

Exploring the Landscape of Cervical Cancer Epidemiology, Risk Factors, and Prevention Strategies

Ankit Raj¹, Anshuman kumar², Rashmi Chaudhary³

^{1,3}M.Sc. Student Department of Microbiology, MGM Medical College Kamothe, Navi Mumbai

²Project Technical support, Department of Microbiology, All India Institute of Medical sciences Jodhpur

Abstract

Cervical cancer, which is largely preventable, is one of the most prevalent cancers among women, especially in low- and middle-income countries. The implementation of successful national screening programs, which use cytology based Papanicolaou smears to detect precancerous changes, has significantly reduced the concern of mortality rates of this disease.

However, because of high costs and the need for well-established healthcare systems, these programs have not been initiated or maintained in many low- and middle-income countries, resulting in high incidence and mortality rates. This disparity in the burden of cervical cancer highlights the impact of unequal healthcare access.

Fortunately, alternative strategies for preventing cervical cancer have been extensively researched and evaluated. The recent availability of two commercially produced vaccines against the human papillomavirus (HPV) provides an opportunity for primary prevention of cervical cancer.

Despite its preventability, in 2020, cervical cancer was reported in 604,127 women worldwide, and 341,831 women died from the disease. Cervical cancer primarily affects the cervix, the lower part of a woman's uterus.

In India, there has been a significant decrease in the age-standardized rates of incidence and mortality of cervical cancer from 1990 to 2019. However, cervical cancer continues to be a major public health issue in the country.

Keywords: Cancer, Cervical Cancer, Immunology

Introduction

Cervical cancer still a pressing global public health concern, especially in low- and middle-income countries (LMICs) where limited healthcare infrastructure hinders the implementation of organized screening and treatment programs. Despite most new cases and deaths occurring in LMICs, Cervical cancer is predominantly caused by persistent infection with specific strains of human papillomavirus (HPV). [1]

Cervical cancer begins in the cervix, the narrow opening connecting the uterus to the vagina, and is comprised of two main regions: the ectocervix and the endocervix. The ectocervix is lined with stratified squamous epithelial cells, while the endocervix is composed of simple columnar epithelial cells. At the junction of these regions lies the "transformation zone," where metaplastic epithelium replaces the

columnar lining. This area is particularly prone to the development of cervical cancer due to its frequent exposure to persistent HPV infection.[2] CC has two primary histological subtypes: squamous cell carcinoma (SCC) and adenocarcinoma. SCC arises from squamous cells in the ectocervix and constitutes approximately 75% of cervical cancer cases. Adenocarcinoma originates from glandular cells in the endocervix that produce mucus. Given that SCC is the predominant subtype of the cancer.[3]

Pathogenesis

HPV infection

Human papillomavirus (HPV), family, the *Papovaviridae*. HPV is a compact DNA virus that lacks an envelope and typically infects either skin or mucosal cells. Its genome, a circular double-stranded DNA, spans around 8 kilobases in size. This genetic material codes for six early proteins that facilitate virus replication, along with two late proteins, L1 and L2, which serve as the viral structural components. especially strains like HPV-16/18, stands out as the primary culprit behind cervical cancer. Factors like engaging in sexual activity with multiple partners or having weakened immune responses to HPV infection, as seen in individuals with immunodeficiency disorders, heighten the risk of developing cervical cancer. The review aims to delve into the mechanisms underlying the disease's development and evolution [4]

Genetics

Carcinogenesis in cervical cancer involves the buildup of genetic and epigenetic changes. These alterations can include mutations, deletions, copy-number variations, and chromosomal rearrangements. Such genetic modifications can lead to either loss or gain of function, playing an important role in the development of cervical cancer.[5]

Loss of heterozygosity (LOH)

Loss of heterozygosity (LOH) plays an important role in tumorigenesis and is seen as a predictive factor in various malignant tumours. Numerous chromosomal regions have been linked to LOH [6]. The loss of function in tumour suppressor genes due to LOH contributes to the development of cancer. For example, LOH in the retinoblastoma gene (Rb) at intron 1 and/or 17 has been reported in 63% of cervical cancer (CC) patients. [7] The region 3p21 has been identified as a target for LOH in CC, with a high number of allelic deletions, indicating the potential presence of tumour suppressor genes in this region. The Ras effector gene RASSF1, located at 3p21.3, may also function as a tumour suppressor gene [8]. The simultaneous presence of RASSF1A hypermethylation and LOH at 3p21 in approximately 67% of CC samples suggests that both hypermethylation and LOH are involved in the inactivation of the tumour suppressor gene. [9]

Oxidative stress

Oxidative stress, which is known to play a role in the development of cervical cancer (CC), arises from an imbalance between oxidants and antioxidants. This imbalance leads to the overproduction of free radicals, specifically reactive oxygen species (ROS), which cause lipid peroxidation and damage to DNA, RNA, and proteins [10] These damages can lead to mutations that accumulate over time and contribute to the transformation of normal cells into malignant ones [11]. It's common to observe increased ROS production in cancer cells. ROS not only have mutagenic effects that can lead to carcinogenesis, but they

also have pro-apoptotic, pro-survival, and mitogenic effects. The oxidative modification of transcription factors and genes involved in cell proliferation and apoptosis by ROS promotes cell division. ROS have been reported to activate the PI3K and hypoxia-inducible factor (HIF) pathways, as well as metabolic adaptations. These activations play a role in cellular proliferation and survival, thereby contributing to tumorigenesis [12].

Oxidative stress, high-risk HPV (hrHPV), and chronic inflammation may work together to cause cervical cancer. The integration of the hrHPV viral genome into the host genome is facilitated by oxidative stress and inflammation, leading to an increase in HPV oncoproteins E6 and E7. These oncoproteins can interact with tumour suppressors like p53 and pRb, ultimately contributing to the development of cervical cancer. [13]

HPV infection triggers inflammatory responses, which disrupt the balance between the production and removal of reactive oxygen species (ROS). An excess of ROS can cause cell damage. Additionally, E6*, a shorter version of the oncoprotein E6, leads to a decrease in the expression of superoxide dismutase isoform 2 and glutathione peroxidase. This results in increased ROS levels, which enhance oxidative DNA damage [14].

The reduced expression of tumour suppressor miR-34a, caused by E6, decreases the expression of TrxR2, an antioxidant, promoting cancer development. The Nuclear factor erythroid 2-related factor 2 (NRF2) is a part of the antioxidant system of the cervical epithelial tissue. It is bound to the Kelch-like ECH-associated protein 1 (Keap1), which mediates the degradation of factors involved in cell survival and apoptosis via the ubiquitin-proteasome pathway. NRF2 is usually expressed at low levels due to the activity of Keap1. [15]

However, exposure to stress causes the modification of cysteine residues on Keap1, leading to the nuclear translocation of NRF2. NRF2 then binds to the antioxidant-responsive elements (AREs), inducing the transcription of antioxidant enzymes and reducing oxidative stress. Overexpression of NRF2 due to the loss of function of the tumour suppressor Keap1 is associated with the development and progression of cancer, as NRF2 promotes proliferation and inhibits programmed cell death. Elevated levels of NRF2 have been reported in SiHa and C33A cervical cell lines.[16]

Hormonal dysregulation

Oestrogen

The steroid hormone oestrogen plays a crucial role in the reproductive, musculoskeletal, cardiovascular, and central nervous systems in both men and women. It's implicated in various cancers, including breast, endometrial, and colon cancer. Oestrogen and its receptor ER α may also play a role in the development, persistence, and progression of cervical cancer, as suggested by HPV transgenic mouse models.[17]

In human models, the role of oestrogen has been hypothesized based on the increased risk of cervical cancer with prolonged use of oral contraceptives containing oestrogen, with or without progesterone, and the higher risk of cervical cancer with an increased number of pregnancies. In contrast to oestrogen, progesterone has been suggested to inhibit cervical carcinogenesis, as evidenced by the decreased risk of cervical cancer in HPV-infected women who used the synthetic progesterone, medroxyprogesterone acetate (MPA).[18]

During the normal physiological process of the menstrual cycle, the epithelial cells in the uterine cervix proliferate and differentiate in response to oestrogen levels, leading to epithelial hyperplasia. ER α is

crucial in mediating the carcinogenic activities of oestrogen, as demonstrated by the failure of HPV transgenic mice deficient in ER α to develop cervical hyperplasia when administered with oestrogen.[19] The binding of oestrogen to its cytosolic receptors induces homo- or hetero-dimerization of ERs. The translocation of the oestrogen-bound ERs to the nucleus then results in the activation or repression of the genes of interest through classical and non-classical pathways. Cervical dysplasia may progress to cervical cancer if left untreated.[20]

Infection by the high-risk subtypes of HPV promotes the abnormal squamous differentiation of cells in the cervical transformation zone, leading to atypical squamous metaplasia, which then progresses to cervical intraepithelial neoplasia (CIN) and ultimately cervical cancer. Alterations of the cervical cancer microenvironment by high-risk HPV oncogenes, with or without oestrogen, can also contribute to cervical carcinogenesis.[21]

Testosterone

Testosterone, an androgen formulated in the ovaries, plays an important role in the female reproductive, cardiovascular, and musculoskeletal systems. There is a positive correlation between testosterone levels and female sexual function, and testosterone may be used to treat sexual dysfunction in women.[22]

A prospective study has indicated a link between invasive cervical carcinoma and free testosterone in premenopausal women, and total testosterone in postmenopausal women. This suggests that testosterone could take part in prognosis of cervical cancer.[23]

The role of testosterone in occurrence of cervical cancer may also be connected to oestrogen, as both testosterone and oestrogen are biochemically closely related. In fact, testosterone serves as the biosynthetic precursor of oestradiol. This close relationship could potentially influence the development and progression of cervical cancer.[24]

Insulin

Insulin-like growth factor 1 (IGF-1) has been linked to the development and progression of cervical cancer (CC) by promoting cell proliferation. It has been found that IGF-1 receptors mostly expressed in CC cells compared to normal epithelial cells. Insulin, which is secreted by the β cells of the pancreatic islets of Langerhans, plays a role in regulating blood glucose levels by facilitating glucose uptake into cells from the bloodstream and managing the metabolism of carbohydrates, lipids, and proteins.[25]

Type 2 diabetes, characterized by insulin resistance and relative insulin deficiency, is a well-known risk factor for cancer and plays a role in tumour development and progression. Hyperglycaemia and hyperinsulinemia encourage cell proliferation and decrease programmed cell death without changing the cell cycle. The binding of endogenous or exogenous insulin to both insulin and IGF-1 receptors leads to glucose uptake into cancer cells and promotes cell proliferation, metastasis, and invasion. A recent systematic review and meta-analysis by Chen et al also reported that diabetes is associated with a worse prognosis for CC [26]

Cortisol

Cortisol, a steroid hormone synthesized in the zona fasciculata layer of the adrenal cortex, is often referred to as the stress hormone. It plays a role in managing stress responses, regulating metabolism, inflammation, and immune responses. When the hypothalamus-pituitary-adrenal (HPA) axis is activated due to stress, cortisol is released from the adrenal cortex, helping the body maintain an alert state.[27]

During periods of chronic stress, elevated glucocorticoid secretion can disrupt cell-mediated immunity by upsetting the balance between type 1 T-helper (Th1) cells and Th2 cells. This favours the humoral immune response mediated by Th2 cells and suppresses the cell-mediated immunity mediated by Th1 cells, which is crucial for clearing high-risk HPV (hrHPV). This can lead to persistent hrHPV infection and contribute to the development of cervical cancer.[28]

A recent study reported that both chronic stress and diurnal cortisol levels are associated with baseline hrHPV positivity and HPV-mediated cervical carcinogenesis.

Mutation

Mutations affecting tumor suppressor genes like p53, Rb, PTEN, and LKB1, as well as oncogenes such as PIK3CA, KRAS, EGFR, and ERBB2, have been identified in cervical cancer (CC). While p53 and Rb mutations are relatively rare in early-stage CC compared to other cancers, they play significant roles in tumorigenesis. Mutations in the p53 gene, particularly in its central DNA-binding domain, result in gene repression due to impaired protein-DNA binding, with single base-pair substitutions being the most common.[29]

PTEN mutations are less frequent in CC but may contribute to its progression and prognosis. LKB1 mutations are implicated in CC progression, with single nucleotide substitutions or microdeletions observed in a substantial proportion of cases.

Among the frequently mutated genes in CC, PIK3CA ranks highest, encoding the p110 α protein, a key component of the PI3K pathway involved in various cellular processes.

PIK3CA mutations are found in a significant percentage of CC cases. KRAS mutations, affecting a GTPase involved in cell differentiation, proliferation, and survival, are also prevalent in CC. ERBB2 mutations have been associated with poorer prognosis in CC compared to wild-type or PIK3CA-mutated cases.[30]

Microbiome

The local microbiota in the female genital tract plays a significant role in both persistent HPV infection and the progression of cancer. A healthy microbiome in the female genital tract is primarily composed of *Lactobacillus* species, which create an environment with low pH that protects against exogenous bacteria and viruses. However, an imbalance in the microbiome, known as dysbiosis, can occur due to various factors such as hormonal fluctuations, hygiene practices, and sexually transmitted diseases (STDs). Dysbiosis may lead to an overgrowth of certain bacteria, affecting overall health and potentially contributing to oncogenesis.

Changes in the composition of the vaginal microbiome, characterized by a decrease in *Lactobacillus* species and an increase in anaerobic bacteria and dominance of *Lactobacillus iners*, have been linked to preinvasive disease and increased severity and invasiveness of disease in patients with cervical intraepithelial neoplasia (CIN). *Lactobacillus crispatus*, which produces lactic acid and protective proteins, is associated with a healthy vaginal microbiome, while dominance of *Lactobacillus iners*, found in CIN patients, produces lower amounts of lactic acid and lacks protective peptide production.

Bacterial vaginosis (BV), which shares similar vaginal microbiome alterations with CIN, such as reduced *Lactobacillus* abundance and increased anaerobe predominance, may be involved in the development of cervical cancer. BV-related complications, including bacterial, mucosal, and immune changes, may increase susceptibility to HPV infection, HPV persistence, and CIN. Dysbiosis weakens defence

mechanisms, increasing susceptibility to viral infections, and elevated production of enzymes associated with BV may facilitate HPV infection. Depletion of lactic acid and decreased anti-inflammatory effects may increase the risk of HIV infection related to cervicovaginal inflammation. While vaginal dysbiosis and gut dysbiosis are associated with cancer development through alterations in normal host responses, further studies are needed to establish their specific roles in cervical carcinogenesis.[31]

Smoking

Smoking is a significant behavioural risk factor for persistent infection by high-risk HPV (hrHPV) and the development of cervical intraepithelial neoplasia (CIN) and eventual cervical cancer (CC), along with other risk factors. While both squamous cell carcinoma (SCC) and adenocarcinoma of the cervix share common risk factors such as increased sexual partners, younger age at first sexual encounter, and prolonged use of oral contraceptives, smoking specifically increases the risk for SCC but not adenocarcinoma

Several mechanisms have been proposed to explain how cigarette smoking contributes to cervical carcinogenesis. These include exposure of cervical epithelial cells to carcinogenic components of tobacco smoke, such as nicotine, cotinine, polycyclic hydrocarbons, and aromatic amines. Interaction between carcinogens in cigarette smoke, such as benzopyrene (BaP), and HPV may enhance HPV persistence and promote carcinogenesis. Carcinogens in cigarette smoke may also induce changes in the immune system, such as altered T lymphocyte levels and activity, decreased levels of circulating immunoglobulins (except IgE), and increased risk of acquiring or persisting HPV infection.[32]

Diet

The association between food intake and the occurrence of various cancers, including cervical cancer (CC), has been studied, but significant validation remains limited due to hormonal dysregulation, which is a major factor in many women's health disparities. Seven important hormones regulate women's overall health, and they are significantly associated with certain categories or groups of foods.

Studies have examined the relationship between dietary patterns and CC from different perspectives. For example, a higher risk of cervical intraepithelial neoplasia (CIN) has been observed in individuals with maximum consumption of a semi-western diet, characterized by a higher intake of bread, dairy products, eggs, soft drinks, and fats. Unhealthy dietary patterns, characterized by higher intakes of snacks, fatty dairy products, French fries, mayonnaise, soft drinks, sugars, refined grains, solid oils, nuts, and boiled potatoes, have been significantly associated with HPV infection and CC.

These diets, high in saturated fatty acids, n-6 polyunsaturated fatty acids, and simple carbohydrates, are associated with inflammation, which act as an important role in cervical carcinogenesis. Patients with CC often exhibit markedly elevated levels of inflammatory markers such as sTREM-1, TNF α , IFN β , IL-1 β , and IL-6 compared to healthy controls. Conversely, the consumption of fruits, vegetables, and green tea has been found to provide protective effects against cervical carcinogenesis. Antioxidants, vitamins, and carotenoids found in these foods act as preventive and reductive factors for CC. [33]

Epidemiology

The study aimed to estimate the five-year survival rates of cervical cancer recorded cases between 2012 and 2015 in India using data from Population Based Cancer Registries (PBCRs). A total of 5,591 single primary incidence cases were followed up until June 30, 2021, through various methods including hospital

visits, telephone calls, home or field visits, and public databases.

The five-year Observed Survival (OS) and Age Standardised Relative Survival (ASRS) were calculated. The overall five-year ASRS for cervical cancer was 51.7% (95% CI: 50.2%–53.3%). Among the PBCRs, Ahmedabad urban had the highest survival rate at 61.5% (95% CI: 57.4%–65.4%), followed by Thiruvananthapuram at 58.8% (95% CI: 53.1%–64.3%) and Kollam at 56.1% (95% CI: 50.7%–61.3%). In contrast, Tripura had the lowest overall survival rate at 31.6% (95% CI: 27.2%–36.1%) [34] Furthermore, the five-year OS percentages for pooled PBCRs were 65.9%, 53.5%, and 18.0% for localised, regional, and distant metastasis cases, respectively. This data provides valuable insights into the survival outcomes of cervical cancer patients in India and highlights regional variations in survival rates, underscoring the importance of targeted interventions for improved outcomes. [35]

Screening and early detections

Screening is done for the possible early detection of the cancer hence the credibility of the infection is known therefore according to that the further treatment is prescribed. The various methods of screening of the cervical cancer are listed below,

Pap smear

Pap screening is recommended beginning at age 21, at age 30, HPV testing starts in conjunction with Pap smear cytology. Screening is recommended every 3 years for women with continued negative screening results and those at low risk for cervical cancer. For women older than 30 years, cytology can be done every 5 years with HPV testing, for women with low-risk status and consistently negative screenings is discontinuing cervical cytology and HPV testing at age 65. Women who have had a total abdominal hysterectomy, including removal of the cervix for benign disease, do not require subsequent screening.[36] During pap examination, patient laid on the examination table, knees bended and supported to the end of the table. The pathologist uses a speculum for opening of vagina to see the cervix. A soft, narrow brush or tiny spatula is used to collect a small sample of cells from cervix.

Computer aided detection techniques

The traditional methods of screening of cervical cancer i.e. pap smear examination which focuses on the microscopic examinations of cervical cells.

Hence this method is not sensitive as compared to modern methods of detection techniques the problem arises in this traditional method is that it fails to detect precancerous lesions, leading to false negative results and delayed diagnosis, hence the foundation laid to give emphasis on the computer detection technologies to enhance cervical cancer screening, the effectiveness and reliability of the CAD system is still being evaluated.[37]

Machine learning algorithm imaging system

Early CAD system uses image processing techniques in this process digital images are processed and analysed further; new CAD technologies include Machine learning (ML) algorithms used in the field of cervical cancer detection technologies allowing more accurate analysis of the microscopic images, hence sensitivity and specificity increase from traditional methods.[38]

Colposcopic imaging system

A clinical trial assesses a quantitative colposcopic imaging system intended for early cervical cancer detection. This system utilizes living human cervixes to examine the kinetics of the acetowhitening process, offering diagnostic insights. The imaging method relies on 3D active stereo vision and motion tracking. A diagnostic algorithm allows for distinguishing between normal and HPV-infected tissues, as well as low-grade and high-grade cervical cancer lesions, achieving a sensitivity of 91% and a specificity of 90%. These findings suggest that the quantitative colposcopic imaging system could offer unbiased screening and diagnostic information for early detection of cervical cancer.[39]

Positron emission tomography (PET)/computed tomography (CT)

A PET scan employs a mildly radioactive sugar variant, FDG, which is introduced into the bloodstream and primarily accumulates in cancer cells. Frequently, a PET scan is performed concurrently with a CT scan using a specialized machine capable of both procedures. This dual approach allows physicians to compare regions of heightened radioactivity, offering both anatomical and functional insights about body cells and tissues in one imaging session.

In discussion of locally advanced cervical cancer, use of 18 F-fluorodeoxyglucose (FDG) PET/CT has become crucial in the early analysis of disease progression. It surpasses other imaging techniques in evaluating lymph node status and distant metastasis. Consequently, PET scanning can aid in determining the extent of cervical cancer involvement, identifying the spread of cervical cancer to nearby lymph nodes and other organs like the lungs or liver, and contributing to a more precise or accurate diagnosis.[40]

Treatment

Most cervical cell alterations caused by HPV are temporary, with 90% naturally resolving within 12 to 36 months as the immune system eradicates the virus. The initial immune response to HPV infection is a cell-mediated reaction triggered at local lymph nodes. Although a humoral immune response also forms, the local concentrations of HPV-specific IgG and IgA in the tissue do not align with the clearance of the virus [41].

The surgical method of treatment also follows for treatment of the cervical cancer, but it depends upon numerous factors such as size, stage, histological features lymph node condition these procedures also involved post-surgical complications associated with them.[42]

The common surgical procedures associated with the treatment of cervical cancer are as follows

Cryotherapy

In cryotherapy, the abnormal tissue and an additional 5 mm surrounding it are frozen using an extremely cold probe. Typically, a single freeze is insufficient to cause cell death, so the area is permitted to thaw before being frozen again. Cryotherapy had an advantage that the wound heals faster and with less tissue distortion [43]

Cervical conization

Cervical conization is generally recommended for patients diagnosed with Carcinoma in Situ (CIS) or stage IA1 invasive cervical cancer. This procedure involves the use of a scalpel or laser to perform a cold knife cone (CKC) excision, which removes the transformation zone of the cervix and a part of the cervix itself, ensuring a margin of at least 3 mm.

The examination of the margins for pathological changes and the determination of the presence or absence of lymphovascular invasion (LVI) are crucial. If there is a positive margin or LVI, re-excision or a more invasive surgical procedure may be necessary.

In the absence of LVI in the specimen, the likelihood of lymph node involvement is extremely low, making nodal evaluation unnecessary. Patients with no adverse pathological findings can be monitored. While recurrence rates are typically less than 10%, patients need to be closely followed with regular colposcopy and cytology. The five-year survival rates are over 95%. Potential complications include bleeding, infection, cervical insufficiency, cervical stenosis, and infertility, with the complication rate varying between 2% and 12% [44]

Radical trachelectomy

Patients with more adverse pathologic conditions as well as desire of future fertility Undergo this type of surgery.

The procedure involves the removal of a significant portion of the cervix, resection of the parametria, and mobilization of the ureters, bladder, and rectum. A 5-mm segment of the cervix is retained for cerclage placement, facilitating future pregnancies. Given the heightened risk of nodal involvement, a lymph node assessment typically accompanies a radical trachelectomy [45]

Extrafascial hysterectomy

Extrafascial hysterectomy, also referred to as a Type A radical hysterectomy, is typically indicated for a limited set of clinical conditions. This surgical procedure is generally recommended for patients diagnosed with stage IA1 disease who do not wish to retain their fertility. It involves the complete removal of the cervix and uterus. Since the removal of the ovaries is optional, ovarian function can be maintained. The procedure does not involve the resection of the parametria.[46]

Radiation oncology

Radiation therapies are important considered in treatment of cervical cancer. Radiotherapy treatment depends upon the stage of the cervical cancer.

Early stage of cervical cancer

Radiotherapy can be employed as the primary treatment method for early-stage cervical cancer External beam radiotherapy (EBRT) combined with a brachytherapy (BT) boost results in less morbidity and has comparable 5- and 20-year overall survival rates (83% and 75%, respectively) when compared to radical hysterectomy.[47]

Advanced cervical stage

Diseases that are locally aggressive and/or have positive nodes are usually managed with definitive concurrent platinum-based chemoradiotherapy, followed by a boost from brachytherapy (BT). The integration of chemotherapy with definitive radiotherapy has led to a significant enhancement in overall survival compared to using radiotherapy alone.[48]

Cervical cancer algorithm. *Abbreviations:* BT = brachytherapy; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; LND = lymph node dissection; RT = radiation therapy.

HPV vaccines

The HPV vaccine provides enduring and dependable protection against the most common types of HPV infections associated with cancer. HPV 16 and HPV18 are strains known to carry a high risk of causing cancer.

The incidence of cervical precancers in young women has decreased because of HPV vaccination. Early vaccination is a practical and safe strategy to prevent HPV. Vaccines stimulate cell-mediated immunity. The vaccine is more effective when administered at a younger age. It's important to note that while it can prevent cervical cancer, it cannot treat it.

The primary demographic for HPV vaccination is young women aged 15 to 26, hence it's recommended to get vaccinated within this age range. However, it's not advised for pregnant women to receive these vaccines. The HPV vaccine works by prompting the body to produce antibodies that, upon future encounters with HPV, bind to the virus and prevent it from infecting cells. Vaccination can prevent approximately 70% to 90% of all HPV-related cancers. Women between the ages of 25 and 65 are advised to undergo screening. There are several HPV vaccines available in the market, including Gardasil 9 nonvalent vaccine, Cevaxix bivalent vaccine, and the Gardasil quadrivalent vaccine. The Gardasil vaccine, which is available on the market, is administered in three doses that do not need to be repeated in one's lifetime. The recommended dosing schedule is two months between the first and second doses (with a minimum of four weeks), six months between the first and third doses (with a minimum of 24 weeks), and a minimum of 12 weeks between the second and third doses.[49]

Mechanism of action HPV vaccines

HPV vaccines are known to stimulate both B-cell and T-cell responses, but they are believed to work primarily, if not solely, by triggering the production of antibodies that attach to the virions, thereby preventing the initial infection.[50]

The systemic antibodies, predominantly immunoglobulin (Ig)G, which are induced by intramuscular injection, can reach the sites of cervicovaginal infection through two mechanisms. One is the transudation of IgG across the epithelial barrier into mucosal secretions via the neonatal Fc receptor, a process that is particularly noticeable at the cervix.[51]

The second mechanism involves the direct exudation of serum and interstitial antibodies at trauma sites, which allows virion binding to the basement membrane, a step that seems crucial for initiating the infection process. [52]

Types of HPV vaccines

Quadrivalent HPV Vaccine:

- The quadrivalent HPV vaccine targets four different types of HPV: HPV 6, 11, 16, and 18.
- HPV 6 and 11 are known to cause about 90% of genital warts cases.
- HPV 16 and 18 are responsible for approximately 70% of cervical cancers and a significant portion of other HPV-related cancers, such as cancers of the anus, vagina, vulva, and oropharynx.
- The vaccine is typically administered in a series of three doses over six months.
- Gardasil™, manufactured by Merck, is an example of a quadrivalent HPV vaccine.

1. Bivalent HPV Vaccine:

- The bivalent HPV vaccine targets two HPV types: HPV 16 and 18.
- These two HPV types are responsible for a large majority of cervical cancer cases worldwide.

- The vaccine is also administered in a series of three doses over six months.
- Cervarix™, produced by GlaxoSmithKline, is an example of a bivalent HPV vaccine.

Both types of HPV vaccines are based on similar technology and are designed to trigger the immune system to produce antibodies against the targeted HPV types. By inducing immunity, these vaccines help prevent HPV infection and reduce the risk of HPV-related diseases, including cervical cancer, genital warts, and other cancers caused by HPV. It's important to note that while these vaccines are highly effective, they do not provide protection against all HPV types, nor do they treat existing HPV infections or related diseases. Therefore, routine screening for HPV and cervical cancer remains important, even for individuals who have been vaccinated.[53]

Efficacy of vaccines

The efficacy of HPV vaccines refers to their ability to prevent HPV infection and associated diseases, such as cervical cancer, genital warts, and other HPV-related cancers. Here's an elaboration on the efficacy of HPV vaccines:

Prevention of HPV Infection:

HPV vaccines are highly effective in preventing infection with specific HPV types targeted by the vaccines. For example, the quadrivalent HPV vaccine provides protection against HPV types 6, 11, 16, and 18, while the bivalent vaccine targets HPV types 16 and 18.

- Clinical trials have demonstrated that HPV vaccines can significantly reduce the risk of acquiring HPV infections caused by the targeted HPV types. Reduction in HPV-Related Diseases.
- HPV vaccines have been shown to substantially reduce the incidence of HPV-related diseases, including cervical precancerous lesions (CIN), cervical cancer, genital warts, and other HPV-associated cancers.
- Studies have found that HPV vaccination can significantly decrease the prevalence of high-grade cervical lesions (CIN2/3) and cervical cancer in vaccinated populations.
- In addition to providing protection against the specific HPV types included in the vaccines, some HPV vaccines have demonstrated cross-protection against closely related HPV types not covered by the vaccines. This means that vaccinated individuals may also have reduced risks of infection with certain non-vaccine HPV types.
- Long-term follow-up studies have shown that HPV vaccines provide durable protection against HPV infection and related diseases. The vaccines have demonstrated sustained efficacy for up to several years after vaccination.
- While the duration of protection provided by HPV vaccines is still being studied, current evidence suggests that vaccinated individuals maintain high levels of immunity against HPV for an extended period.

Overall, HPV vaccines have proven to be highly effective in preventing HPV infection and reducing the burden of HPV-related diseases. Wide-scale vaccination programs have the potential to significantly decrease the incidence of cervical cancer and other HPV-associated conditions, leading to improved public health outcomes.[54]

Dosage and schedule

The vaccine is administered as a 0.5 mL dose via an intramuscular injection, in the deltoid muscle or the thigh. It comes as a sterile suspension for injection, available in single shot container or already finned

syringe. Before use, the vaccine must be thoroughly shaken. It's important to adhere to the manufacturer's guidelines for storing and administering the vaccine.[55]

The recommended age for initiating HPV vaccination ranges from 9 to 12 years old, with the option for catch-up vaccination until the age of 26. Both Gardasil™ and Cervarix™ are typically administered in a series of three doses. Gardasil™ doses are spaced at 0, 2, and 6 months, while Cervarix™ doses are given at 0, 1, and 6 months. The intervals between doses should be at least 4 weeks between the first and second doses, 12 weeks between the second and third doses, and 24 weeks between the first and third doses. HPV vaccines can be administered concurrently with other vaccines like Hepatitis B and Tdap. Currently, there's no available evidence supporting the necessity of booster doses [56].

Side effects of vaccines

The HPV vaccine often results in minor side effects mild - moderate pain in 83% of recipients, swelling with redness in 25%, extra side effect like fever in 4% of those vaccinated. No finding of serious adverse events related to the vaccine. Currently, the HPV vaccine is not approved for use in females under 9 years or over 26 years of age, or in males. It's not recommended for individuals with a known immediate allergic reaction to component of the vaccine. it's recommended to postpone vaccination. The vaccine can be administered while the patient is seated or lying down, and it's advised to monitor them for 15 minutes post-vaccination to watch for signs of fainting [57].

It is not recommended for expectant mothers due to insufficient data, even though there's no established connection to negative effects on pregnancy. Any instance of the vaccine being administered during pregnancy should be reported immediately. Nonetheless, nursing mothers and women with compromised immune systems are still eligible to receive the vaccine, although the effectiveness and immune response might be diminished in those with weakened immunity [58]

Future approach for the HPV vaccination programme

Although advancements in the development of the HPV vaccine are encouraging, it might take ten years or max to the vaccine becomes globally available and economically viable. Hence, regular screening remains crucial to diagnose and provide measures of treatment who were infected before administration of vaccines or with whole virus which was not targeted by the vaccine.[59]

There's a need for additional research to understand various facets of HPV vaccines, such as how long they provide protection, whether booster doses are necessary, their effect on the occurrence and prevalence of HPV types targeted by the vaccine, and their safety for pregnant women. Further studies are also required to evaluate the concern and effects when HPV vaccines are given with other vaccines. It's important to determine the effectiveness of these vaccines in women over 26 years old and in men, and to explore the potential benefits of routine HPV vaccination in men for preventing genital warts and the emergence of less common HPV types after the prevalent ones are controlled. Moreover, the effect of HPV vaccines on cervical cancer detection techniques, safe sexual behaviours, and further socio-economic audits are crucial areas for future research. The typical target group for vaccination is pre-pubertal girls aged 9–10 years, which brings up social and cultural considerations. Particularly in India, there's an urgent need for epidemiological studies to assess the long-term effectiveness, logistical hurdles, and economic consequences of implementing universal HPV vaccination programs for eligible females.[60]

Conclusion

Cervical cancer continues to be a significant health concern in developing countries, with a broad range of incidence and mortality rates across different regions worldwide. Persistent infection with the sexually transmitted Human Papillomavirus (HPV) is the primary cause of cervical cancer. Consequently, factors linked to acquiring HPV infection or having a weakened immune response to HPV infection heighten the risk of cervical cancer. Elements such as genetics, epigenetics, microbiota, environmental factors, and hormonal influences play a role in the onset and progression of cervical cancer. With a deeper understanding of the disease's pathogenesis, we can establish effective prevention strategies and treatment options to reduce the impact of cervical cancer.

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