Research Status of HPV and Cervical Cancer

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Abstract. Cervical cancer is a worldwide malignant tumors in gynecology, which does great harm to women's health. The pathogenesis of cervical cancer is mainly related to the persistent infection of high-risk HPV virus. This paper mainly studies the relationship between HPV and cervical cancer, and finds that there is a close relationship between them. The significance of our study of this subject is that it is now clear that cervical cancer is transmitted through viruses and vectors, which is a great discovery. In this way, many years before the occurrence of cervical cancer, there is enough opportunity to find it and eliminate it, which is a very great contribution, so many patients who should have cervical cancer have been blocked, ensuring the health of women to a great extent.

Keywords: HPV, Cervical Cancer, Infection.

1. Introduction

Human papillomavirus (HPV) is a kind of double-linked cyclic DNA viruses, belonging to papillomavirus Family. In 1991, it was concluded that it can be transmitted through skin-to-skin or mucosa-to-mucosal contact and enters the body through skin or mucosal trauma. HPV is the pathogen of some common skin and sexually transmitted diseases and the cause of clinical papillary lesion [1]. HPV infection can cause sexually transmitted disease, although it can usually be prevented by the immune system. In 2015, it was found that people have about a half chance of getting infected at least once in their lifetime. HPV infection can cause common anogenital condyloma and other non-skin diseases. HPV's role in cancer development has been studied extensively, mainly in cervical cancer, but also in other types of tumors [2]. Papillomavirus was designated as a separate family named papillomviridae by the International Commission for viral taxonomy. As of 2004, at least 196 HPV types had been identified by genome sequencing. Extensive research on the role of HPV in the development of tumors has found that the type of papillomavirus in the alpha genus, known as the genital mucosal type, is strongly associated with the cervix. It was concluded that HPV type 16 and HPV type 18 are among the types designated as high-risk and most commonly associated with cervical cancer [3].

Cervical cancer is caused by mutations in the DNA of healthy cells, which appears in the cervical system [4]. A cell's DNA contains instructions that tell them what to do. Healthy cells finish their development and reproduction at a predetermined rate before death at a predetermined time. Mutations cause uncontrolled proliferation and replication of cells, and they do not perish as a consequence [5]. Outliers that join together to form a tumor Cancerous cells can spread to other parts of the body by infiltrating surrounding tissues and breaking out from a tumor. The cervix can be divided into two parts and is covered with two different cell types. The endocervical is the entry of the uterus through the cervix. It is overlaid with glandular cells. The exocervix, which is the outer section of the cervix, be saw in the course of an examination. Malpighia cells cover the entire surface. In the cervix, the transformation zone is where both types of cells meet. The specific position of the processing area changes as you get older and have children. The bulk of malignant cervical tumors start in the processing area [6].

However, there are certain reasons why this topic was chosen. Men and women both have concerns that need to be addressed on a regular basis, but there are a number of issues that are unique to women that must be addressed as well. Many people believe that women's healthcare need far more attention than it now receives. Women have a natural predisposition to prioritize their family. This is frequently at the expense of their own health [7]. So women's health condition need be focused more for the human being. The availability of women's healthcare services is critical. Accordingly, screening clinicians face a significant educational challenge in communicating the complex concerns regarding HPV infection. Women are likely to demand additional HPV information as awareness of the virus grows and HPV testing is examined as a triage during cervical screening [8].

This paper researched the HPV and Cervical cancer deeper by 8 main approaches. First and foremost, the biological characteristics of each would be introduced, which stands for the biological structure. Followed by the pathogenesis, which can determine how the HPV lead to the cervical cancer and search the close relationship between them. After that, why the cervical cancer can happen has to be searched with different risk of HPV. In addition, there are different types of HPV and cervical cancer, which refers why HPV16 and HPV18 can be the most special types among over two hundred of HPV. When it comes to the infection of HPV, path, recovery rate and high factors would be mainly talked about with newest statistics. Because of it, the detecting techniques and the Healthy bigdata are necessary to the modern society. At last, this paper ended with the human foreground with the HPV and cervical cancer.

2. The biological characteristics of HPV

Human papillomaviruses (HPV) infect stratified epithelium and are tiny double-stranded DNA viruses, show in figure 1. HPV separated into those that infect cutaneous surfaces and those that infect mucosal surfaces, show in figure 2. The kinds have traditionally been distinguished by sequence divergence, but it is becoming obvious that the virions are serologically distinct thanks to antibodies to conformational epitopes on the major. While most viruses cause benign proliferative lesions or warts, others might cause premalignant or malignant lesions. The most common place for malignant sickness is the vaginal system, with cervix carcinoma being the most common malignancy [9].

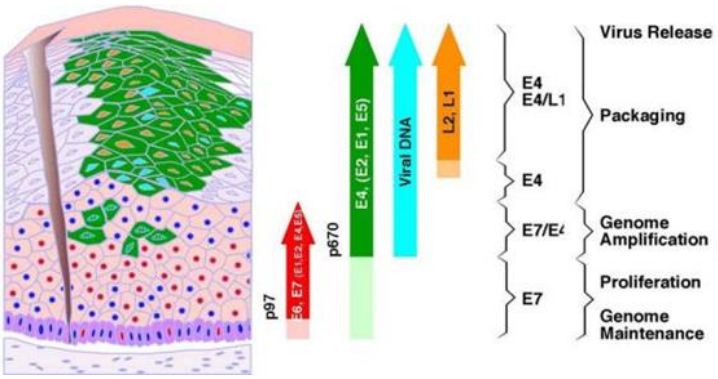

Figure 1. The structure of HPV Virus [10]

After microlesion entrance into the epithelium, viruses infect basal epithelial cells and retain copies of 50 to 100 genomes per cell. After cell division, one daughter cell will stay in the basal epithelium, while the other will migrate to the next stage and begin to differentiate. At this moment, the viral DNA will be isolated from both daughter cells and will replicate in order to maintain the 50-100 copies per cell. When one of the virus's daughter cells begins to grow, the virus faces a dilemma since viral DNA synthesis requires the cell's replicative machinery, which is lacking in terminally differentiated cells. Consequently, when confronted with a terminally differentiated cell, the virus must jump from G1 to S-phase development to generate the right conditions for DNA reproduction. The later sponsor, which regulates the encoding of mRNA for proteins, is only activated in partially differentiated cells, hence the virus requires some differentiation. Therefore, the virus distinguishes

between G1 to S phase progression and differentiation, allowing the two processes to coexist in the same cell. Infected cells slough off the epithelium's surface and can spread to humans directly. Infected cells, form different part to say, may cost some time in the environment before transferring the virus to a new epithelial surface. Viruses that infect cutaneous surfaces fall into this category. Viruses infecting mucosal surfaces can be transmitted directly during sexual contact [12].

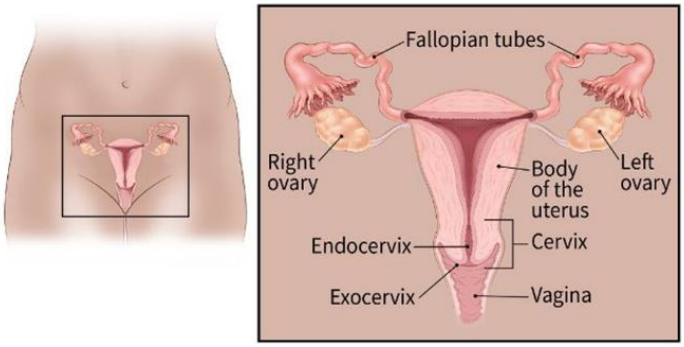

Figure 2. The structure of genital organs [11]

3. Etiology pathogenesis of cervical cancer

3.1. Causes of cervical cancer

HPV interferes with the replication and expression of DNA in cells. In 2003, it was concluded that the HPV replication cycle begins when the virus enters the germinating layer (known as basal layer) of epithelial cells. HPV infection in the basal layer may require minor damage to the epidermis. Once enter the host cell, the HPV can replicate its DNA and progresses to the epithelial cell surface while the basal cells differentiate. In the basal layer, viruses are thought to be unproductive for replication as they can only make themselves into small viruses with a low replication number by using the host DNA replication mechanism to copy their DNA on average once per cell cycle. In keratinocytes differentiated in the suprabasic layer, the virus switches into the cycle of DNA replication, amplifing its DNA to a high copy number, and synthesizes capsid proteins, which leads to viral assembly. Cervical cancer is easily understood examples of how a viral infection can lead to malignancy [13]. High risk human papillomavirus infection can affect the function of cellular proteins, especially the interference with the cell cycle, which can lead to many further complications. Cervical cancer is one of the most serious complications.

In 2007, scientists have found that HPV infection itself is not enough to cause cancer as a major risk factor [14]. however, in some cases, persistent infection can lead to cervical intraepithelial neoplasia or precancerous changes in adenocarcinoma in situ. If these lesions are not treated in time, it will take years to decades to deteriorate from stunting to invasive cancer for most women. However, in about 10% of patients, the transition can occur within 1 year [15]. HPV 16 and HPV 18 were found to be the two HPV types which are the most associated with cervical cancer. In 2007, it was concluded that the most common type of HPV at diagnosis of squamous cell carcinoma (SCC) is HPV 16, followed by HPV18. Besides, HPV 18 is the type that is most strongly associated with cervical adenocarcinoma [16]. The cervix is made up of laminated squamous epithelium and mucous columnar epithelium. The transition between these two kinds of cells is known as the squamous column junction, and this region is considered to be the site that is the most likely to be occured by viral tumor transformation. Tumors of the external cervix are usually squamous cell carcinoma, accounting for about 75% of invasive cervical cancer cases. In contrast, endometrial cancer is more likely to be adenocarcinoma. In addition to the above, cervical adenosquamous carcinoma, small cell or neuroendocrine carcinoma, serous papillary carcinoma and clear cell carcinoma are less common [17].

3.2. Development of cervical cancer: latent host susceptibility

Studies have found that HPV causes genetic mutations in a person's immune system. In 1994, a study conducted in the 1990s found that these common mutations in the MHC system were DQB1 * 0303 and DQB1 * 0604 [18]. Just a few years later, another study conducted in Norwegian patients also reported the similar susceptibility loci DQA1 and DQB1 in the MHC region [19]. Since then, more MHC gene variants have been identified and linked to cervical cancer in different populations [20]. The genetic variation of immune system will make the immune system function abnormal, and then lead to the cancer cells with genetic variation can not be eliminated by the immune system, and the cancer cells continue to accumulate and eventually cause cervical cancer.

Another common epigenetic mechanism in HPV carcinogenesis concluded in 2015 is DNA methylation, where methyl (-CH3) is covalently added to the cytosine in the DNA sequence [21]. To determine more specific methylation changes in HPV DNA, in 2009, research used sulfite methylation-specific PCR (MS-PCR) and sequencing, then the result shows that hypermethylation in the HPV 16 LCR region is associated with carcinogenic progression of cell line and cervical lesions [22]. In 2012, research Found that cervical cancer was associated with methylation in L1, L2, E2/E4 regions of the HPV16 118 genome by pyrosequencing [23].

4. HPV typing and cervical cancer

HPV is the most common sexually transmitted infection, with about 14 million people infected each year [24]. Most female patients do not realize that they are infected after being infected with HPV because there are no obvious symptoms in the early stages of HPV infection [24]. Of the more than 200 types of HPV, about 40 types of HPV can infect your organs [25]. A person can be infected with more than one strain of HPV. The strains are identified by number and can be divided into two types: low-risk and high-risk.

4.1. Low-Risk

HPV low-risk type can lead to condyloma acuminatum, is a sexually transmitted disease, some patients infected with low-risk virus, because the physical resistance is better, and most patients can self-clear. Some patients may have low resistance or large viral load, which can produce some reactions. They will not further develop into cancer. Among them, HPV16 and 11 are the main types of genital warts [24].

4.2. High-Risk

High-risk strains can cause carcinogenesis, and the carcinogenic effect is relatively strong. Especially in the female cervix, causing epithelial neoplasia, epithelial neoplasia can become malignant after long-term malignant stimulation, especially cervical cancer. Among them, HPV16 and 18 are the main types of cervical cancer [26]. High-risk HPV positive patients have an increased risk of onset, and colposcopy biopsy should be performed if necessary to determine whether cervical lesions have occurred [24].

4.3. The relationship between HPV DNA and serum IgG and HPV16,18

In 2022, Carter, J. et.al concluded that although the serum antibody of HPV capsid is not clear about infection, it can provide protection against the same type of infection and can be used as a marker of persistent or previous infection. In order to study the relationship between HPV DNA and serum IgG and HPV16,18, an investigation was carried out among more than 500 female college students. The study found that the percentage of seropositive results in women infected with hpv16 was 54.2%, and 85% in the follow-up after 18 months. In HPV16,18,6, the seroconversion rate of HPV6 was the highest, while HPV18 was the lowest. It is concluded that the antibody reaction of HPV16 and 18 is longer than that of HPV6, and they are more likely to persist during the follow-up. Following that, it was observed that the seropositivity time was efficient within 12 months of tracking,

with HPV6 serology having occurred faster after HPV6 DNA detection than HPV16 seropositivity having occurred faster after HPV16 DNA detection. Because the HPV16 immunoglobulin test is related to the continuity of HPV16 DNA, the failure of seroconversion is attributed to the fact that HPV16 has only one HPV DNA constructive visit, whereas hpv6 seroconversion does not affect the number of HHPV DNA positive visits [27].

4.4. Low-risk HPV types and their organizational similarities with high-risk types

HPV infections are usually, and a number of different of high- and low-risk HPV types can be discovered on the skin of immunocompetent people as part of the usual microbial skin flora without causing symptoms.[28]. Infection is generally self-limited and will eventually be cleared by the host immune system. If it is not cleared and controlled, it will lead to a series of other infections such as cervical cancer [28]. Figure 3 depicts the function and expression of a viral protein. Low-risk HPV types rarely use their E6 and E7 genetic instructions to generate significant cell growth in the stromal and multisectoral layers of cells, which is one of the primary differences between them and high-risk HPV types [28].

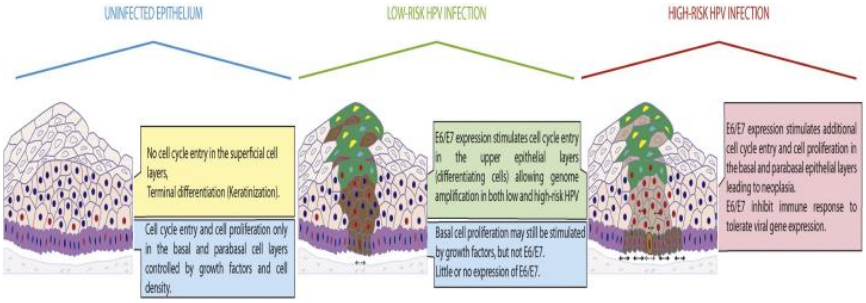

Figure 3. The different function and expression of viral proteins underl disease phenotype [28]

5. HPV infection and cervical cancer

In1994, cervical cancer become the common cancer for US women [29]. Also in some developing countries, it was found that cervical cancer alsobecome common in women in 2001, accounting for perhaps 25 per cent of all cancers in women [30]. As the figure 4 shows, cervical cancer is also the most usual cause of cancer death among women worldwide. The link between HPV and cervical cancer has become a research hotspotd. In 1996, some researches and the Cervical Cancer Consensus of the National Institutes of Health identified HPV as a significant cause of cervical cancer. In 2003, Burd concluded that scientists have used genetic sequencing to identify about 30 types of HPV, which are mainly transmitted through sexual contact and mainly infect the cervix, vagina, vulva, penis and anus, with four most common malignant cells in cervical cancer [13].

Younger people were found to be more susceptible to HPV. In 2016, scientists used PCR kits to detect HPV genotypes in different age groups which aged 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 perspectively. 1661 people were tested in 2013-14, but the proportion of only HPV 16 and 18 genotypes was not included in the statistical analysis. Males are only a minority (N=90). Results Showed that the total number of HPV positive cases was 26.0%, accounting for 286 cases. HPV infection was highest in the age group 16-29 (62.4%) [14].

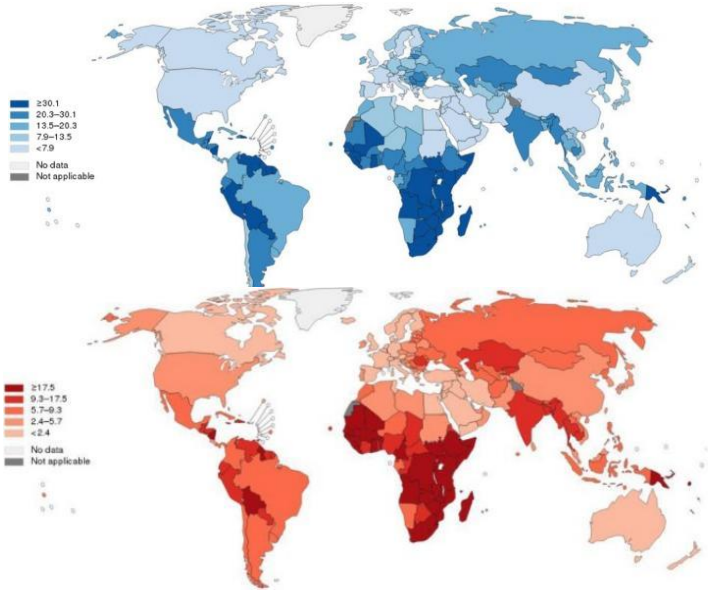

Figure 4. Estimated age-standardized incidence and mortality rates for cervical cancer among women in 2012 [31]

6. HPV detection technology for treat cervical cancer

Testing is critical to the treatment and prevention of HPV-related cancers and the HPV virus itself. By influencing citizens to participate in pap smears and other types of testing regularly, the mortality rates of HPV-related deaths in United States have decreased over the last 4 decades. This is an effective method of detecting the virus at early stages and preventing cervical cancers. The types of tests are divided into the following categories: pap smears, colposcopy, biopsy, type-specific PCR, general primer PCR, HPV mRNA Detection and liquid hybridization.

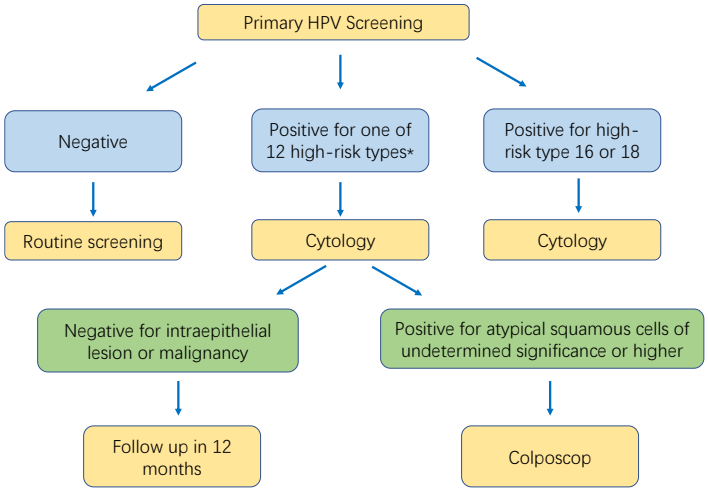

Figure 5. Primary HPV screening in US [34]

6.1. Pap Smears and the Bethesda System

The pap smear is the most prevalent sort of testing, which is a screening technique that looks for alterations in cells of the cervix's transformation zone, which are frequently caused by HPV [33]. Pap smears, on the other hand, have limits. It's possible that false positive and negative findings will appear. A false-positive result indicates that the patient is infected with the high-risk HPV virus, necessitating additional testing. A false-negative is the opposite of false-positive: the test indicates that the patient does not have high-risk HPV virus when they really are infected, leading to delays in the follow up procedures [32]. Inadequate samples, cells clumping owing to not being adequately

distributed out on the microscope slide, other components of the specimen contaminating the sample, long periods of exposure to air, and human error can all contribute to false-negative results [33]. Because each sample has 50,000 to 300,000 cells to evaluate, if only a few aberrant cells are present, readers may overlook them, resulting in incorrect results. [33].

The Bethesda Classification is a pap smear reporting classification that was created to represent a more sophisticated understanding of cervical neoplasia and to standardize descriptive histologic nomenclature [33]. The approach divides squamous cell abnormalities into four groups: ASC (atypical squamous cells), LSIL (low-grade squamous intraepithelial lesions), HSIL (high-grade squamous intraepithelial lesions), and squamous cell cancer. [33]. ASC refers to squamous cells that have abnormalities that are more severe than those caused by reactive alterations but do not match the requirements for a squamous intracpithelial lesion. LSIL refers to alterations in cells that are mildly aberrant whose changes are almost invariably caused by HPV virus. HSIL means squamous cells that are moderately to severely aberrant. Although the likelihood of cancer is high enough to urge immediate evaluation, having carcinoma does not imply that the patient has cancer. The Bethesda method could help provide a more specific classification of the severity of the HPV infection and provide accurate diagnoses.

6.2. Colposcopy and Biopsy

In 2003, Burd, E. concluded that colposcopy is used to evaluate patients with abnormal pap testing results but no cervical lesions. After applying 3% of acetic acid solution, a bright light will examine the patient’s cervix. The patterns of dysplasia or carcinoma could be seen, but microinvasive diseases could not be detected. The cervical cone biopsy could be done if there are no abnormalities found. This method is used to confirm diagnoses by looking at the pathological characteristics of the HPV virus [33].

6.3. Type-specific and General primer PCR

Burd, E. concluded in 2003 that this type of testing examines the HPV virus's E6 and E7 sequence variations. (Under electron microscopy, the virus resembles a golf ball.) The E6 and E7 proteins are crucial in the virus's replication and oncogenesis.) Type-specific PCR is actively being employed in research. General primer PCR is using consensus primers to increase the spectrum of HPV types tested. Both type-specific and general are used for research purposes [33].

6.4. Liquid Hybridization

In 2003, Burd, E. concluded that this method of testing detects HPV DNA in cervical samples. It can detect low-risk HPV and high-risk HPV. However, one drawback is that this cannot distinguish the types of HPV it detects. Liquid hybridization is used in epidemiology and research since it is not that significant in clinical applications [33].

6.5. HPV mRNA Detection

HPV mRNA detection checks the mRNA of the virus's E6 and E7 genes to see if the cancer-causing genes are present and active, similar to type-specific PCR testing. Compared to a pap smear, this method of testing has a 70% higher specificity [33].

HPV DNA testing and Pap smears could reduce the costs by categorizing the patients into appropriate measures of further screening and specific treatment. All of the testing methods mentioned above are used to detect HPV and start treatment early and to prevent further HPV transmission. Regular testing every 2-3 years greatly lowered the number of confirmed cases of cervical cancers and identification have lowered HPV-related deaths [33].

7. Future Direction of HPV research in cervical cancer treatment

There will be modifications of the testing and screening strategies in the future. Accuracy of the testing would be improved to prevent and identify HPV virus early. Education of the disease is crucial too. There is no widely used testing methods in detecting for HPV in men. The screening methods used to detect cancerous changes in cells or the virus itself in women, such as pap smears, HPV DNA testing and colposcopy are lacking for men. It is hard to determine whether if your partner has HPV unless it turns into cancer, which may result in transmission to others if not careful. Detection strategies for men may be established in the future.

8. Conclusion

HPV is a DNA virus that is the cause of common skin and sexually transmitted diseases. It is spread by contact and enters the body through skin or mucosal trauma. HPV interferes with the replication and expression of DNA in cells, which can lead to complications including cervical cancer. Therefore, through the detection of HPV, cervical cancer can be prevented and treated to a certain extent. Currently, the most common test is pap smear, which is used to screen for changes in cells in the cervical transition zone that are usually caused by HPV. However, there are false positives and false negatives with this method. PCR, which detects genetic variations of HPV virus with type specificity and universal primers, is more specific than Pap smear. Both methods test for HPV to treat early and prevent transmission of HPV. Future research continue to improve the accuracy of testing and screening, and establish testing and screening strategies for men to prevent transmission between partners. In addition to these, education about the disease is also important, which are the direction of future research on the prevention and treatment of HPV and cervical cancer.

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