REVIEW ON CERVICAL CANCER

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Abstract

Cervical cancer is one most common gynaecological cancer occurring in women. It is also one of the commonest cancers of woman that can be detect and treated completely at precancerous stages. STD is main cause of cervical cancer and also due to the Human Papillomavirus (HPV), mainly HPV-16 and HPV-18. It continues to be major public health troubles for female in India. The incidence of cervical cancer is 55-59 years and a considerable proportion of women report in the late stage of disease. Prophylactic vaccines against HPV-16 and 18 therapeutic vaccines in opposition to cervical cancer. Other epiderma logical risk factor is premature at sexual activity, Teen age pregnancy, Family past, Oral contraceptive. This article, explain history of cervical cancer, histopathological variety, risk factor, avoidance, treatment and Drug approved to prevent cervical cancer. The most common type of cervical cancer is called Squamous cell carcinoma. Vaccine is helpful only in people who have no previous infection with HPV.

Key words: *Cervical cancer, Human papilloma virus Treatment, Prevention, Etiology, Pathophysiology, Symptoms, Diagnosis.*

INTRODUCTION:

History of Cervical Cancer: The first description of cervical cancer was found in 400 B.C. by the Greek physician Pericles Hippocrates. It was considered in curable at the time until. Some 2000 years later, the opinion of the pathogenic mechanism was recognized through pioneer work by an Italian surgeon. During in the mid 19 th century, Dr. Rigoni Stern noticed that the incidence of cervical cancer was rare among nuns (Rigoni-stern, 1842). All these works have indications that the causation of cervical cancer is linked with sexual intercourse. Hence cervical cancer was considered highly transmissible. Transmitting agents was only reported later in 1976 publication by German Scientist Zur Hausen where they discovered human papilloma virus (HPV) DNA in cervical cancer and warts. In 1985 Zur Hausen, Gissmann and their co-workers further identified the structure and sequence of HPV. Further later discovery of HPV vaccine led to the milestone in curing the disease. In 2020, an estimated 10 million cancer-related deaths were reported making it one of the leading causes of death globally. Although this number is predicted to increase worldwide, the rise is expected to occur predominantly in low- and middle-income countries (LMICs) as they currently face the greatest challenges in tackling the cancer burden. Globally, cervical cancer is the fourth most common female cancer after breast, colorectal, and lung cancer and accounts for 600 000 new cases and 340 000 deaths annually Importantly, approximately 83% of all new cervical cancer cases and 88% of all deaths occur in LMICs. Indeed, cervical cancer is the leading cause of cancer-related deaths in 36 countries which includes regions such as sub-Saharan Africa, Latin America and India. This burden needs to be contextualised in terms of socio-economic conditions, health care infrastructure and competing health needs, which are not only risk factors of this disease, but significantly impact its prevention and management. It is concerning that despite important advances in our understanding of cervical cancer as a potentially preventable disease, there have yet to be major improvements in patient survival and therefore the disease burden remains high the single most important etiological agent of cervical cancer is infection by high-risk Human Papillomavirus

(HPV). Indeed, persistent infection with high-risk HPV types is responsible for up to 99.7% of cervical cancer cases. The link between HPV and cervical cancer was established in the last 30 years based on the detection of HPV type 16 in cervical cancer tissue by Harald Zur Hausen. HPV is estimated to infect around 291 million women worldwide, with a particularly higher prevalence in women younger than 25 years. The estimated worldwide prevalence of HPV among women with normal cytology is 11.7%, but there is considerable geographic variation with sub-Saharan Africa having the highest HPV prevalence (24.0%). Sub-Saharan Africa also has a high burden of HIV with over 70% of all global HIV positive individuals residing in sub-Saharan Africa. There is compelling evidence that women infected with HIV are at increased risk of persistent infection with multiple types of HPV at an early age (13–18 years) These factors lead to an increased risk of developing cervical cancer at an earlier age. Indeed, HIV infected individuals have a 6 times higher risk of developing cervical cancer when compared to the general population. Furthermore, in a study in South Africa between 2001 and 2009, the increase in cervical cancer incidence could be explained by the increased number of HIV infections observed during this period. Moreover, the increased number of HIV positive women receiving anti-retroviral therapy results in improved life expectancy and therefore they have to be adequately screened because they have a higher risk of developing cervical cancer.

2. Initiation and progression of cervical cancer: Cervical cancer originates in the cervix which is the narrow opening into the uterus and is connected to the vagina through the endocervical canal. The cervix is divided into the ectocervix and endocervix and while the ectocervix is covered with stratified squamous epithelial cells, the endocervix consists of simple columnar epithelial cells. Stratified squamous and columnar epithelium form the squamocolumnar junction in the endocervical canal. The area where these regions meet is called the "transformation zone", which consists of metaplastic epithelium that replaces the columnar lined epithelium of the endocervix. This zone is the most likely site for the development of cervical cancer because it is a major site of premalignant transformation via persistent HPV infect

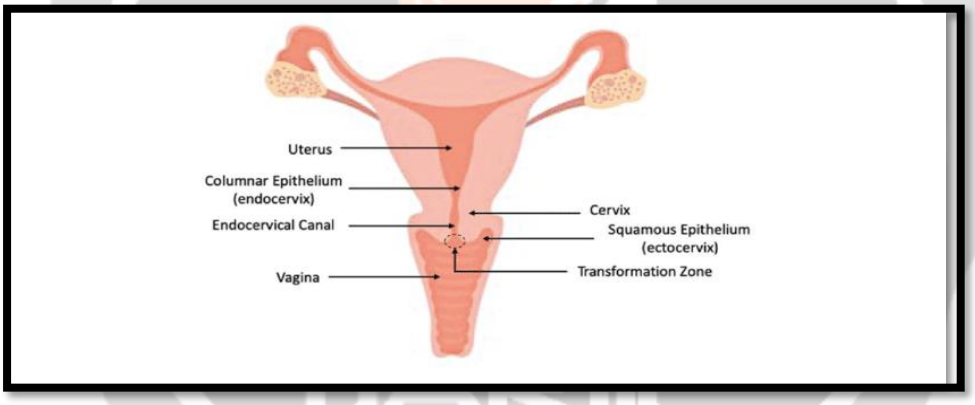


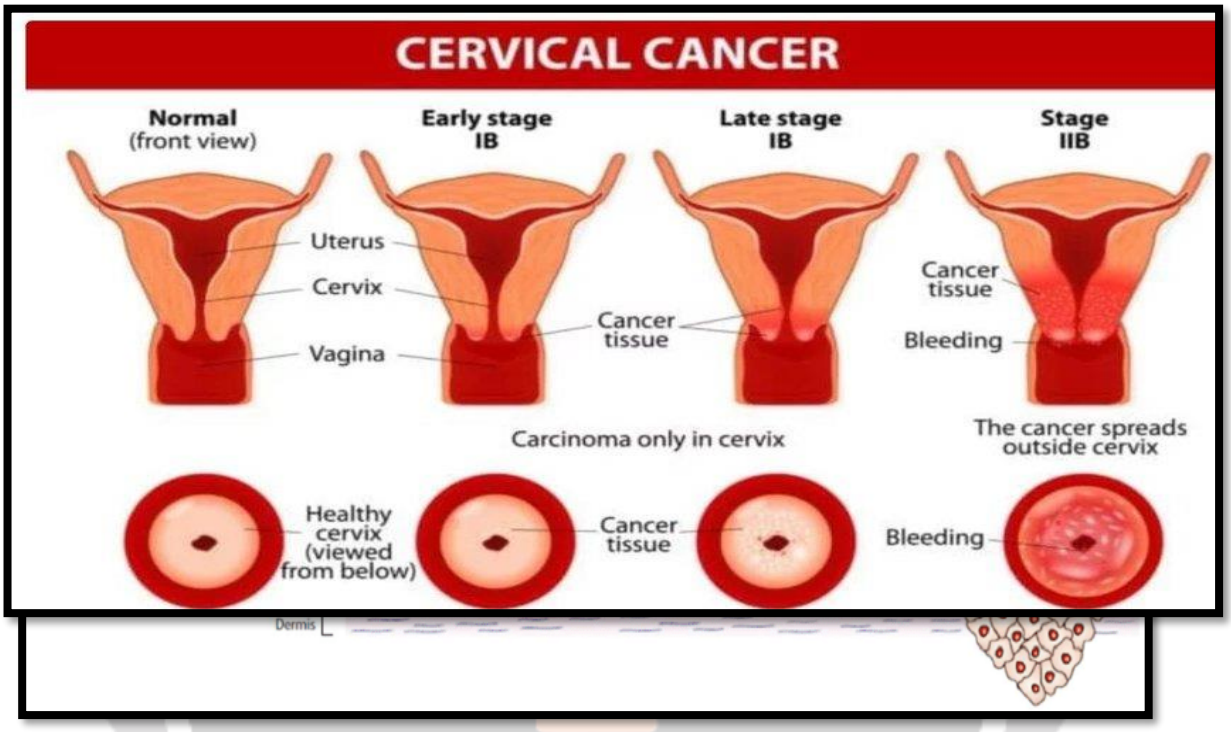
Figure: 1 Anatomy location of cervical cancer origin progression from an invasive normal squamous cell carcinoma mediated by HPV

There are two major histological sub-types of cervical cancer, squamous cell carcinoma (SCC) and adenocarcinoma. Whereas SCC develops from squamous cells in the ectocervix and accounts for approximately 75% of cervical carcinoma cases, adenocarcinoma originates from glandular cells that produce mucus in the endocervix. As SCC is the major subtype, this review will focus on describing its progression During SCC progression, squamous cells in the cervical epithelium undergo dysplastic changes following HPV infection and these precursor lesions are referred to as cervical intraepithelial neoplasia (CIN). The majority of HPV infections clear within a few years after exposure and only 10–20% of persistent infection potentially leads to the development of cervical cancer. Indeed, in South Africa, a number of cross-sectional analyses have revealed that between 60 and 80% of women test positive for HPV infection, while an age standardized rate of 30.2 cases per 100 000 women are diagnosed with cervical cancer. Upon establishment of persistent infection, HPV can integrate into the host genome with 80% of HPV 16- and 100% of HPV 18-positive cervical carcinomas displaying viral integration. It is worth noting, that a small percentage of women who are HPV positive develop cervical cancer in the absence of viral DNA integration and in these cases the HPV DNA remains in its episomal form. The viral E5, E6 and E7 proteins contribute to the induction and maintenance of the cervical cancer phenotype by exploiting host cell machinery. Indeed, E5 does this by regulating and interacting with, among other host growth factor receptors, the epidermal-growth-factor receptor (EGFR), the platelet-derived growth-factor-β receptor and the

colony-stimulating factor-1 receptor. E5 was also shown to prevent apoptosis following DNA damage by disrupting the host FAS receptor and degrading the proapoptotic factor BAX. In addition, E5 aids in the immune evasion of infected host cells by reducing the surface expression of major histocompatibility complex (MHC) class I and II as well as the surface receptor CD1d. E6 and E7 promote cervical cancer by disrupting cellular checkpoints and co-operating with host factors, including tumour suppressors and tumour promoters.

Figure:2 Stages of Cervical cancer

For example, E6 and E7 mediate malignant transformation through degradation of p53 and inactivation of



retinoblastoma (pRb) tumour suppressor proteins, respectively. When the HPV DNA integrates into host cells, a substantial loss of the HPV genome occurs, including the E5 coding sequence. Viral DNA integration however results in the constitutive expression of E6 and E7 because the E2 repressor protein either cannot bind to the viral upstream regulatory regions (URR) due to methylation, or its open reading frame (ORF) is disrupted. In cervical

Figure:3 Schematic representation of HPV infection and cervical cancer development

cancer arising from HPV-integration into the host cells, E5 is therefore not a critical player and E6 and E7 are responsible for driving and maintaining the malignant phenotype HPV-infected cervical epithelial cells that undergo transformation, change from being well organised to highly dysplastic and the degree of dysplasia is graded based on severity. CIN1 is characterized by mild dysplasia with the presence of koilocytes (cells with a perinuclear halo and enlarged and irregular nuclei), binucleate cells, and dyskeratotic cells (individual cell keratinisation). CIN2 consists of heterogeneous lesions affecting two thirds of the epithelium, followed by CIN3 which represents severe dysplasia and affects greater than two thirds of the epithelium. The invasive stage of cervical cancer is associated with poor prognosis and involves the spread of cancer cells either by direct extension into the parametrium, vagina, uterus and adjacent organs. While CIN staging refers to the precancerous condition, the most widely used staging method for invasive cervical cancer is the International Federation of Gynaecology and Obstetrics (FIGO) guideline, which is divided into stages I, II, III, and IV. When the cancer spreads beyond the inner lining of the cervix but is still confined to the cervix it is termed

ETHILOGY:

Human papillomavirus (HPV) is a common sexually transmitted infection which can affect the skin, genital area and throat. Almost all sexually active people will be infected at some point in their lives, usually without symptoms. In most cases the immune system clears HPV from the body. Persistent infection with high-risk HPV can cause abnormal cells to develop, which go on to become cancer. Persistent HPV infection of

the cervix (the lower part of the uterus or womb, which opens into the vagina – also called the birth canal) if left untreated, causes 95% of cervical cancers. Typically, it takes 15–20 years for abnormal cells to become cancer, but in women with weakened immune systems, such as untreated HIV, this process can be faster and take 5–10 years. Risk factors for cancer progression include the grade of oncogenicity of the HPV type, immune status, the presence of other sexually transmitted infections, number of births, young age at first pregnancy, hormonal contraceptive use, and smoking.

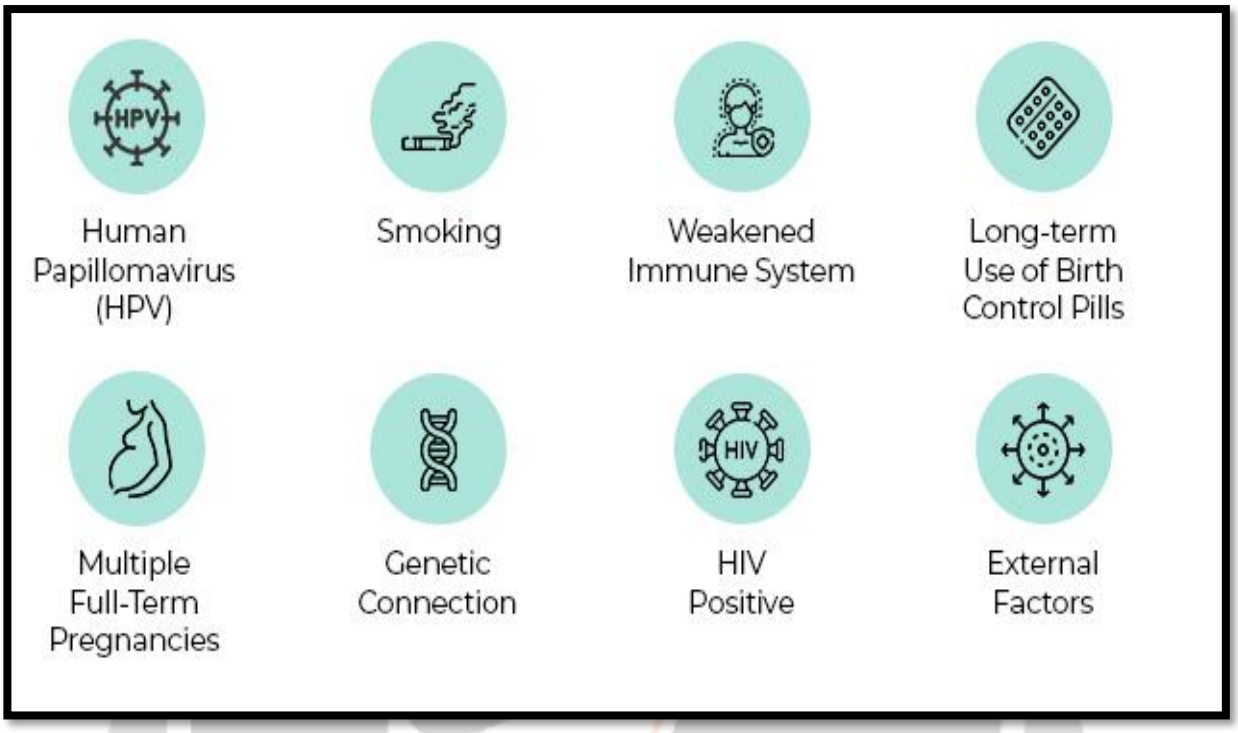


Figure:4 Causes of cervical cancer

EPIDEMOLOGY:

Persistent HPV infection causes more than 99% of all cervical cancers. Every year, there are more than 500,000 new cases of cervical cancer and approximately 250,000 deaths due to cervical cancer worldwide. Eighty percent of cases occur in developing countries. In the United States, about 4000 women die yearly from cervical cancer. Blacks, Hispanics, and women in low-resource areas have more disparity in evidenced-based care and a significantly higher mortality rate. Mortality is higher among women not screened in the past 5 years and those without consistent follow-up after identifying a precancerous cervical lesion. Trends show that women with the highest-mortality risk may be less likely to receive HPV vaccination. Globally, cervical cancer is the fourth most common female cancer after breast, colorectal, and lung cancer and accounts for 600 000 new cases and 340 000 deaths annually Importantly, approximately 83% of all new cervical cancer cases and 88% of all deaths occur in LMICs.

DIAGNOSIS:

Visual examination

- **Cystoscopy** is a procedure to look inside the bladder and urethra to check for abnormal areas. A cystoscope is inserted through the urethra into the bladder. A cystoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue samples, which are checked under a microscope for signs of cancer.
- **Sigmoidoscopy** uses a sigmoidoscope to look inside the rectum and sigmoid (lower) colon for abnormal areas. A sigmoidoscope is inserted through the rectum into the sigmoid colon. A

sigmoidoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue samples, which are checked under a microscope for signs of cancer.

- **Colposcopy**

Colposcopy is a procedure in which the health care provider inserts a speculum to gently open the vagina and view the cervix. A vinegar solution will be applied to the cervix to help show abnormal areas. The health care provider then places an instrument called a colposcope close to the vagina. It has a bright light and a magnifying lens and allows the health care provider to look closely at the cervix. A colposcopy usually includes a biopsy.

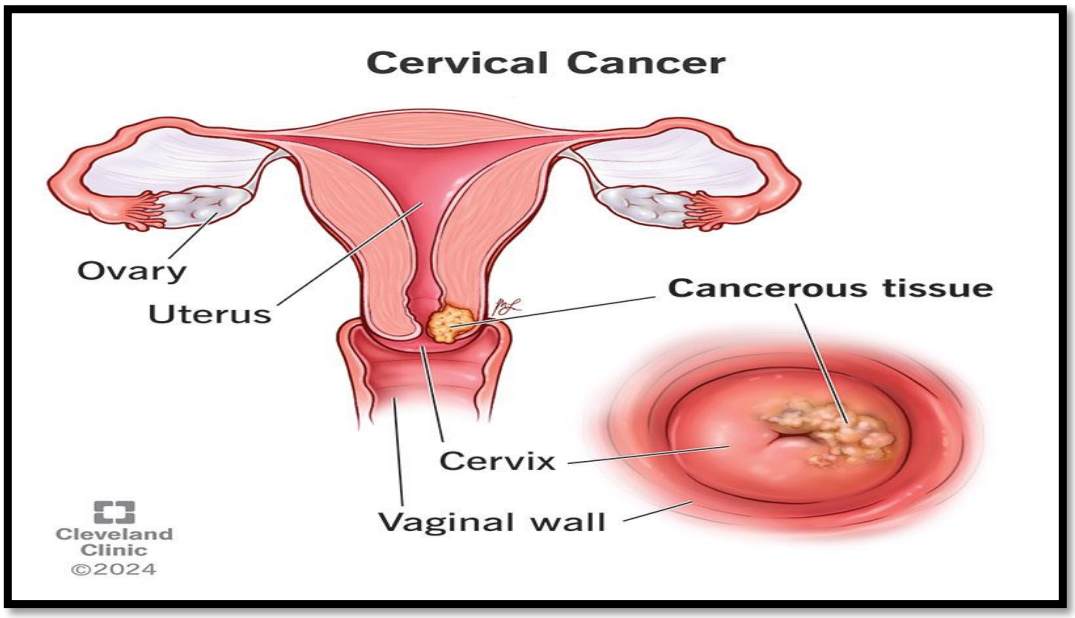


FIGURE:5 Diagnosis image of cervical cancer

Biopsy:

Biopsy is a procedure in which a sample of tissue is removed from the cervix so that a pathologist can view it under a microscope to check for signs of cancer. The following types of biopsies are used to check for cervical cancer:

- **Punch biopsy** is a procedure in which a small, round piece of tissue is removed using a sharp, hollow circular instrument. Sometimes several different areas of the cervix will be checked with punch biopsy. This procedure is usually done in the doctor's office.
- **Endocervical curettage** is a procedure to collect cells or tissue from the cervical canal using a curette (spoon-shaped instrument). This procedure removes only a small amount of tissue and is usually done in the doctor's office.
- **Loop electrosurgical excision procedure (LEEP)** uses a thin wire loop, through which an electrical current is passed, to remove tissue from the cervix. LEEP may be used to diagnose cervical cancer. It also may be used to remove precancer or early-stage cancer. This procedure is typically done in a doctor's office. It usually takes only a few minutes, and local anesthesia is used to numb the area.

- **Cone biopsy** is surgery to remove a larger, cone-shaped piece of tissue from the cervix and cervical canal. A cone biopsy may be used to diagnose cervical cancer. It also may be used to remove precancer or early-stage cancer. This procedure is also called conization. A cone biopsy is done at the hospital under general anesthesia.

SYMPTOMS:

Many women with cervical cancer don't realize they have the disease early on because it usually doesn't cause symptoms until the late stages. When symptoms do appear, they're easily mistaken for common conditions like menstrual periods and urinary tract infections (UTIs).

Typical cervical cancer symptoms are:

- unusual bleeding, like in between periods, after sex, or after menopause
- vaginal discharge that looks or smells different than usual
- pain in the pelvis
- needing to urinate more often
- pain during urination
- Increased vaginal discharge.
- Bleeding after menopause.
- Light bleeding or Blood spots intermittently.
- Longer and heavier menstrual bleeding.
- Pain during sexual intercourse
- Consistent back pain or pelvic pain.

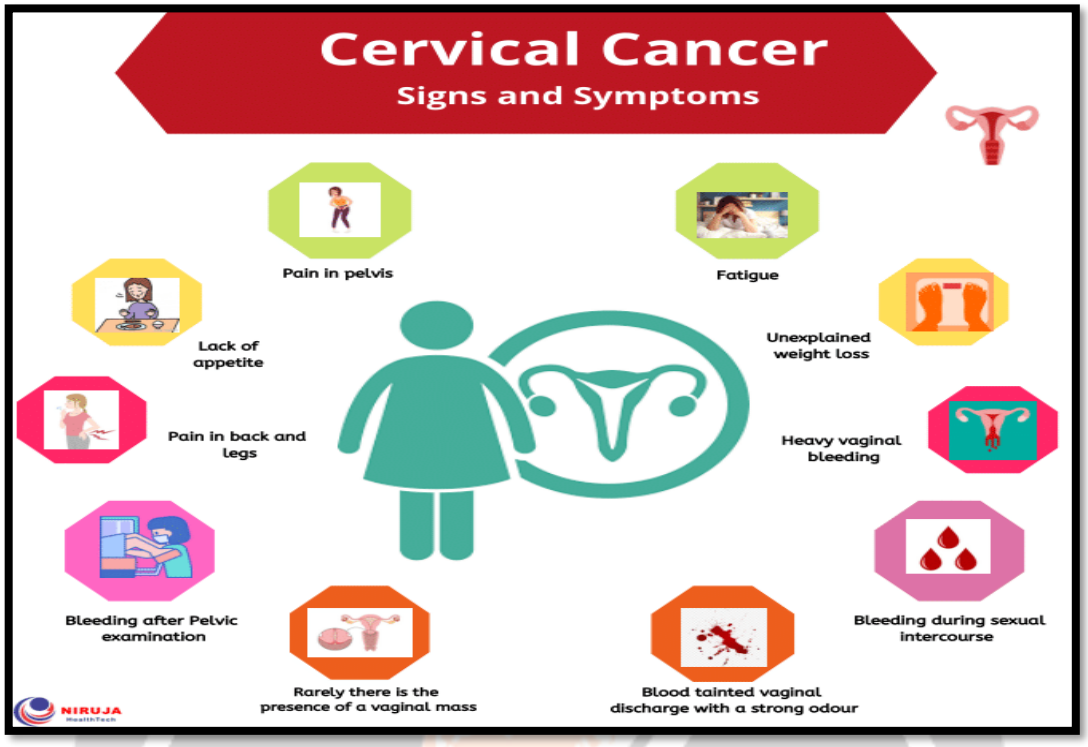


Figure:6 Symptoms of cervical cancer

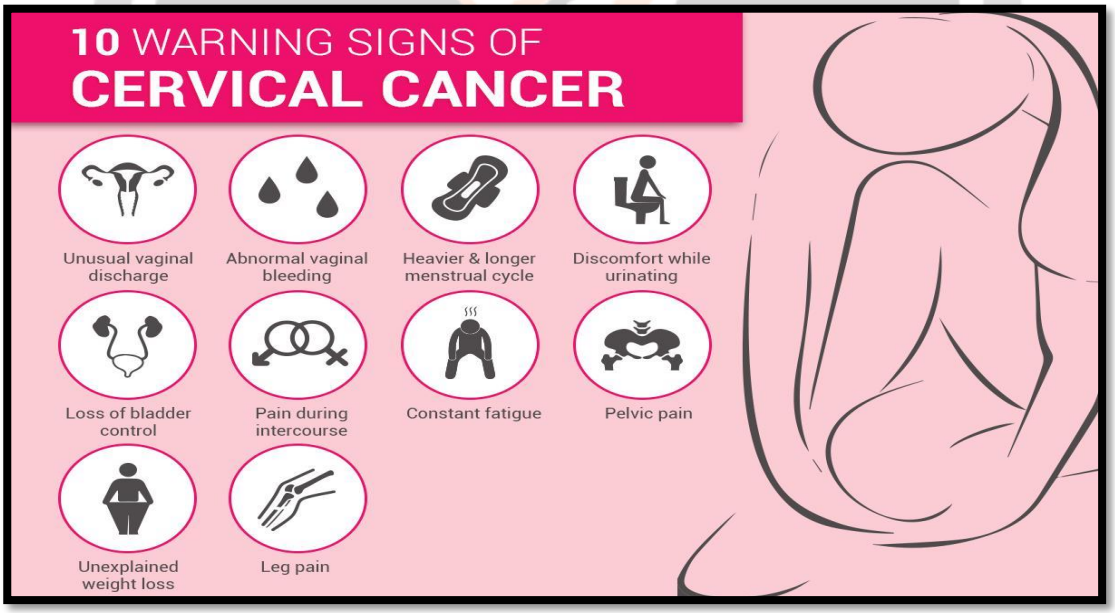


Figure:7 Signs of cervical cancer

PATHOPHYSIOLOGY:

Human papilloma virus:

It has been known since the 1970s that we came to know about the HPV (human papilloma virus) infection, which is one is among the primary reasons for cervical carcinoma. And there are varieties of Papillomavirus that can induce the malignancy of the cervix epithelium.14 Human papilloma virus is rapidly evolving into a global issue, mainly to developing countries, HPV triggering malignancy and the most significant

and common of which is cervical cancer.15Most people consider HPV infection can only spread through sexual activity, still, HPV can also spread by non-sexual routes such as vertical transmission during pregnancy and casual physical contact.16 Human papillomavirus (HPV) has double stranded DNA viruses, they belong to the Popova virus family, comparing to the other virus HPV does not have any envelope to surround its capsid, the diameter of the PV virion is 55 nm, its DNA can replicate within the nucleus and has more than 7900 base pair genome and they are further divided into three groups 1. Early (E1, E2, E3, E4, E5, E6, E7), 2. Late (L1, L2), and 3. Control. These genomes' main functions are to encode viral proteins which are crucial for capsid formation. The outer shell of PVs is called capsid. This capsid possesses different types of symmetry called as icosahedral means it 'shave 20 equilateral triangular faces with roughly spherical shape, they also have subunits called as capsomers approximately 72 capsomers join themselves to create a capsid structure and capsid main function is to provide protection to genetic material.17 Over 200 kinds of HPV virus are recognized for mankind but not all of them cause any serious health issue or development of any kind cancerous cell, however HPV virus divided into five genera: nu (ν), mu (μ), alpha (α), beta (β) and gamma (γ), additionally alpha and beta are thoroughly researched. The alpha papilloma virus group members cause infection in mucosal epithelia, furthermore according to the tendency to induce cancer the alpha papilloma virus separated into kinds that are high-risk (HR) and low-risk (LR). The low hazard virus causes viral infection such as benign tumors, and commonly caused by Ninety percent of genital warts are caused by HPV 6 and HPV 11. means they generally does not cause cancer but on the other hand HPV 16 & HPV 18 are the major reason of the 80% cervix cancer.

TREATMENT:

Surgery is a useful for treatment to most cervical cancer.

- If the cancer has spread locally within the tissue, one of two type hysterectomy may be required. A straight forward hysterectomy that removes the Uterus and cervix will be enough in some Cases.

- **Radical Hysterectomy**: It is necessary to remove the primary connective tissue. (parametrium) and ligaments along with the upper section of the vagina. If necessary either of these surgeries may be done in conjunction with elimination of the fallopian tubes and ovaries, results infertility and removal of the ovaries causes' female directly set into menopause. Lymph nodes may also be detached during the surgery.

- **Radiation Therapy:** It may also use in treatment of cervical cancer frequently in conjunction with surgery. If the cancer is enveloping and spread away from the surface of the cervix.

- **Brachytherapy:** Uses, implanted radioactive rods or pellets to focal point the radiation on the cancer and greatly reduce side effects. Pelvic radiation, therapy may also cause premature menopause. Bladder irritation or a narrowing of the vagina due to scar tissue buildup

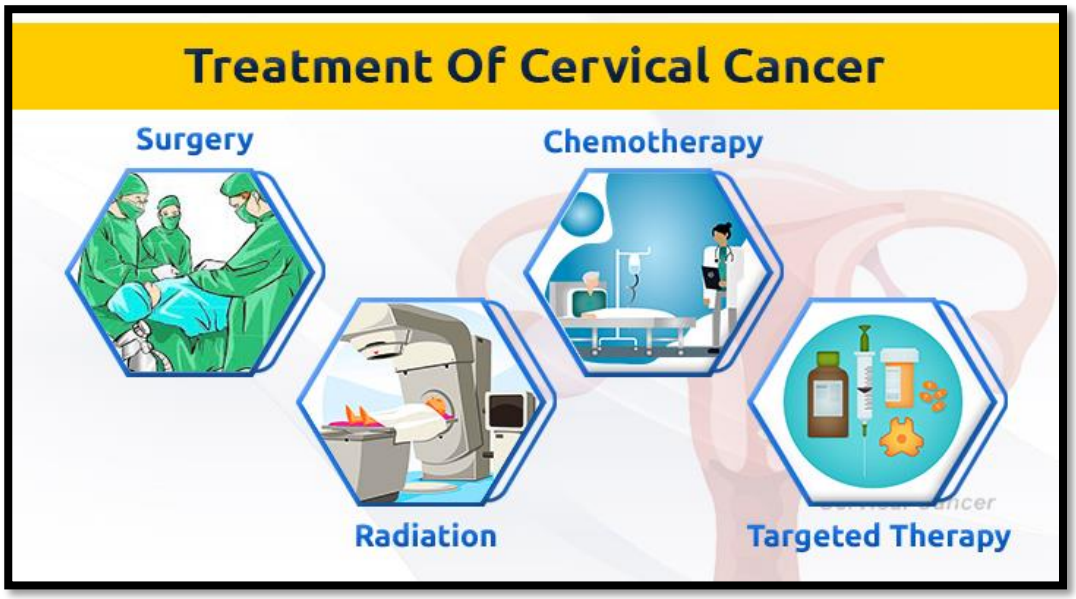


Figure:8 Different types of treatments in cervical cancer

Chemotherapy: It is commonly used in cervical cancer of the uterus. Such chemotherapy is essential to search for and destroy as various cancerous cells as possible Drugs Treatment with drugs that target gene changes in cells causing cancer is often called targeted therapy.

- Cisplatin, carboplatin, (chemotherapeutic agents and bevacizumab) targeted therapy is available treatment choice.

PREVENTIVE MEASURES:

- **Eat healthy and exercise regularly:**

  Eat foods that are high in antioxidants and other cancer-fighting nutrients. Avoid diets that include large amounts of saturated and trans fats, sugar and sodium. Studies have shown that getting at least 30 minutes of exercise a week can help prevent cervical cancer.

- **Get the HPV vaccine:**

  The HPV vaccine is a safe and effective way to prevent cervical cancer. It's recommended for all people, ideally before they become sexually active. The CDC recommends the vaccine for girls and boys at age 11 or 12, but it can be given starting at age 9.

- **Get regular cervical cancer screenings:**

  The Pap test and HPV test are screening tests that can help prevent cervical cancer or find it early. The CDC recommends starting Pap tests at age 21 and repeating them every three to five years.

- **Practice safe sex:**

  Use a barrier method of birth control, such as a condom, during sexual activity. Having sex at an early age increases your risk of HPV, and the more sexual partners you have, the more likely you are to contract HPV.

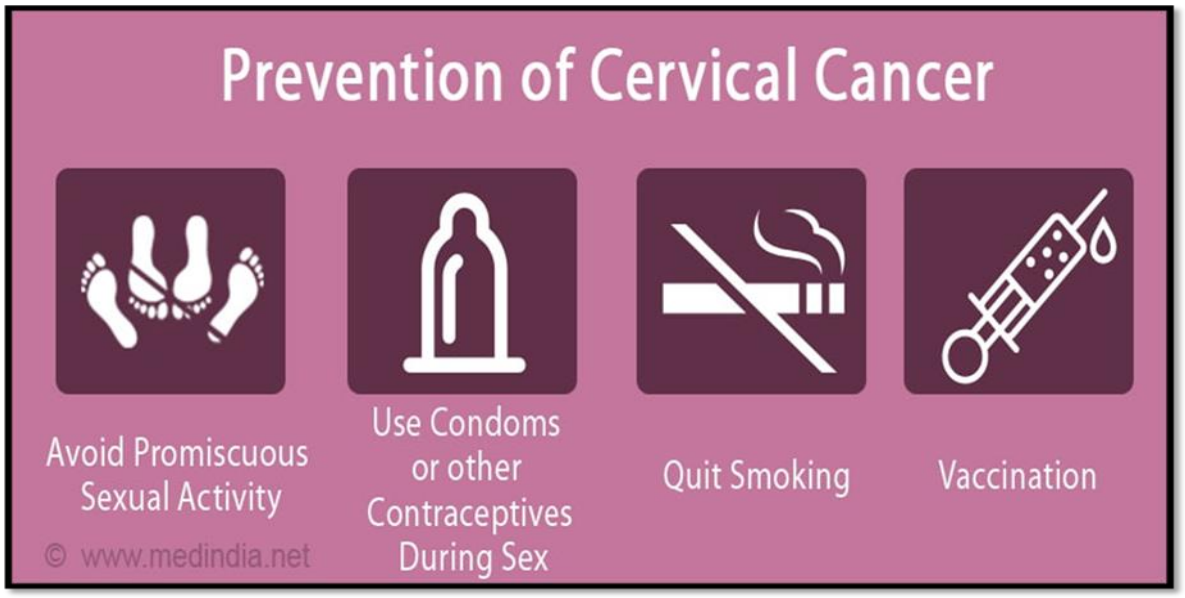


Figure:9 Prevention of cervical cancer

DRUGS USED:

Treatment with drugs that target gene changes in cells causing cancer is often called targeted therapy. Cisplatin, carboplatin, (chemotherapeutic agents and bevacizumab) targeted therapy is available treatment choice

Drug name	Brand name
Cisplatin	Platinol - Platinol
Carboplatin	Par Platin
Topotecan	Hycarmitin
Bevacizumab	Avastin, Mvasi
Cyclophosphamide	-
Ifex	-

Table:1 Drugs used for cervical cancer

CONCLUSION:

Histopathology and immunizationization important for reducing cervical cancer. HPV vaccine is highly efficacious and is probable to significantly reduce the occurrence of abnormal pap smears, cervical cancer and genital warts. Successful implementation of vaccination programs will have a huge support from health care provides great have been made decreasing the cancer rate. Cervical cancer poses a significant global burden and remains a serious therapeutic challenge especially in LMICs where resources are limited and current therapeutic options are often unaffordable and inaccessible. It is therefore essential for all countries to endorse the resolution passed by the World Health Assembly in 2020 calling for the “Elimination of Cervical Cancer” by 2030 through achieving the following 3 targets: (HPV vaccination of 90% of girls by the age of 15 years, screening of 70% of women at 35 years and then 45 years with high-performance tests, and treatment of 90% precancerous lesions and management of 90% invasive cancer cases. Furthermore, current therapeutic options for cervical cancer are associated with debilitating side effects and tumour drug resistance, and despite considerable advancement with the use of combination therapies to improve the efficacy of single-agent treatments, new and improved therapies to treat cervical cancer are still urgently needed. Some examples of alternative therapies that have been explored in cervical cancer include immunotherapy, targeted therapy, and genetic approaches such as CRISPR/Cas9 and RNAi. While these therapies show increasing promise in treatment outcomes, many of them remain investigational and are expensive alternatives. An approach that may lead to rapid and cost-effective drugs is to identify commercially available non-cancer drugs that target the host factors that co-operate with the HPV oncoproteins, particularly E6 and E7, that drive cervical cancer progression. This strategy which combines a targeted approach with drug repurposing is attractive as, compared to conventional anti-cancer therapies, it should identify more efficacious drugs with significantly reduced side effects and because their safety profiles are known they are expected to be rapidly advanced into clinical trials.

REFERENCE:

- Rebecca B Perkins, Nicolas wentzensen, Richard S Guidi, Mark Schiffman, Cervical cancer screening: A Review, Journal of national library of medicine, 2023, 330 (6): 547-558.
- Amrit Nerkar, Review on Cervical cancer, Journal of current trends in pharmacy and pharmaceutical chemistry, 2020, 2(2):39-44

- Carry A. Burmeister, Sai. F. khan, Georgia Schafer, Nomonde Mbatani, Tracey Adams, Jennifer Moodely, Sharon prince, Cervical cancer therapies; Current challenges and future prospectives, Journal of tumour virus research, 2022, 13 (2): 26-76
- Yasmin Medeiros Guimares, Luani Rezendo Goday, Adhemer Longatto-Filho, Ricardo dos Reis, Management of early-stage cervical cancer: A literature review, Journal of national library of medicine, 2022, 14 (13): 572-582
- Tomoko Nakamura, Ayako Sasaki, A literature review regarding cervical cancer prevention targeting junior and senior high school students, Journal of scientific research, 2020, 12(8): 35-65)
- Namra Aziz, Vikrant Abbot, Aishwarya Bajpal, Pranay wal, Ankith wal, Rakesh Varma and Mukesh Chandra sharma, Comprehensive review on cervical cancer, Journal of Bentham science, 2024, 14(20): 2534-265
- Hui juen Hon, Pei pie Chong, Hui Leng choo, Pwint Phyu khine, A comprehensive review of cervical cancer screening devices, Journal of Asian pacific of cancer prevention, 2023,24(7):2207-2215
- Crosbie, Ej. Einstein, MH. Franceschi, S. *etal*, Human papilloma virus and cervical cancer, journal of Lancet, 2013;382(15):889-899
- Paul acohen, MD. Prof anjuajhingram, MD. proff anaoaknin, MD. proff lynette Denny, cervical cancer, Journal of Lancett, 2019, 393(101):169-182
- Nwabichie, chinemeran Cecilia, Rosiliza A.M, Suriani.L, Global burden of cervical cancer: A literature review, international journal of public health and clinic sciences,2017, 4(2);36-46