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INDIAN SCENARIO OF HUMAN PAPILLOMAVIRUS INFECTION: MOST IMPERATIVE RISK FACTOR FOR CERVICAL CANCER

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ABSTRACT: Cervical cancer is one of the common gynecological cancer distressing women. It is also one of the commonest cancers of females that can be detected and treated completely at precancerous stages. The failure to detect cancer in an early stage often leads to high cost of care. Despite of this, so many cervical cancer cases they die every year. The main purpose of this study is to know recent knowledge, advances in screening, prevention as well as optimized management of cervical cancer at an early stage, so as to reduce the burden of deaths resulting from this disease. The topics covered overview of cervical cancer, Functions & mechanism of oncogenes present in HPV, life cycle of HPV, brief classification of cervical cancer, Current cancer scenario in India, cancer therapy options available, HPV Vaccine for prevention and treatment, with an emphasis on advances in the diagnosis and treatment of cervical cancer.

Key words: Cervical cancer, Human Papilloma virus, HPV Vaccine, oncogenes, chemotherapy.

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INTRODUCTION

Cervical Cancer is malignant Carcinoma type of cancer originate in cervix region which is the narrow portion of the uterus where it joins with the top of the vagina. The cervix has two different parts and is covered with two different types of cells.

- The part closest to the body of the uterus is called the endo-cervix and is covered with glandular cells.
- The part next to the vagina is the exocervix *(or* ectocervix*)* and is covered in Squamous cells.

The junction between these two cells types, called the transformation zone, is the usual site of origin of Cervical Cancer as per shown in Figure No .01. The development of Cervical Cancer occurs gradually and the process of pre-cancerous changes (dysplasia) leading onto invasive cancer, generally takes place over years. Cervical cancer has emerged as a second most common cause of cancer deaths among Indian women aged between 15 and 44 years. On average, India reports about 122,000 new cases of cervical cancer annually, with around 67,500 women succumbing to the disease, accounting for 11.1% of total deaths related to cancer. More than 100 subtypes of Human papillomavirus (HPV) that exist, there are certain high-risk subtypes that are associated with causing cervical cancer. High-risk subtypes 16 and 18 of HPV are considered globally as the most widespread reason for cervical cancer for which vaccines are available worldwide including in India. The increasing burden of cervical cancer among women, 62,416 women died of the disease in 2015-16, accounting for 24% of all cancer cases in women in India.3.1% women in India get screened, leaving a large population vulnerable to death from the disease. This is common amongst lower class, less educated and more child women. Persistence of HPV infection is the most important factor in developing cervical cancer. There are more than 100 genotypes of HPV, but only 13 types are oncogenic.

Using animal study human papilloma virus (HPV) 16 E6 and E7 oncogenes in cervical cancer, E7 was identified as dominant oncogene. These HPV are classified into low- or high-risk types according to their presence in malignant lesions of the cervix. Oncogenes inactivate tumor suppressor p53 and/or retinoblastoma protein (pRb) is a event for the carcinogenesis of human cells. E6 and E7 together cause polyploidy soon after they are introduced into cells. This appears to result from deregulation of Plk1 by the loss of p53 through E6, and pRb family members by E7, overcoming the safeguard arrest response (Incassati A et al, 2006) as shown in Figure No .01:Functions of E6.

I. **Inactivation and degradation of p53 through the E6/E6AP complex:** E6 protein promote degradation of p53 through its interaction with a cellular protein, E6 associated protein (E6AP), an E3 ubiquitin ligase. The *p53* tumor suppressor gene itself regulates growth arrest and apoptosis after DNA damage. a DNA site-specific transcription factor, and one of the key signaling coordinators in the cell following genotoxic or cytotoxic stress. E6 inactivate of pRb family members induce apoptosis through p53, HPV-infected cells avoid such cell death by E6 inactivation of p53. In addition, E6 interferes with other pro-apoptotic proteins, Bak, FADD and procaspase 8, (Garnett TO et al, 2006) to comprehensively prevent apoptosis. Alternatively, the susceptibility of E6-induced degradation of p53 has been suggested to link the polymorphisms in codon 72 of *p53*. List of Target molecules of E6 with observed biological effect.
   E6 inhibit p53 signaling independent of protein degradation is by sequestration of p53 in the cytoplasm. As both High Risk and Low Risk E6 proteins are able to bind to the C-terminus of p53, masking the p53 nuclear localization signal. (F. Mantovani et al, 2001).
   E6 carry out abrogation of the transactivation of p53 responsive genes via interaction with either the CBP/p300 or histone acetyltransferases. Following DNA damage, p300 is known to acetylate p53, thus enhancing its ability to bind to specific DNA sequences in the promoters of p53-responsive genes, leading to decreased expression from a p53 responsive luciferase reporter. (M.C. Thomas et al, 2005) Following Figure No.03 which provide details of Target molecules of E6 and its effects.
II. **E6-mediated hTERT induction**: E6 that might contribute to cellular transformation with telomerase which is a ribonucleoprotein complex composed of at least the reverse catalytic transcriptase hTERT (expressed in specific germ-line cells, proliferative stem cells of renewal tissues, and cancer cells which reconstitutes telomerase activity) and an RNA component (hTR). The expression of hTERT in normal cells and suppresses senescence. Telomeres shorten with each cell division, eventually leading to senescence (aging), due to incomplete lagging DNA strand synthesis and end-processing events. High telomerase activity is observed in more than 85% of human cancer cells, strongly indicating a key role in tumorigenesis (Pendino F et al, 2006). E6 and Myc interaction has been shown to activate the telomerase reverse transcriptase promoter, and in the presence of E6, a repressor complex of TERT promoter, containing USF1 and USF2, is replaced by Myc, which corresponds to higher levels of *TERT* transcription and consequently, telomerase activity. NFX1-91 novel cellular repressor of the *hTERT* promoter that is degraded in a E6/E6AP dependent manner so that myc binding to the *hTERT* promoter can occur and result in increased hTERT expression.
III. **Notch1 gene:** *Notch1* has been shown to function as an oncogene in the development of human T-cell leukemia, but also acts as a determinant of keratinocyte differentiation, and a tumor suppressor in the mammalian epidermis. Induction of Notch1 through p53 occurs in response to genotoxic stress.
IV. **Targeting of PDZ-containing proteins by E6:** E6 has been shown to interact with PDZ- specific domains on cellular proteins (90 amino acid stretches found in a wide variety) its C-terminal motif leading to their degradation. PDZ-domain-containing proteins are involved in a variety of cellular functions such as cell signaling and cell adhesion and E6 binding leads to transformation, tumorigenesis, hyperplasia, carcinogenesis . Targets of E6 proteins, including. post synaptic density protein (PSD95), *Drosophila* disc large tumor suppressor (DlgA), zonula occludens-1 protein (ZO-1). Among the PDZ proteins bind E6 are Dlg1 and hDlg4, human homologs of Dlg, hScrib, a homolog of the Drosophilia scribble protein , MAGI 1, MAGI 2 and MAGI 3, *M*embrane *A*ssociated *G*uanylate kinase homology proteins with an *I*nverted domain structure, MUPP1, a *mu*lti *P*DZ *p*rotein , and PTPN3, a membrane associated tyrosine phosphatase. E6-induced degradation of these proteins potentially causes loss of cell–cell contacts mediated by tight junctions and thus contributes to the loss of cell polarity seen in HPV-associated cervical cancers.E6 also affect the physiological status of G protein-coupled receptors such as β1-adrenergic receptor through the regulation of PDZ-containing-proteins. (H.S. Grm et al, 2004)
V. **The tumor suppressor gene** : *TSC2* product, Tuberin, has been proposed as a possible target of E6, implying a contribution to E6-induced oncogenesis

The HPV life cycle (Yoon CS et al, 2001, Um SJ et al, 2002)

Details of HPV life cycle shown in Figure.No.04. HPV infects the skin, cause irregular cell growth or warts. Genital skin-to-skin contact with another individual is believed to be the most common route of transmission. Transmission of the virus is possible even when there are no visible signs of infection. Non-sexual transmission of HPV has been reported.

- HPV has been found quite frequently in young women without prior experience of sexual intercourse.
- A mother with HPV can pass the infection to her child during birth, which detected in the linings of the nose and mouth of the child.

Cervical cancers can be classified

- **Squamous cell carcinomas**: arising in the squamous (flattened) epithelial cells that line the cervix. 70-80% of all cervical cancers are squamous cell carcinoma. In a normal situation, squamous epithelium lines the cervix from this opening outwards. The inside of the cervix normally has a more fragile epithelium lining, which under normal circumstances is not exposed to the environment. Certain hormonal changes such as pregnancy and the oral contraceptive pill may cause the inner lining from inside the cervix to migrate outwards to be visible on the outside of the cervix. This is sometimes referred to as erosion. This is common and occurs during child bearing years, usually in the 20's, 30's or 40's with sex incidence being obviously in females. Squamous cell carcinomas common in women in the western world. This type of cervical tumour spreads by lymphatic spread to local and then regional lymph nodes. Blood borne malignant cells spread to bone and lung.

Prognostic factors:

- Clinical stage, nodal status, size of largest node and number of involved nodes, tumor size, depth of invasion, endometrial extension, parametrial involvement, angiolymphatic invasion
- Possibly tissue associated eosinophilia
- Squamous cell carcinoma antigen serum level in patients with advanced disease
- Spreads usually through cervical lymphatics in sequential manner; via direct extension to vagina, uterus, parametrium, lower urinary tract, uterosacral ligaments; distant metastases to aortic and mediastinal lymph nodes, lung, bones, ovary (1%)
- 2/3 are stage I or II when diagnosed

Treatment: Surgery (Cervicectomy), radiation therapy, radioactive implants, pelvic extenteration

- **Adenocarcinoma:** arising in glandular epithelial cells is the second most common type. 10-20% of all cervical cancer are Adenocarcinoma. Cervical adenocarcinoma develops from the mucus-producing gland cells of the endocervix. Cervical Adenocarcinoma usually occurs in women during their mid-life (average age around 37 years).

The following factors increase the risk of Adenocarcinoma of Cervix:

- Infection with human papilloma virus (HPV):
  - HPV virus is transmitted sexually
  - Different subtypes of the virus exist: Types 16, 18, 31, 33, and 45, are the high-risk types associated with cancer
- History of diethylstilbestrol use
- Lack of periodic/regular Pap smear tests
- Weakened immune system as a result of disease, like AIDS, or due to immune-suppressing drugs
- Smoking
- History of cervical cancer in the family
- Having the first child at a young age and having multiple pregnancies

Signs and symptoms of Adenocarcinoma of Cervix may include:

- Abnormal vaginal bleeding
- Pain during and bleeding after intercourse
- Menstrual cycle disturbances
- Abnormal vaginal discharge
- Anemia (due to bleeding)
- Loss of weight, loss of appetite

Diagnosis: Detailed history followed by a physical and pelvic exam.

- A Pap smear
- Colposcopy
- Cervical biopsy: Colposcopic biopsy, Endocervical curettage , Cone biopsy or conization

Treatment options for Adenocarcinoma of Cervix include:

- Surgery
- Chemotherapy: Medications are may be given as oral pills or injected into veins,Drugs commonly used cisplatin, carboplatin, paclitaxel, gemcitabine, and topotecan Chemotherapy may be used in addition to radiation and/or surgery
- Radiation therapy: These beams may be delivered from outside the body (external beam radiation therapy) or the radioactive material maybe placed inside the vagina or the uterus (internal radiation therapy or brachytherapy)

- **Small cell carcinoma:** Small cell cancer of the cervix is a very rare type of cervical cancer. It comprises 1-3% of cervical tumors It is called small cell because under a microscope the cells appear small with a large nucleus. Histopathologically, it resembles small cell carcinoma of the lung and is classified as small cell carcinoma of the cervix in the World Health Organization International Histologic Classification of Tumors Small cell cancers tend to grow quickly and need to be treated early. It associated with the human papilloma virus (HPV) 18. It is also called as neuroendocrine cancers. These are cancers that form in the hormone-producing cells of the body's neuroendocrine system, which is composed of cells that are a cross between traditional endocrine cells (or hormone-producing cells) and nerve cells.

Symptoms of cervical cancer

- Bleeding: between periods, during or after sex, at any time if you are past your menopause
- Discomfort or pain during sex: dyspareunia.
- A vaginal discharge that smells unpleasant
- Pain in the area between the hip bones (pelvis)

Diagnosis:

- Physical and pelvic exam
- Biopsy

The main treatment is a combination of:

- Chemotherapy: Chemotherapy drugs are cisplatin or carboplatin, etoposide, paclitaxel
- Radiotherapy: External radiotherapy treatment alongside chemotherapy. internal radiotherapy or brachytherapy
- Surgery: Removal of womb (a total hysterectomy).

- **Neuroendocrine tumour :** Neuroendocrine tumors (NETs) are neoplasms that are composed of cells which have features of both the endocrine (hormonal) as well as the nervous system (Klimstra, D.S, 2010). Account for 0.5% to 1% all cervical carcinomas.1 They can be classified as benign or malignant (cancer). These tumors can originate from many different sites in the body, including the uterine cervix. The following discussion will be limited to malignant neuroendocrine carcinoma (NEC) of the cervix. **Neuroendocrine tumors** (NET) are difficult to detect because symptoms can vary enormously, and some patients have no symptoms at all. A biopsy is a definitive tool for a NET cancer diagnostic. Many of the symptoms associated with NET are similar to those of other diseases such as: of Irritable bowel syndrome (IBS), Crohn's disease, peptic ulcers, gastritis, other gastric disorders, asthma and pneumonia.[www.crs-src.ca/,] Four subtypes of NEC have been
    - Small cell neuroendocrine carcinoma
    - Large cell neuroendocrine carcinoma
    - Typical carcinoid tumor
    - Atypical carcinoid tumor

Risk factor of neuroendocrine tumor:

- Age: Most common in people between the ages of 40 and 60. Merkel cell cancer is most common in people older than 70.
- Race/ethnicity
- Family history
- Immune system suppression. People with human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS), and people whose immune systems are suppressed because of an organ transplant have a higher risk of developing a neuroendocrine tumor.
- Merkel cell polyomavirus (MCV). Research indicates that there is a link between this virus and Merkel cell cancer. MCV is present in up to an estimated 80% of Merkel cell cancers.
- Arsenic exposure: Exposure to the poison arsenic may increase the risk of Merkel cell cancer.
- Sun exposure. Because Merkel cell cancer often occurs on the sun-exposed areas of the head and neck, many doctors think that sun exposure may be a risk factor for this type of cancer.

Symptoms of neuroendocrine cancer

- Vaginal discharge
- Abnormal vaginal bleeding including postcoital bleeding (bleeding after intercourse),
- Pelvic pain.
- Weight loss,
- Abdominal bloating
- Hypercalcemia
- Neurologic disorders,
- Cushing's syndrome.
- Hyperglycemia (too much sugar in the blood)
- Diarrhea
- Persistent pain in a specific area
- Persistent cough or hoarseness
- Thickening or lump in any part of the body
- Changes in bowel or bladder habits
- Unexplained weight gain or loss
- Jaundice (yellowing of the skin)
- Unusual bleeding or discharge
- Persistent fever or night sweats
- Headache, leg swelling
- Anxiety
- Gastric ulcer disease
- Painful urination

Diagnosis of neuroendocrine tumor

- Gynecologic pelvic exam
- Biopsy
- Routine screening Pap smear.
- CT imaging. PET/CT imaging may also be considered, although trials are lacking to prove its superiority over routine CT scan in this disease. More dedicated imaging may be required based on symptomatology or findings on initial imaging such as a bone scan or brain imaging. Equally important to imaging, referral to a gynecologic oncologist for a thorough pelvic exam is essential to help to determine if surgical resection is appropriate.

- **Glassy cell carcinoma :** Glassy cell carcinoma is a rare aggressive malignant tumour of the uterine cervix and poor prognosis because of its rapid growth, its frequent distant metastases, and its relative resistance to conventional treatment modalities including surgery, radiotherapy, and chemotherapy (Nasu, K et al, 2009). Its cytoplasm has a glass-like appearance, solid nests of markedly pleomorphic, polygonal tumor cells with prominent cell membrane, glassy and eosinophilic cytoplasm, large eosinophilic nuclei, prominent nucleoli, surrounded by heavy inflammatory infiltrate containing eosinophils.1-2% of cervical carcinomas. Younger age group (mean 41 years), associated with pregnancy, HPV 18 and 16. May have peripheral blood eosinophilia Cytokeratin expression is similar to that of reserve cells or immature squamous cells of cervix.

Risk factors of Glassy Cell Carcinoma

- Infection with human papilloma virus (HPV) types
- Sexual promiscuity (multiple sexual partners) and high-risk sexual behavior
- Poor immune system
- Lack of periodic/regular Pap smear tests
- Smoking
- Use of oral contraceptives for long time duration
- Having the first child at a young age (before 17 years) and having had multiple pregnancies
- Presence of other sexually transmitted infections (such as chlamydia)
- Chronic inflammation
- Family history of cervical cancer
- A diet lacking fruits and vegetables

Signs and symptoms of Glassy Cell Carcinoma of Cervix may include:

- Abnormal vaginal bleeding
- Pain during and bleeding after intercourse
- Menstrual cycle disturbances
- Abnormal vaginal discharge
- Anemia
- Ulceration of the cervical wall
- In some cases, the tumor infiltration causes the cervix to take a barrel-like form
- The tumor is poorly-differentiated and a rapid growth is observed

Diagnosis of Glassy Cell Carcinoma of Uterine Cervix:

- Detailed medical history
- physical and pelvic exam
- Pelvic examination: To exam the uterus, cervix, vagina, ovaries, fallopian tubes, bladder, and rectum to check for any abnormal changes in these organs A Pap smear
- HPV DNA testing
- Complete blood count (CBC) with differential of white blood cells
- Liver function test and kidney function test
- Blood tests called serum tumor markers that include: CA-125 test,Human chorionic gonadotropin (hCG), Alpha-fetoprotein (AFP), Lactate dehydrogenase (LDH), Inhibin (hormone), Estrogen and testosterone levels
- Some of the definitive tests that help in diagnosing the cancer include: Colposcopy,

Cervical biopsy; Types of cervical biopsies include Colposcopic biopsy, Endocervical curettage, Cone biopsy or conization .

- **Villoglandular adenocarcinoma:** Also called as villoglandular papillary adenocarcinoma, papillary villoglandular adenocarcinoma, abbreviated VGA, is a rare type of cervical cancer that is typically found in younger women. Villoglandular papillary adenocarcinoma (VGA) of the cervix involves papillae lined by different types of epithelial cells that are histologically subclassified into endocervical, endometrioid, or intestinal subtypes.VGA's may be under diagnosed as benign lesions by cytology because of their minimal cytologic atypia (Choi Y, 2012). Excellent prognosis only if pure; must examine carefully for squamous differentiation or other growth patterns. (Bouman A, 1999). Lower rate of ovarian metastasis compared to common forms of cervical cancer (Zhu Xiaqin, 2015). Often in women age 40 years or less which is associated with HPV types 16 and 18

The following factors increase the risk for Villoglandular Carcinoma of Cervix

- Infection with human papilloma virus (HPV) types
- Sexual promiscuity (multiple sexual partners) and high-risk sexual behavior
- Poor immune system
- Lack of periodic/regular Pap smear tests
- Smoking
- Use of oral contraceptives for long time duration
- Presence of other sexually transmitted infections (such as chlamydia)
- Family history of cervical cancer: This is a relatively ‘low strength’ risk factor
- A diet lacking fruits and vegetables
- Poverty or poor socio-economic status

Signs and symptoms of Villoglandular Carcinoma of Cervix

- Abnormal vaginal bleeding is present in a majority of cases
- Pain during and bleeding after intercourse
- Menstrual cycle disturbances
- Abnormal vaginal discharge
- Ulceration of the cervical wall
- Tumor infiltration causes the cervix to take a barrel-like form

Diagnosis:

- Detailed history and physical and pelvic exam.
- A Pap smear
- Colposcopy
- Cervical biopsy: Colposcopic biopsy, Endocervical curettage , Cone biopsy or conization

Treatment options for Adenocarcinoma of Cervix include:

- Surgery
- Chemotherapy
- Radiation therapy

- **Melanoma (Non Carcinoma Maligancies of Cervix):** Primary malignant melanoma is a rare neoplasm involving the uterine cervix. It may be misdiagnosed especially when amelanotic, in which case immunohistochemistry is useful in reaching the diagnosis. Though its staging and treatment are not yet well codified, prognosis is generally poor and unpredictable and hence early diagnosis is needed.
- **Lympho (Non Carcinoma Maligancies of Cervix): (**Zhu Xiaqin, 2015)
  Lymphoma of Cervix is an uncommon lymphoma, which is mostly observed in middle-aged women. The cervix is a tissue connecting the vagina and uterus The condition may be primary (highly uncommon) or secondary (more common):
  - Primary Lymphoma of Cervix: This type of lymphoma first involves the cervix and later can involve other parts of the body including the lymph nodes and bone marrow
  - Secondary Lymphoma of Cervix: This type of lymphoma involves other parts of the body first, such as peripheral blood, lymph nodes, bone marrow, and other organs; cervical involvement occurs later

  Lymphoma of Cervix can either be a B-cell lymphoma or a T-cell lymphoma. There are various (histological) subtypes of Cervical Lymphomas and some of these include:
  - Diffuse large B-cell lymphoma of cervix: It is among the most common subtype of Cervical Lymphoma
  - Follicular lymphoma of cervix
  - MALT lymphoma of cervix

The prognosis depends on many factors including the subtype and stage of lymphoma, progression of the condition, response to treatment, and overall health of the individual. In general, the prognosis of Lymphoma of Cervix is guarded. There is often a delay in diagnosis due to the uncommon nature of the tumor and the healthcare provider may not suspect a lymphoma.

Lymphoma is a type of cancer stemming from uncontrollably dividing lymphocytes (type of white blood cells). There are two types of lymphomas:

- Hodgkin lymphoma
- Non-Hodgkin lymphoma

Risk Factors for Lymphoma of Cervix

- Chronic inflammation of the cervix
- Advanced age; older individuals commonly have a higher risk
- Individuals with weak immune system
- Family history of immune disease
- The presence of any systemic disease
- Smoking
- Exposure to radiation and industrial chemicals
- Chemotherapy
- Viral infections: Epstein-Barr virus infection
- X-ray, CT scan exposure, radiation exposure: nuclear plant workers, pilots, astronauts, etc.
- Elevated level of serum lactate dehydrogenase - LDH (a type of enzyme)
- Already suffered from lymphoma, or other types of blood cancers, may have a relapse or a recurrence

Symptoms of Lymphoma of Cervix

- Presence of a painless mass in the area
- Abnormal vaginal bleeding or discharge
- Pain during and bleeding after intercourse
- There may be associated abdominal pain and back pain
- Unintentional weight loss; changes in appetite
- Fatigue and weakness, headache
- Anemia (low red blood cell count)
- Frequent infections
- Low blood pressure
- Frequent urination

Diagnosis of Lymphoma of Cervix

- Physical examination
- Blood tests that may include: Complete blood cell count (CBC) blood test, Absolute lymphocyte count on peripheral blood, Liver function blood test (LFT),Lactate dehydrogenase (LDH) blood test
- Colposcopy
- Tissue biopsy from the cervix: Studied initially using Hematoxylin and Eosin staining, immunohistochemical stains, molecular testing, flow cytometric analysis and electron microscopic studies. The biopsy may be performed through following procedures:
    - ❖ Endocervical curettage (endocervical scraping)
    - ❖ Cone biopsy or conization
    - ❖ Cervical biopsy
- Radiological imaging may be performed specific to location and to determine the extent of lymphoma including:
    - ❖ Plain x-ray of the abdomen and pelvic region
    - ❖ CT or MRI scan of the abdomen and pelvis
    - ❖ Ultrasound scan of the abdomen
    - ❖ Vascular radiological studies
    - ❖ Whole body bone scan
    - ❖ Whole body CT-PET scans
    - ❖ Brain MRIs
- Exploratory laparoscopy (diagnostic laparoscopy)
- Bone marrow aspiration and biopsy
- Flow cytometry
- Fluorescence in situ hybridization (FISH)
- Immunophenotyping
- Polymerase chain reaction (PCR)

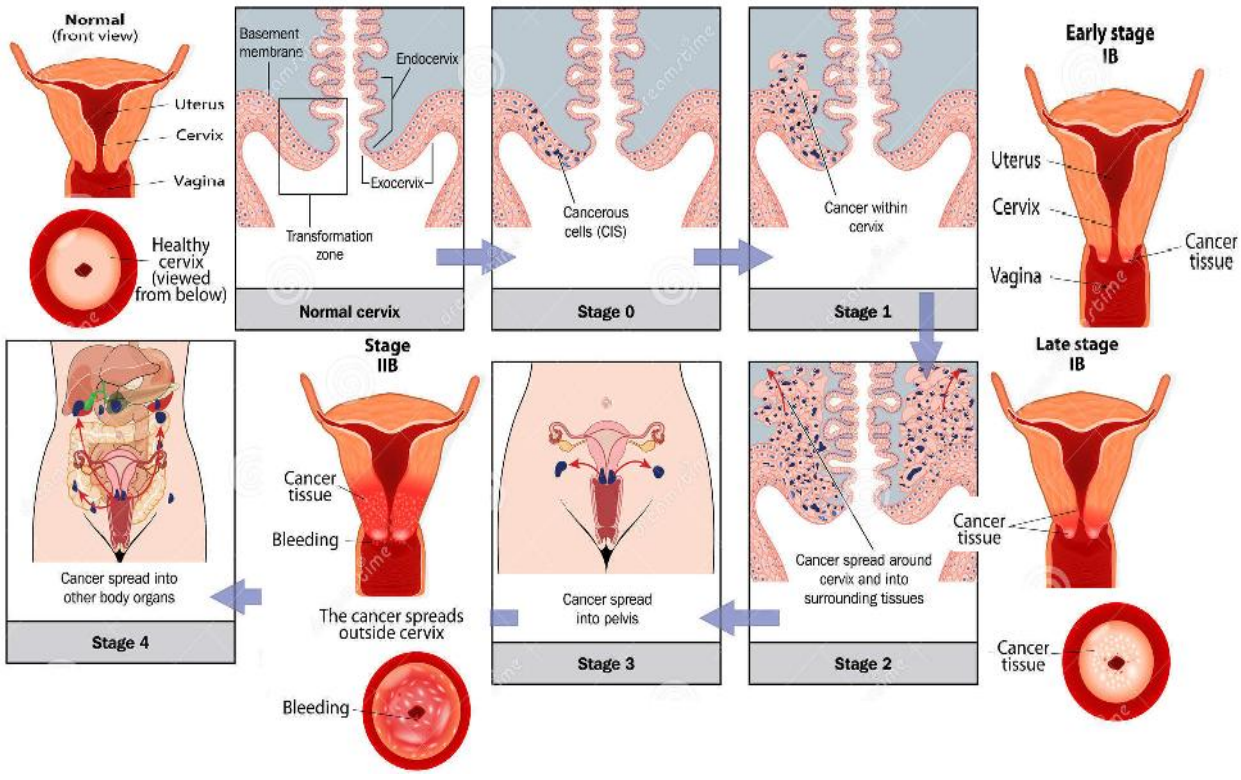

Figure No.1: Overview of cervical cancer and various stages of cervical cancer

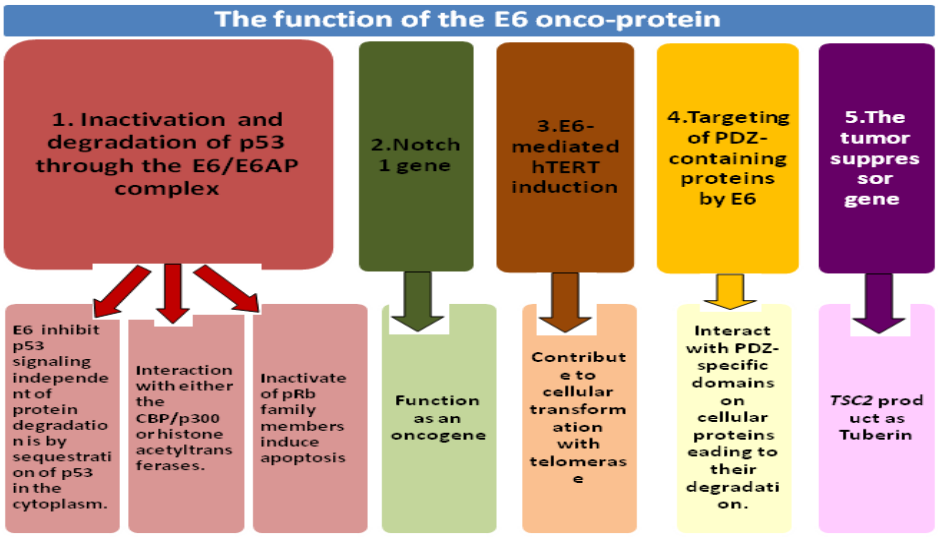

Figure No .2: Functions of E6 onco-protein

E6AP/p53	•Degradation of p53/suppression of apoptosis
PDZ-domain-containing proteins	•Degradation of PDZ proteins/loss of cell polarity
CAL	•Deregulation of the vesicular trafficking processes
NFX1-91	•Degradation of NFX1-91/activation of hTERT, immortalization
Paxillin	•Interference in the association of paxillin and focal adhesion kinase
IRF3	•Inhibition of IRF-3's transcriptional activity thereby inhibiting the IFN-induced signaling
Bak	•Degradation of Bak/suppression of apoptosis
FADD	•Degradation of FADD/suppression of apoptosis
Procaspase 8	•Degradation of procaspase 8/suppression of apoptosis
GADD34/PP1	•Suppression of apoptosis
Tyk2	•Impairment of Tyk2 activation thereby inhibiting IFN-induced signaling
CBP/p300	•Down-regulation of p53 activity by targeting the transcriptional coactivator
MCM7	•Induction of chromosomal abnormalities
TSC2 (tubulin)	•Activation of mTOR signaling
BRCA1	•Release the inhibition of ER signaling
Target molecules of E7	•Implicated/observed biological effect
pRb family proteins	•Disruption of pRb–E2F complexes thereby initiating the E2F mediated transcription
Cyclin A	•Regulation of cell cycle (binding through pRb)
Cyclin E	•Regulation of cell cycle (binding through p107)
p27	•Binding to and subsequent inactivation of the CDK inhibitor p27
p21	•Binding to and subsequent inactivation of the CDK inhibitor p21
AP1	•Interaction with and transactivation of the AP1 family of transcription factors
TBP	•Deregulation of the TBP mediated transcription
S4 subunit OF 26 S proteasome	•Targeting of pRb for degradation
MPP2	•Activation of MPP2-specific transcriptional activity(81)
hTid 1	•Genome replication
p48	•Down-regulation of IFN α-mediated signal transduction
M2 pyruvate kinase	•Modulation of type M2 pyruvate kinase activity
p600	•Contribution to anchorage-independent growth and transformation
Mi2	•Form complex with HDAC to promote the E2F2-mediated transcription
IRF1	•Abrogation of transactivation function of IRF1

Figure No.3: Details of Target molecules of E6 and its effects.

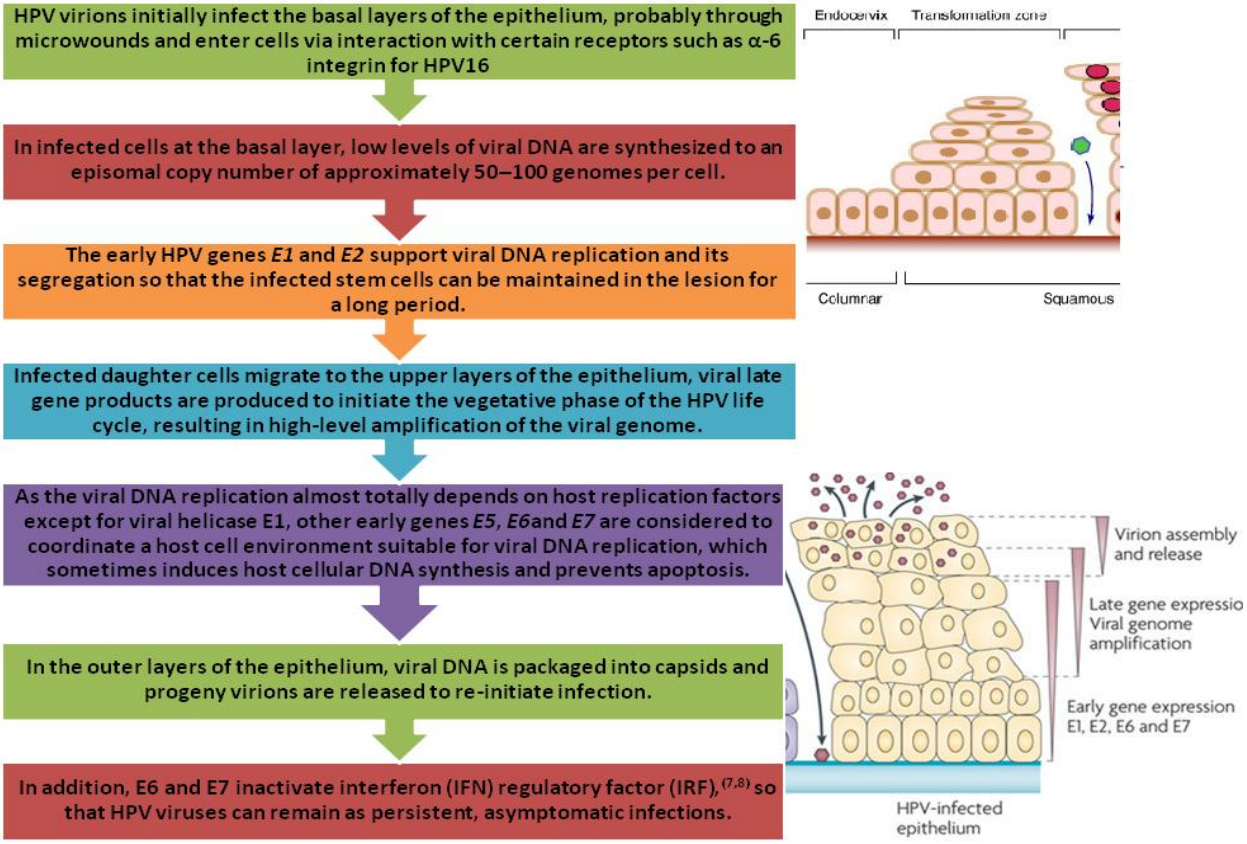

Figure No.4: HPV life cycle

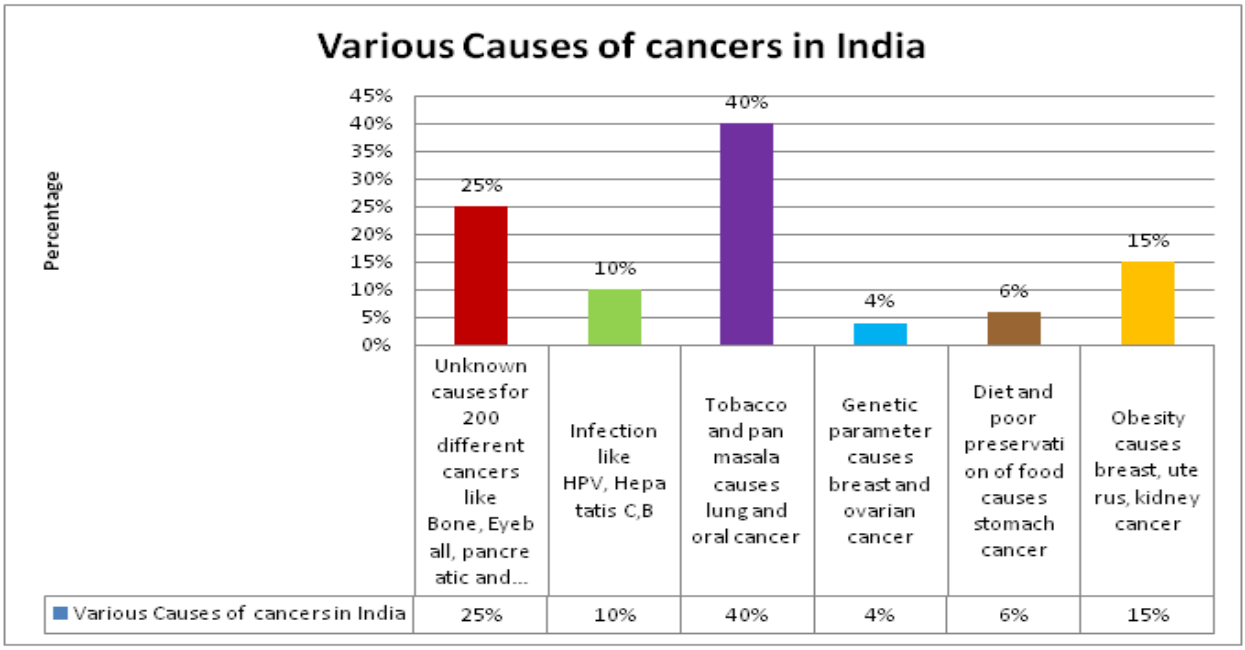

Figure No.5: Various causes of cancer in India

Table No.1: Details of cancer types with their region

Name of states in India	Type of cancer	Cause of cancer
North East area	Oesophagus cancer	Tobacco
West bengal	Lung , Uninary Bladder Cancer	Polluated air and water
South and coastal area	Stomach Cancer	Diet rich in spice and salt
Goa	Colon Cancer	Consumption of red meat, alcohol, tobacco
Gujrat and Rajastan	Head , Neck Cancer	Consumption of tobacco and pan masala
Panjab	Kidney, Urinary Bladder, Breast Cancer	Pollution, pesticides, toxins in food

Current cancer scenario in India:

To raise awareness of cancer and to encourage its prevention, detection and treatment, the World Cancer Day is marked on February 4, every year. The World Cancer Day was founded by the Union for International Cancer Control (UICC) to support the goals of the World Cancer Declaration, written in 2008. The primary goal of the World Cancer Day is to significantly reduce illness and global burden caused by cancer by 2020. (Sanchari Pal, 2016). In cancer therapy three options are available

1. Radiotherapy: 50% of new cancer patients need radiotherapy
2. Chemotherapy: 46 % cancer medicines on WHO model list of essential medicine
3. Surgery: 65% surgery responcible for cure and control of cancer (World Cancer Day 2017)

Even cervical cancer can often be successfully treated if detected at an early stage.

- WHO recommends screening strategy i.e Visual Inspection with Acetic Acid (VIA). The VIA test is based on application of diluted acetic acid (vinegar) to the cervix during examination. Abnormal cervical tissue appears white after application. The advantage of this method is that it is inexpensive and abnormal tissue can be found and treated in early stage.
- Pre-cancer treatment: Abnormal precancerous cervical changes discovered during screening can be treated Cryotherapy, (generally nitrous oxide) , Thermo-coagulation, (generate temperatures of 100–120 °C) . It is, Loop electrosurgical excision procedure (LEEP), which removes abnormal tissue with a wire loop heated by electric current.

New approach to treat Cervical cancer and HPV infections

1. HPV Vaccine (NCI, 2011)

HPV 16 and 18 are responsible for the majority (about 70%) of cervical cancers. HPV 6 and 11 are responsible for 90% of genital warts. The HPV vaccine triggers the formation of antibodies to produce immunity and therefore protects the body from disease. Hpv vaccine has been approved for use in over 100 countries .An FDA-approved vaccine called Gardasil 9 protects against 9 HPV types and can prevent about 90 percent of cervical, vulvar, vaginal and anal cancer cancers, and also protects against genital warts. Gardasil protects against 70% of vaginal cancer cases and up to 50% of vulvar cancer cases. Cervarix vaccine protects only against two types of HPV and prevents infection with HPV types 16, 18, 6 and 11. HPV vaccine, It is an injection - given as a series of three injections over a six-month period. The second dose is given one to two months after the first dose, and the third dose is given six months after the first dose. The most common side effects of HPV vaccines include soreness, swelling or redness at the injection site, dizziness or fainting occurs after the injection. In addition, headache, nausea, vomiting, fatigue or weakness also may occur. Routine screening for through regular Pap tests beginning at age 21 remains an essential part for preventive measure for cervical cancer. (NCI, 2016, Cox JT, 2016)

2. **Targeted Therapy:**

Which target onco gene changes in cells causing cancers is often called targeted therapy, without causing damage to normal cells (Carrington C, 2015). Pazopanib is a targeted therapy drug that blocks effect of certain growth factors on cancer cells. This drug is basically a kinase inhibitor and act on several kinase proteins These proteins either promote tumor cells to grow and divide or help form neo-angiogenesis. Examples are VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-A, PDGFR-B, FGFR-1, FGFR-3, Kit, Itk, Lck, and c-Fms. Pazopanib help stop growth of cancer cells and can be used for management of cervical cancer.

3.Cryosurgical Ablation (CSA): Cryosurgery is an ablation technique for tumors which destroys tumors by cycles of freezing and thawing. By two major mechanisms, one immediate, the other delayed. The immediate mechanism is the damaging effect of freezing and thawing the cells. The delayed mechanism is the progressive failure of microcirculation, vascular stasis becomes operative as an important cause of tumor tissue destruction. Freezing the tumor before excision minimizes the risk of spreading the cancerous cells during excision. Cryosurgery is performed through intraoperative, endoscopic or percutaneous routes by using argon-helium system. It can be combined with other treatments such as surgical operation, chemotherapy, radiotherapy.

4.Seed Knife Therapy (Brachytherapy) : Seed implantation with iodine-125(which have a half -life of 59 days-release a short-course of gamma ray) or palladium-103 seeds . The seeds implanted into cancerous tissue and nearby tissue radiate targeted cells and ultimately destroy it. This prevents unnecessarily exposing the whole body to radiation. With the use of CT or MRI, Computational optimization techniques; a three-dimensional conformal treatment plan is made for making the correct dose calculation . Then, the number and location of seeds implanted (percutaneously) is calculated. Seed therapy is a local ablation; therefore, it is not harmful to whole body. It does not expose the entire body to radiation.The seeds cannot be absorbed by body or excreted out of body.

5.Combined Immunotherapy: Immunotherapy as a key treatment to greatly enhance the immune system especially after harsh chemotherapy,to slow the spread of cancer, prevent metastasis, and improve general health. Immunotherapy includes following cell whichshow strong inhibiting effect on cancer, preventing metastasis and recurrence

- Cytokine Induced killer Cells (CIK)
- Dendritic Cells (DC)
- Traditional Chinese Medicines (TCM)

Cervical cancer can often be prevented with regular screening tests (called Pap tests) and follow-up care.

CONCLUSION

Cervical cancer is a disease of considerable worldwide morbidity and mortality. From epidemiologic and cancer prevention, perspective have been made towards noticeably dropping the incidence and mortality by cervical cancer. Surgical, radiotherapeutic, and more recently, chemoradiotherapy approaches comprise the successful treatment modalities for invasive cervical carcinoma. Further efforts at early detection and prevention, however, are likely to produce even more significant gains. Computers, artificial intelligence, and molecular biology are beginning to merge at the clinical level to refine and enhance the cervical cytologic assessment.

REFERENCES

Bouman A. (1999). Villoglandular papillary adenocarcinoma of the cervix. Beware of a wolf in sheep's clothing. Eur J Obstet Gynecol Reprod Biol. 87(2):183-9

Carrington C. (2015). Oral targeted therapy for cancer. Australian Prescriber 38(5):171-176

Cervical cancer treatment In India, Fuda Cancer Hospital Information Centre & Administration Office in India, http://www.fudacancer.in/about.html

Cervical cancer treatment (2016). Patient version. National Cancer Institute. http://www.cancer.gov/types/cervical. Accessed July 9,

Choi Y. (2012). Liquid-based cytology of villoglandular adenocarcinoma of the cervix: a report of 3 cases.Korean J Pathol;46(2):215-20

Cox JT, (2016). Recommendations for the use of human papillomavirus vaccines. http://www.uptodate.com/home. Accessed July 7,

Garnett TO, Filippova M, Duerksen-Hughes PJ. (2006). Accelerated degradation of FADD and procaspase 8 in cells expressing human papilloma virus 16, E6 impairs TRAIL-mediated apoptosis. *Cell Death Differ* 13: 1915–26

Grm H.S., L. Banks Degradation of h Dlg and MAGIs by human papillomavirus E6 is E6-AP-independent .J. Gen. Virol2004;85 (10) :2815–2819

HPV vaccine may help prevent cervical cancer, Health 24 Cervical Cancer http://www.health24.com/medical/cervical-cancer/cervical-cancer-vaccine/hpv-vaccine-may-help-prevent-cervical-cancer-20160705

Klimstra, D.S., (2010). The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas, 39(6): 707-12

Incassati A, Patel D, Mc Cance DJ. (2006). Induction of tetraploidy through loss of p53 and upregulation of Plk1 by human papillomavirus type-16, E6. *Oncogene* 25: 2444–51

Mantovani F., L. (2001). Banks.The human papillomavirus E6 protein and its contribution to malignant progression. Oncogene20 (54) :7874–7887

Nasu, K., Takai, N.Narahara, H. (2009). Multimodal treatment for glassy cell carcinoma of the uterine cervix. J Obstet Gynaecol 35 (3): 584–7

National Cancer Institute (NCI). (2011, Dec. - Last reviewed). Fact sheet: human papillomavirus (HPV) vaccines.

Pendino F, Tarkanyi I, Dudognon C . (2006). Telomeres and telomerase: Pharmacological targets for new anticancer strategies?. Curr Cancer Drug Targets 6: 147–80

Sanchari Pal. (2016). Cancer in India and The Fight Against It: What Every Indian Should Know, Cancer India Information ;7 http://www.thebetterindia.com/74188/cancer-awareness-india/

Thomas M.C., C.M. Chiang (2005). E6 oncoprotein represses p53-dependent gene activation via inhibition of protein acetylation independently of inducing p53 degradation .Mol Cell 17 (2):251–264

Thomas, A., Ram, T. S., Chandramohan, A., Abraham, A., Manojkumar, R., & Peedicayil, (2015). A. Cervical Lymphoma Mimicking Cervical Fibroid: A Report of Three Cases and Review of Literature. Indian Journal of Gynecologic Oncology 14(1):1-5

Um SJ, Rhyu JW, Kim EJ, Jeon KC, Hwang ES, Park JS. (2002). Abrogation of IRF-1 response by high-risk HPV E7 protein *in vivo*. Cancer Lett 179: 205–12

Yoon CS, Kim KD, Park SN, Cheong SW. (2001). Alpha(6) Integrin is the main receptor of human papillomavirus type 16 VLP. Biochem Biophys Res Commun 283: 668–73

Zhu Xiaqin. (2015). Clinical analysis of 16 cases of cervical .Chinese Medical Journal;95 :07

http://www.dovemed.com/diseases-conditions/lymphoma-cervix/

World Cancer Day 2017: A closer look at the importance of cancer awareness .New Delhi, February 3. http://indiatoday.intoday.in/education/story/world-cancer-day-2017/1/873951.html

https://www.acscan.org/policy-resources/eliminating-death-cervical-cancer

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