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Human papillomavirus infection: Current global scenario of disease burden and prevention strategies

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***Abstract*---**In the past decade, cervical cancer has increased alarmingly in different parts of the world especially in developing regions. Cervical cancer is caused by persistent infection with high-

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risk HPV. Interestingly, HPV infection is associated with other cancers also besides cervical carcinoma. Therefore, a proper understanding of epidemiology, pathophysiology,and treatment and prevention strategy is required to combat this commonly occurring cancer. To eliminate cervical cancer from the global map the only strategy is rigorous vaccination in school-going teenage girls. The WHO wants to eliminate HPV by 2030. Its goal is to vaccinate 90% of females by 2025. However, proper awareness and government initiatives are far behind the required drive. Moreover, the low use of cervical cancer screening techniques like Pap smear and visual inspection with acetic acid hindered HPV infection and cervical cancer control in affected countries. In addition, we try to describe the whole pathological cycle of HPV in humans with prominent risk factors that can be a key to control the incidence of HPV-associated cancers. Finally, we showed the significance of the only available strategy to prevent HPV infection-i.e. vaccination. We tried to make the reader understand about the current practice of vaccination and the associated challenges to achieve the desired vaccination goal.

***Keywords*---**HPV, cervical cancer, HPV vaccine, HPV epidemiology.

Introduction

Cervical cancer develops in the cells of the cervix, the tube-shaped lower section of the uterus caused by the sexually transmitted human papillomavirus (HPV). Although initially female patient is unable to show any kind of symptoms but this type of cancer is characterised by the heavy watery bloody discharge along with pelvic pain while intercourse and between menstruation and menopause(27). Almost all cervical cancers are caused by the different types of HPV particularly, type 16 and 18 are representing 50 % of agents (WHO). The other risk factors that attributes to the prognosis of disease are smoking, very long time use of birth control pills, intercourse with several partners and HIV infection.

It was discovered that the amount of socioeconomic development in a country has a negative correlation with the mortality rate and incidence rate of cervical cancer. Different regions of the world are affected differently by cervical cancer, with more than 85% of deaths happening there. According to the Human Development Index (HDI) data countries having a lower index showed CC is the second position after breast cancer concerning the incidence and mortality rate and the fourth most common cancer type worldwide(16). A cross-sectional study showed high-risk HPV in China is at least 14.3% among other cancers (47). In India, it is the highest second level among women up to the age of 44 (1). The highest mortality rate was observed in Africa compared with Western Asia, North America and New Zealand (36). Finding that the occurrence of cervical cancer among African women renders the race inferior to white females (30). Weak health care infrastructure and inadequate screening have boosted cervical cancer in the former Soviet Union (38). The transmission rate is also depending on the sexual partners, type of sexual partner, number of sexual partners and sexual behaviour. Lesbians and bisexual women are thought to have poorer hygiene and

are prone to infection, lesbian women may have less chance of infection (Steele et al., 2009). Men play a role in the transmission of HPV, just as they do with every other type of STD.

The most common types of treatment included surgery – conisation, loop electrosurgical excision procedure, exenteration, radiation therapy, chemotherapy, and immunotherapy. The most effective prevention method is the vaccination, Gardasil which is the HPV effective vaccine that has been approved recently by US FDA for women, especially girls aged between 9 - 26 attributing the promising results(42). Although vaccine therapy is effective against most strains of HPV, not all vaccination is thought to prevent 80 % of cervical cancer when taken before the infection. Clinical trials showed that it is not effective when taken after infection by a particular strain but even after that it is effective against other types of strains. In most vaccination programs, only female subjects are targeted. To prevent the spread of a gender-neutral contagious disease, a large number of people should acquire the vaccine(27). Herd immunity against HPV is not possible unless men are vaccinated since female-to-female HPV transmission is low compared to male-to-female and male-to-male transmissions(23). Adolescent males are a secondary WHO vaccination target (14).

Epidemiology

The Human Development Index (HDI) measures a country's overall development based on life expectancy, education, and gross national income(12). It causes cancer. HDI increases prostate cancer risk. HDI increased colorectal cancer and mortality. Cervical cancer incidence and death rank second in low HDI countries(2). 71% of cervical cancers around the world are caused by HPV types 16 (HPV16) and 18 (HPV18). Other risk factors, like having HIV, using oral contraceptives, or engaging in high-risk sexual behaviours, may affect HPV infection or immune response. In women with normal cytology, the global prevalence of cervical HPV infection is 11.7% (95% CI:11.6%-11.7%). In some nations, HPV infection peaks in the late 20s. The most prevalent HPV strains infecting women with normal cytology are 16, 52, 31, and 53; HPV 16 and 18 cause 55% and 14% of cervical cancer cases, respectively(Wei et al., 2021). GLOBOCAN 2018 estimates HPV impact globally. In 2018, there were 690,000 HPV-related cancer cases globally. Sex-specific estimates are utilised because most HPV-related malignancies affect women. Global cervical cancer ASIR is 13.1, with a 6.9 per 100,000 fatality rate (34). Cervical cancer ranks second among women under 50 and fourth overall. HPV has superseded cervical cancer as the primary cause of OPSCC in HMICs. LMICs show no such pattern. Some oral malignancies are HPV-positive, but it's uncertain if that's the cause. Screening and preventive vaccinations are the best ways to stop cervical cancer from happening(32). According to the study, the majority of the countries included in our analysis have stable or even declining incidence and fatality rates, which is likely due to increased cervical cancer screening programmes and higher standards of care.. The early implementation of systematic screening programmes as well as advances in screening, diagnosis, and treatment, can explain this disparity(Lin et al., 2021

Demography

In Ouagadougou, HR-HPV infection among women without lesions was found to be more prevalent than in the general female population and research conducted elsewhere in the world. Human papillomavirus (HPV) and related risk factors are prevalent in Curacao's female population. In women with normal cytology, HPV35 is the most common genotype, followed by HPV18, 52, and 16 (20). The number of high-risk human papillomavirus (HPV) infections among Chinese women is comparable to the global average. Infection with HR-HPV was more prevalent in the female population of Jumla than in the female population of Nepal across the country (41). Human papillomavirus (HPV) infection is more common in HIV-positive patients and increases the risk of malignancies caused by HPV in Africans (26).

Age and gender distribution

As the population ages, an increasing number of instances of HNC are identified. Oral cavity cancer is becoming more prevalent in young women, which may explain why a greater proportion of newly diagnosed cases include younger patients. Except for oropharyngeal cancer, the median age of cancer diagnosis was 40. Oropharyngeal carcinoma is increasingly being diagnosed in adults of middle age. Anal cancer is almost exclusively caused by high-risk human papillomavirus (HPV) infection, which disproportionately affects men who have interacted with other men (MSM)(Tounkara et al., 2020). While the number of oral sex partners continues to be a major risk factor for HPV-OPC, the duration and intensity of oral sex are independent risk factors. These results indicate that the causes and transmission of HPV-OPC are more complex than previously believed. In two West African nations, the rate of HPV infection among FSWs is dangerously high, as is the incidence of numerous HPV types(18). Anal cancer caused by the human papillomavirus (HPV) is one hundred times more prevalent in homosexual, bisexual, and other men (GBM) who have sex with HIV-positive men (HBM) than in the overall population.

Risk factors

Studies have shown that HPV and cervical cancer precursors were more prevalent in HIV-positive women (R. Tagne Simo et al., 2021). Some research suggests that continuous use of oral contraceptives may increase the risk of developing the high-grade cervical disease because high-risk HPV contains sequences that are parallel to the responsive elements of glucocorticoids that can be probably caused by steroid hormones like progesterone, the ingredient in oral contraceptives, and dexamethasone (Richard Tagne Simo et al., 2021). Smoking may play a part in HPV diligence or malignant adjustments in the cervix through its demonstrated capacity to dampen the local immune system response and through the mutagenic interaction of tobacco components (Keller et al., 2022). An unbiased potential risk for continual HPV infection and cervical cancer is an increasing quantity of full-term pregnancies. Some hypothesise that this occurs because of pregnancy effects on hormone levels and immune responses, respectively. The transition zone is more likely to linger on the ectocervix for long durations in multiparous women, allowing for more direct contact with the virus and other

possible cofactors. Scientific evidence for the relationship between diet and cervical cancer risk and prolonged HPV infections was classified as "reassuring," "possible," "viable," or "totally inadequate." Folate, retinol, vitamins E, C, and B12, alpha- and beta-carotene, lycopene, lutein/zeaxanthin, and cryptoxanthin have been found to have anti-cervical carcinogenesis properties in the diet. Consuming foods rich in antioxidants such as lycopene, beta and alpha-carotene, lutein/zeaxanthin, vitamins C and E, and cryptoxanthin may also help keep HPV infections in check (45).

Pathogenesis and Transmission

Association of HPV and cervical cancer

HPV oncogenes cause cervical cancer and other cancers directly associated with HPV. Indirectly, these cancers could have been caused by HPV oncogenes that cause inflammation in the body(13). Chronic inflammation causes damage to the body's tissues over and over again and changes the genes that stop cancer from expanding. HPV is the consequence of long-term inflammation and HPV infection that can lead to cancer. When HPV E5, E6, and E7 turn up COX-2 and PG E2, they turn on the COX-PG pathway. Throughout this process, HPV causes inflammation(19). Due to HPV oncogenes, people who've had HPV and are HPV+ might produce more cytokines that cause inflammation. When you have an HPV infection, those same cytokines make the pain and swelling worse. MicroRNAs are connected to both inflammatory pathways and the ageing process. They make more cytokines that cause inflammation, which could make cervical cancer and inflammation caused by HPV happen faster(35).

Other cancers associated with HPV

Head and neck cancers (HNC) account for 4.8% of all malignancies and cancer-related deaths worldwide. 90% of squamous cell carcinomas in the head and neck arise from oral, pharynx, larynx, or, in rare cases, nasal epithelial cells. From benign lesions to malignancy, HPV is connected to a spectrum of clinical disorders (Table 1). Oral squamous cell carcinomas (OSCC) develop in the lips, tongue, and oral cavity, among other places. OPSCCs (oropharyngeal squamous cell carcinomas) form near the base of the tongue, soft palate, tonsils, and the back of the throat. Laryngeal squamous cell carcinomas are induced by the supraglottis, glottis, and subglottis (LSCC). Lymphocytes, connective tissue (muscle, blood vessel), and salivary gland cells make up 10% of HNC (6). HNC is made more likely by the use of alcohol, smoking, and/or chewing tobacco. HPVs are responsible for approximately 25% of all HNC cases. HPVs are responsible for the majority of cervical cancers, a portion of anogenital cancers (vaginal, vulva, anal, penile, etc.), and nearly all genital warts(4).

Table 1: Other Diseases Associated with HPV

Disease-associated with HPV infection	HPV Types involved
Epidermodysplasia verruciformis	17, 2, 3, 10, 21, 5, 9, 12,36, 14, 15, , 8,19, 20, , 22, 24, 25,40.
Conjunctival papillomas/carcinomas	16, 6, 11.

Cervical intraepithelial neoplasia	
High risk	16, , 11, 31, 34, 39, 42, 51, 52, 66, 58 .
Not specified	30, 34, 53, 57, 59, 64, 66, 69.
Low risk	6, 11, 18, 31, 33, 35, 42, 45, 52, 74.
Flat warts	3, 27, 28, 38, 75, 76.
Focal hyperplasia of Heck	32
Recurrent papillomatosis in the respiratory system	6, 15, 11, 20.
Cutaneous lesions including epidermoid cysts, and laryngeal carcinoma)	6, 11, 32, 16, 30, 40, 33, 36, 37, 46, 38, 41, 48, 55, 72, 73, 96.

Life cycle of HPV

HPV affects cutaneous or mucosal squamous epithelia, which have a layer of undifferentiated cells at the bottom and a layer of suprabasal, granular, and cornified squamous cells at the top (10). Because the virus needs enzymes and polymerases that help it make copies of itself, it can only infect cells that are actively dividing. Differentiated epithelial cells don't divide, so infected basal cells don't happen very often(Basukala and Banks, 2021). Most infections are caused by tiny cuts or tears in the skin. At the transition zone, where the endocervix changes into the ectocervix, basal cells in the cervix are even more likely to be exposed. Infection can happen there without tears or cuts(22). Reserve cells, which are often infected with HPV, are found in this area. Endocytosis helps cells stick together and lets viruses in. After endocytosis, HPVs are moved to endosomes and/or lysosomes, where a low pH is needed for the capsid to come off. During prophase, L2 stays connected to viral DNA and helps DNA move through the trans-Golgi network (TGN), which gives the virus access to the nucleus of the host cell. During mitosis, the viral DNA stays in a transport vesicle so that the host cell's innate immune system doesn't recognise it(11; 15).

Prevention strategy: HPV vaccination

Current status of treatment: Why prevention is important?

Vaccination against human papillomavirus is a cost-effective public health strategy, especially for young women, in areas with poor rates of cervical cancer screening. Taking into account the burden of HPV-associated head and neck malignancies, as well as the inadequate frequency of vaccination in females, cost-effectiveness scenarios of HPV vaccination, have been established (21). A comprehensive review analysis of the cost-effectiveness of HPV immunizations, which included non-cervical HPV-associated disease, found that female-only vaccination regimens were generally 2.85 times higher cost-effective than gender-neutral vaccination, with the latter having a cost-effectiveness ratio of 3.89 to 1 (24).

Current practice according to clinical guidelines

Despite being evidence-based, several clinical guideline recommendations remain contentious. The perfect age to vaccinate girls and women is between the ages of nine and twenty-six, but this recommendation supports vaccinating middle-aged

women. Vaccination is considered safe for women aged 27 to 45, but its efficacy may be reduced due to prior viral exposure. Besides that, the evidence for the 9-valent vaccine is insufficient only because one controlled trial in middle-aged women was conducted. So, before administering a vaccination, clinicians must have a thorough discussion with their patients about the benefits of vaccination. More research is needed to assess the cost-effectiveness of immunisation among middle-aged women, as well as to recognise the women who would benefit from vaccination (8).

Efficacy and Adverse events

The complainants say the HPV vaccine caused cognitive difficulties. Injecting HPV vaccines into experimental mice caused CNS damage, inflammation, and cognitive impairment. Several studies suggest molecular mimicry between host proteins and pathogens including viruses and bacteria contributes to immune-mediated tissue damage (29). Because of the molecular similarities between HPV16 and human proteins, immunisation with HPV will certainly lead to autoimmune disorders because of the generation of cross-reactive antibodies. A recent meta-analysis by Boender et al. found contradictory data on the risk of Guillain-Barré syndrome after HPV vaccination (31).

Challenges, myths and public awareness

The general public should be concerned about HPV because it can cause OPC, but few are aware of this connection. People's awareness of HPV has grown significantly as a result of the availability of highly effective vaccination. In terms of HPV vaccine awareness, women outperformed men, and the topic is still viewed through a feminist lens. The internet and social media had little influence in spreading the word about the HPV vaccine (7). The recognition that HPV contributes to the occurrence of uterine cervical cancer seems to be the primary motivator behind the increase in women's awareness of HPV, the HPV vaccine, and the link between HPV and OPC. Adolescents who received injections as college freshmen Even after accepting the HPV vaccine, several women were unaware of the importance of regular Pap tests in the prevention of cervical cancer (33). The summary of the role of HPV in the pathogenesis of cervical cancer and its associated elements are represented in the following schematic diagram. (Figure 1).

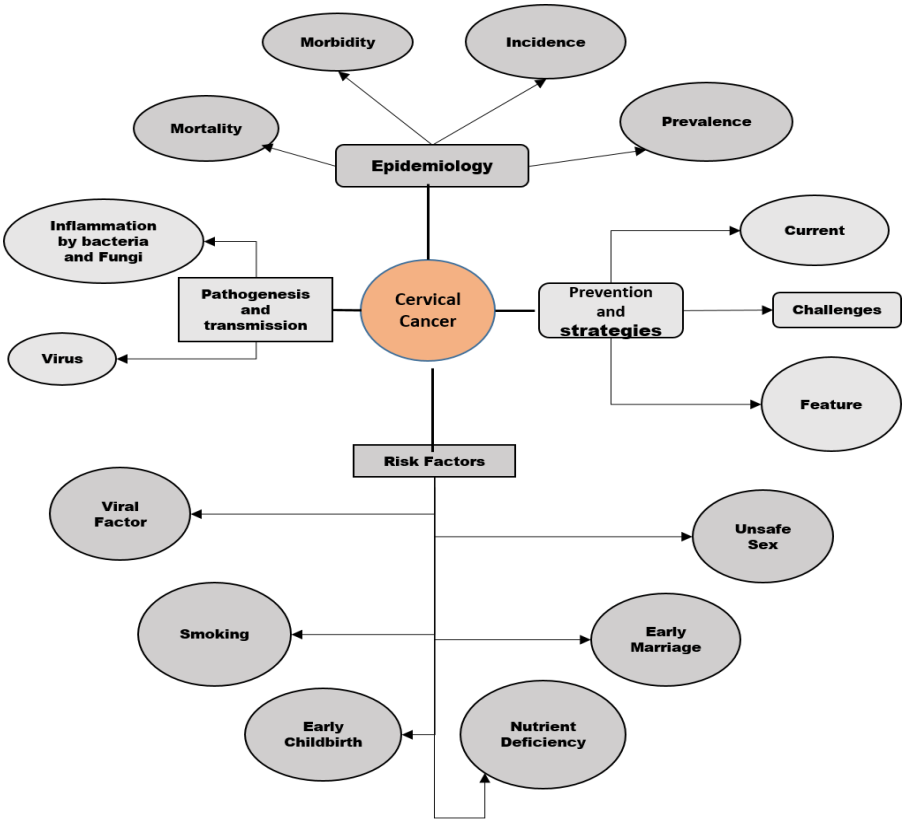

Figure 1: Schematic representation of Human Papillomavirus infection and prevention in cervical cancer

Conclusion and prospects

People who are sexually active in any part of the world are at risk of contracting the human papillomavirus (HPV), but there is good news: the condition is typically mild and the associated lesions have a high remission rate. On the other hand, persistent HPV infection with high-risk subtypes is responsible for a significant disease burden, particularly in females and those who are immunocompromised. Invasive carcinomas are the disease that this burden is most closely associated with. If a vaccine had been properly delivered, lesions of this nature may have been completely avoided. Vaccines that are now on the market offer protection against the most common strains of the human papillomavirus (HPV), as well as the precancerous cervical and anogenital lesions that are linked with those strains. Despite this, there is not a single country in the entire globe that has adopted a vaccination strategy that does not prioritise one gender over the other.

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