasound probes) are less common (8, 40).

3.8. Screening for HPV infection

Since more than 90% of HPV infections go away on their own within two years, screening for Pap smears every three years is enough between the ages of 21 and 29, and there is no need for co-testing (HPV and Pap smear). In the age range of 30 to 65 years, it is recommended that co-testing be performed every five years. For women over 65 years of age: If they do not have a previous history of cervical cancer or CIN2 / 3, they may have adequate negative screening status (referred to as those who have had three consecutive normal Pap smears or two tests in the last 10 years). Normal Pap smear with a concomitant negative HPV test and at least one of these tests in the last 5 years indicates that screening in these women can be discontinued.

If any of the above (history of cervical cancer, CIN2/3, etc.) are present, screening should be continued for another 20 years. In patients with a history of CIN2/3 in the last 20 years, individuals with HIV, people with suppressed immune systems (such as transplant recipients) need to be screened for HPV annually. Screening can be stopped if a person has had a hysterectomy (removal of the uterus) with cervical resection and has no history of cervical cancer or CIN2/3, but if the person has a history of CIN2/3 and even if the cervix is removed or even over 65 years old, HPV screening in the vaginal cuff should continue for up to 20 years. HPV screening should also be continued if the hysterectomy is performed without removing the cervix.

3.9. New screening protocol

As of April 24, 2014, the FDA has approved the use of the Cobas HPV test alone as a preliminary screening test in women 25 years of age and older that identified the types 16 and 18 separately. In addition, BD On clarity HPV Assay, also known as the Aptima method in Iran, has been accepted by the FDA as the primary screening test in women, which determines 14 high-risk types of HPV undifferentiated, and the 16, 18, 45 types separately (41).

Screening with First line HPV testing or High Risk HPV testing begins at age 25 and stops at age 74, and screening intervals change every 5 years. Studies show that this method

can provide more protection against CIN3 and cervical cancer than cytology (42). At the same time, in addition to sampling and performing diagnostic tests for the virus, the management of positive cases of the disease should be practiced in the screening program, (figure 3) (43)

3.10. Prevention of sexual transmission of papilloma virus

Although avoiding unprotected sex is the safest way to prevent infection with the virus, it can be done in other situations, including monogamy and limiting the number of sexual partners, condom use, removal of genital warts, and HPV vaccination. However, it should be borne in mind that HPV infection is so common that most infected people infect their sexual partner before seeing a doctor, so even in people with a sexual partner for life it is also possible to be infected. Although the use of an IUD with a 50% reduction in cervical cancer has played a protective role, the potential protective mechanisms of the IUD remain unknown. Located in the cervix, it creates a protective inflammation or leads to the mechanical elimination of HPV-related damage (44).

3.11. Diagnosis of papillomavirus infection

Unlike many viruses, papilloma viruses cannot be cultured in monolayer cell cultures. The history and prevalence of HPV in the cervix are well described. Recognition of the various dimensions of precancerous and cancerous lesions in this area, along with diagnostic tests including the search for viral DNA in the lesions as well as the search for HPV-specific antibodies, are known as biological markers in papillomavirus pathogenesis (23, (45)). Pap smear is used to check for different types of cervical lesions. In this test, cervical cells are collected with a swab and examined after Pap smear. Southern Blot, In Situ Hybridization, and Dot Blot Hybridization tests are hybridization-based diagnostic methods (46, 47). However, molecular detection is necessary to accurately identify the type of HPV to determine the risk and isolate low-risk and high-risk types. These methods include PCR, PCR-RFLP, Real Time PCR, and microarray (35, 48).

there is currently no approved test for HPV in men. Routine testing (also called 'screening') to check for HPV or HPV-related disease before there are signs or symptom, is not recommended by the CDC for anal, penile, or throat cancers in men in the United States. However, some doctors perform anal tests Pap smears are used for gay and bisexual men who are at high risk for HPV-induced anal cancer. Studies also use HPV testing to detect the virus in men, making cell damage impossible. Oral human papillomavirus is found in men through Oral rinse/gargle specimens. For HPV DNA testing, samples are taken from the, coronal sulcus, glans penis, shaft, and scrotum (49).

3.12. Vaccination

Three commercial papilloma virus vaccines are licensed for use by both the FDA and EMA for men and women. These vaccines are used in women aged 13 to 26 years and men from 13 to 21 years. According to the ACIP recommendation, HPV vaccination can be started from the age of 9 (50). Gardasil (qHPVv) which contains four types of HPV 6, 11, 16, 18was approved for use in 2006. Gardasil 9, in addition to the four mentioned types, also includes 5 types of HPV 31, 33, 45, 52 ,58 (51). The cervarix vaccine (bHPVv) was approved in 2007 and covers two high-risk types of HPV16,18. All three vaccines contain non-infectious and inactivated subunits of the virus. The difference between these vaccines is in the adjuvant compounds used in them. In Gardelsil vaccine, aluminum hydroxyphosphate sulfate is used as an adjuvant and in Cervarix, one of the compounds of lipid A and aluminum is used as an adjuvant. These vaccines also differ in the manufacturer's expression system. Recombinant proteins in Gardasil are produced by Saccharomyces cerevisiae cells and in the cervix by Trichoplasia cells infected with the L1 gene baculovirus.

Both vaccines have been successful in preventing HPV16,18-associated precancerous lesions in women with no previous history of papilloma virus infection in clinical trials of level 3 to about 90%. qHPVv also protects against types 6 and 11 and all types of genital warts. In a study of more than 4,000 men, it was found that vaccination in men and boys with qHPVv could reduce the incidence of genital warts. All three vaccines contain L1 proteins specific for the HPVs in question, produced by recombinant technologies, known as non-infectious viral-like particles, or VLPs. As long as VLPs lack viral DNA, they cannot infect, proliferate, or cause disease. According to studies to date, the average serum level of antibodies protecting against types 16 and 18 is up to 100% detectable with serum ELISA. However, universal access to and use of vaccines may not be available to all, especially in developing countries where disease is more prevalent ((1), (52, 53)). Studies on the long-term protective effects and side effects of vaccines require studies and follow-up. It is in a long period of time and otherwise it is not predictable (54).

According to the ACOG Committee's latest theory on the HPV vaccine in August 2020, the vaccine should be given to women 27 to 45 years of age based on clinical decisions based on obstetricians and other health care providers, in the case of a former patient. Use of medical experience. This prescription approval, in the above age group, is only for the 9-valent vaccine and does not include the quadrivalent and divalent vaccines. These vaccines have no therapeutic properties, and if a woman is vaccinated before starting sexual activity or exposure to HPV, the vaccine will be more effective. However, if you are already infected with one type of HPV, getting vac-

cinated against that type of virus will not provide immunity, but it will provide immunity against other types of HPV that are present in the vaccine and in general, patients with any current HPV lesion that is in the high-risk group as carriers of HPV, vaccination can reduce the risk of transmitting the virus from one person to another (50, 55).

4. Discussion

Cervical cancer is the second most common preventable cancer among women worldwide (56). According to the IARC, about 530,000 new cases of cervical cancer are reported worldwide each year, and more than 288,000 women worldwide die as a result. More than 80% of these cases have been reported in developing countries. Papilloma virus types 16 and 18 together account for about 70% of cervical cancers worldwide, and type 16 alone is responsible for about 60% of Oropharyngeal cancers. Stability of high-risk types is a key step in the transformation of normal epithelium into precancerous and cancerous lesions (8, 56, 57).

About 9,300 men in the United States are diagnosed with HPV-induced cancers each year, including those with oralpharyngeal cancers, although studies have shown that Gardasil vaccine is cost-effective for men and prevents throat and throat cancers. In women, the Gardasil and Cervarix vaccines also protect against 70% of cervical cancers and 90% of genital warts (58). These vaccines are typically more effective in the 15-19 year age group than in the 19-25 year age group. The vaccine is probably less effective at older ages due to the presence of refractory infections at the time of vaccination in these women (59). According to several articles, there is no specific treatment for HPV infection. Eliminating treatments such as cryotherapy, trichloroacetic acid, laser and surgical resection are used to treat precancerous lesions (60, 61). A study on the antitumor effect of HPV-DNA therapeutic vaccines with a chitosan-based nanoparticle gene delivery system to efficiently deliver the DNA-HPV16 E7 vaccine to improve immunization-induced immunization in mice showed that mice vaccinated with chitosan carriers were able to produce strong anticoagulant and protective effects with strong stimulation of TCD8 + and interferon gamma against tumors caused by E7HPV protein, and with this method, they took a step towards cervical cancer immunotherapy. Therapeutic effect of chitosan-based nanotechnology suggests that nanoparticles may be an effective carrier for improving the immunization of DNA vaccination and that this substrate could be used as a potential candidate for cancer vaccination in humans (40).

Cervical cancer and many other HPV-induced malignancies are very common. In 2015, Grabuska and colleagues considered new therapies as a viable option for the treatment of HPV infections and precancerous lesions, as well as for the treatment of HPV diseases (62). Vaccines are one of the most prominent achievements in the history of medicine, which play an effective role in increasing the quality of human life by reducing or eliminating the complications of infectious diseases. About three million children and nearly six million people will be saved each year by vaccines. In addition, vaccines are essential medical tools to fight cancer, side effects of viral and bacterial infections such as HPV, HIV, meningitis, autoimmune diseases, and more. However, there are still important pathogens for which no vaccine has been developed and vaccines that still need to be upgraded (63).

Studies show that more than 63 million women and girls worldwide are vaccinated with Gardasil vaccine and more than 19 million with Cervarix vaccine. However, problems such as lack of knowledge, high cost of vaccine production and distribution, difficulties in producing and purifying recombinant proteins in eukaryotic systems, and the need for cold chain storage and transmission of vaccines, vaccination complications, are barriers to public use of this vaccine. Is (1, 52, 53), (64-66). There is currently no strategy to modify the structure of VLPs in existing L1 protein vaccines, but many studies are underway to reduce production costs and use low-cost expression systems such as bacteria (1). In 2015, the Gardasil 9 vaccine was shown to increase the efficacy of the quaternary Gardasil vaccine from 70% to 90% in cervical cancer. It is approximately 90% effective in HPV-related vulvar, vaginal, and anal cancers (51). The CDC has not mentioned any serious side effects from HPV vaccination, and in general, the benefits of using the vaccine outweigh its potential risks, and in this regard, of course, to reduce side effects such as dizziness and hypotension, etc. it is recommended that the vaccine be injected while lying down or sitting and stays in the same position for 15 minutes after injection (67).

A comprehensive study was launched by the International Agency for Research on Cancer and the University of Oxford on 16,573 women with cervical cancer and 35,509 women without cervical cancer from 26 countries worldwide, and almost half of the studies were in less developed countries. Cervical cancer was studied and their role was examined by considering the age of individuals and the effect of behavioral factors on cervical cancer risk such as smoking, use of oral contraceptives, and high number of deliveries (more than 5 complete deliveries). All factors independently doubled the risk of cervical cancer, while continuous smoking increased the risk by 46%, and a large body of prospective European research on cancer and nutrition found that doubling CIN3 in cervical cancer is associated with the duration and frequency of smoking (68-72). According to a study in 2019, using the results of a clinical trial of a 9-valent vaccine against papilloma virus in women aged 26 to 45 years, the Food and Drug Administration raised the approved age for use of this vaccine from 9-26 years to 9-45 years (73).

5. Conclusion

According to international statistics, cervical cancer is one of the most common cancers in women in the world with an annual infection of about 530,000 women, and with the stabilization of high-risk types of HPV, this cancer is constantly increasing. To reduce the complications of papillomavirus infection, appropriate preventive and therapeutic measures such as timely vaccination, attention to new therapies, education and correction of sexual misconduct, recognition and correction of susceptible to these infections such as smoking and overuse an overdose of contraceptives is essential to prevent the growing trend of papillomavirus disease.

Screening can provide a clearer perspective for the control and management of diseases caused by this virus in human society, especially in developing countries. Therefore, in order to achieve such goals, by using these tools, by establishing a registration system and providing basic health information with the ability to track and train program managers, public education, program management and quality control measures, we can hope to achieve approved global goals and programs. Since 2018, the world health strategy has focused on eradicating cervical cancer as a global health problem. Therefore, preventing infection through vaccination, screening, and treatment of precancerous lesions, and identifying and treating their primary invasive cancers, is a must-do. As a result, up-to-date measures to prevent it seem vital. In this regard, the program of proper disease registration and providing free screening methods, appropriate treatment measures and adequate training on the need to use these methods along with strategies to overcome vaccination barriers, is of great importance. Also, recognizing the types of papilloma virus that cause cancer and examining their prevalence can be associated with vaccine design and creating a higher immune coverage with fewer complications in the community. Research in the field of new vaccines and therapies is one of the points that can be considered by researchers in this field.

6. Appendix

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6.2. Author contribution

All the authors have the same contribution.

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6.4. Conflict of interest

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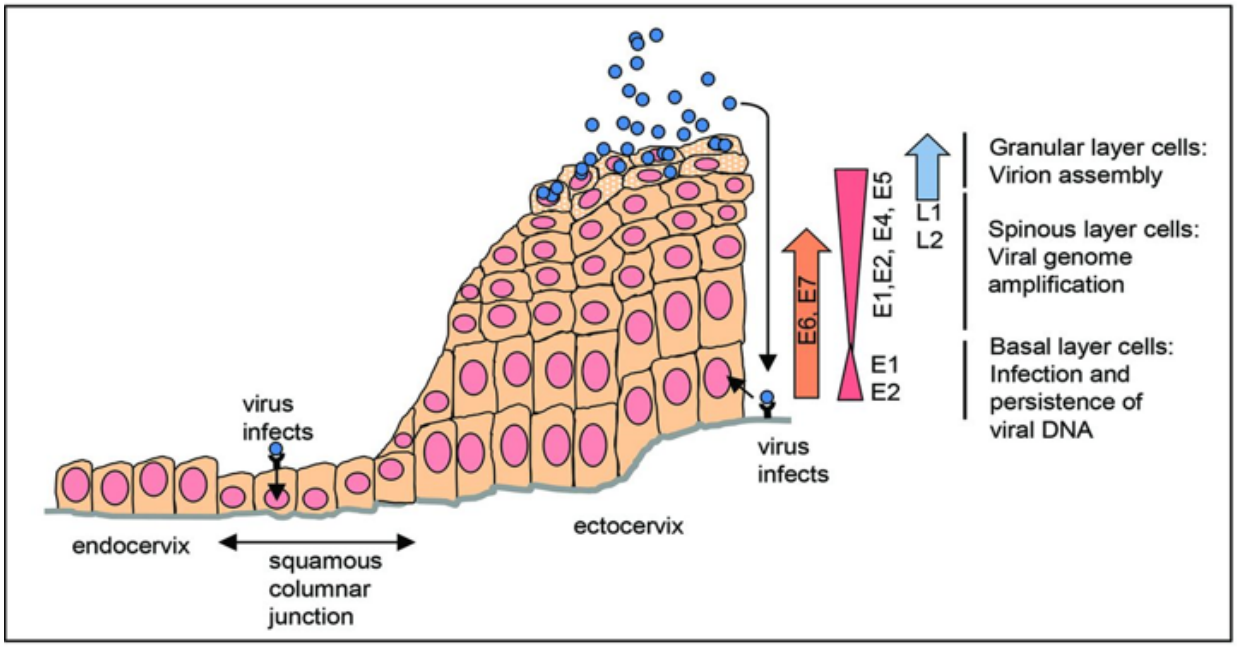

Figure 1: Cervical viral infection, keratinocyte differentiation and expression of human papillomavirus proteins (14).

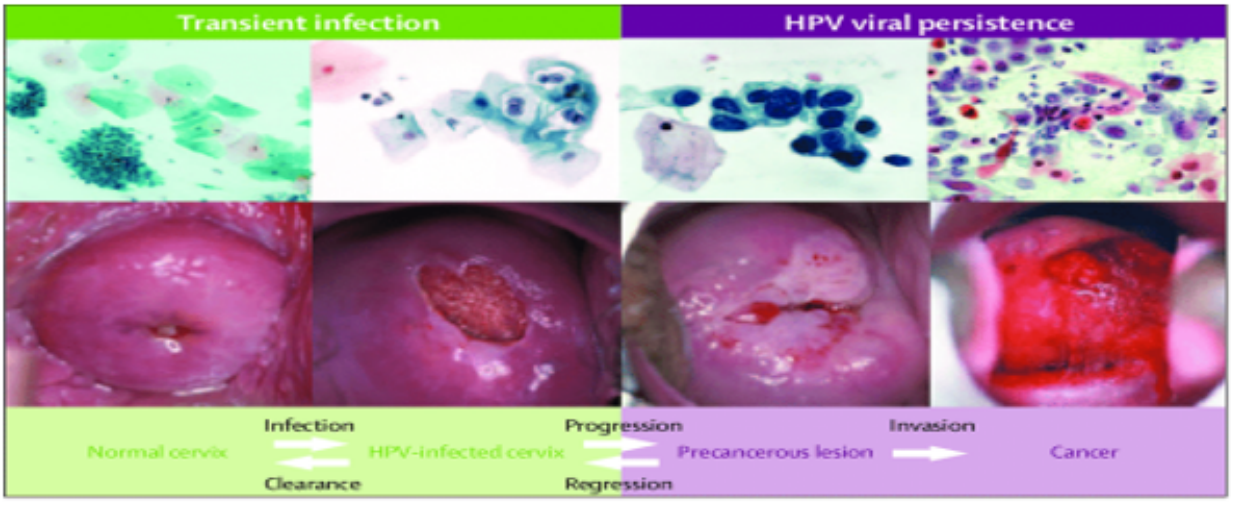

Figure 2: Overview of the process of cervical cancer with the stabilization of HPV. Top row cytology and bottom row is the result of colposcopy (8).

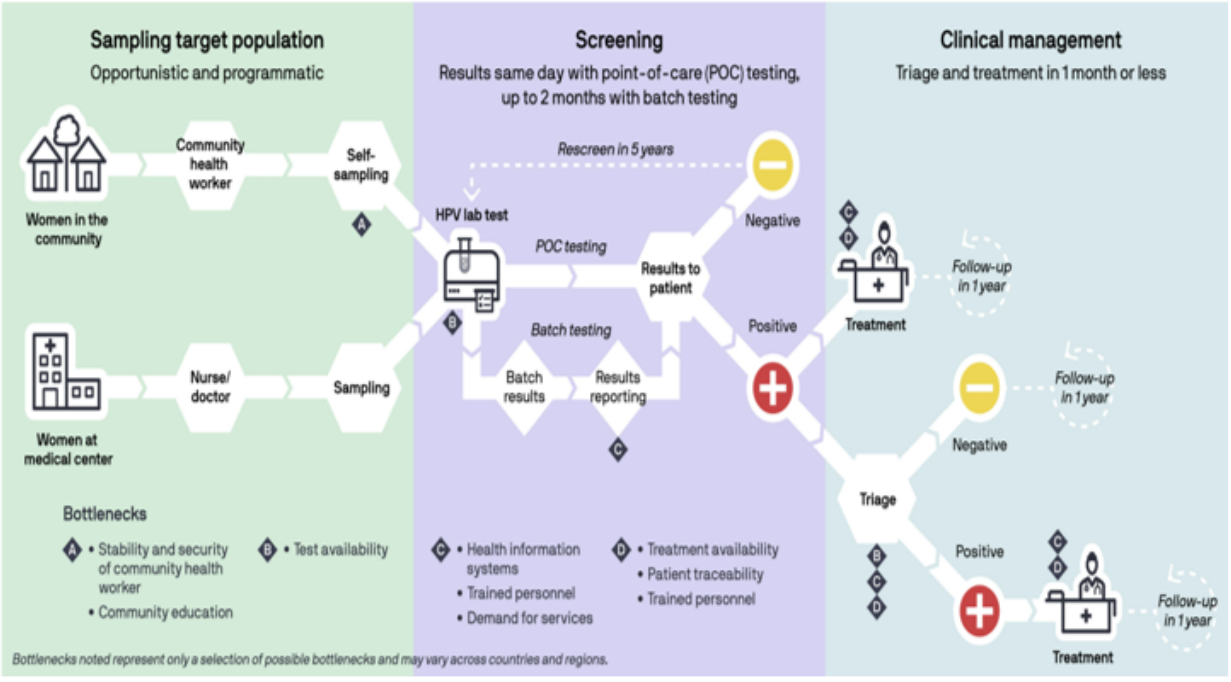

Figure 3: Papillomavirus-based cervical cancer screening program algorithm including main interventions, timeline and main bottlenecks (43).

Table 1: Overview of the function of HPV proteins (10)

Protein	Protein function
E1	Essential for viral replication and control of gene transcription - Helicase function - ATPase function
E2	Cell transcription factor - essential for viral replication and control of gene transcription - inhibition of transcription of E6 and E7 genes
E4	Degradation of the cytoskeleton to increase the release of the virus from the cell - role in virus assembly
E5	Binding to EGF cell growth factor and increasing cell growth and transformation in mice - oncoprotein in bovine papilloma - reduction of MHC class 2 and inhibition of endosome acidification
E6	P53 depletion - anti - apoptotic effect - telomerase activation - cell immortality by inhibiting cellular apoptosis
E7	RB binding and inactivation - activation of E2F-dependent promoters - induction of genomic instability
L1	Capsid core protein - VIP formation
L2	Capsid sub - protein - involvement in the nuclear transport of viral DNA