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EXPLORING TRENDS AND STRATEGIES IN CERVICAL CANCER PREVENTION AND TREATMENT CERVIAL CANCER

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ABSTRACT

HPV vaccination, with a focus on administering vaccines before the onset of sexual activity. Safe sexual practices, including condom use and limiting sexual partners, contribute to reducing transmission risks. Intervention and Treatment: Treatment modalities vary based on the Cervical cancer, primarily attributed to persistent high- risk human papillomavirus (HPV) infection, remains a significant global health challenge. This abstract provides a concise overview of key aspects related to cervical cancer, including risk factors, early detection methods, and intervention strategies.

KEYWORDS: HPV Vaccination and its impact cervical cancer prevention.

INTRODUCTION

Cervical cancer, predominantly caused by persistent human papillomavirus (HPV) infection, ranks among the most common malignancies affecting women worldwide. Despite advancements in screening programs and vaccination efforts, cervical cancer remains a major public health concern. This section introduces the prevalence and impact of cervical cancer, emphasizing the need for continuous research to enhance our understanding of the disease and improve preventive measures.

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 (fig1)A).[1] 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.[2] 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 infection (fig1) A). 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 (fig1 B).

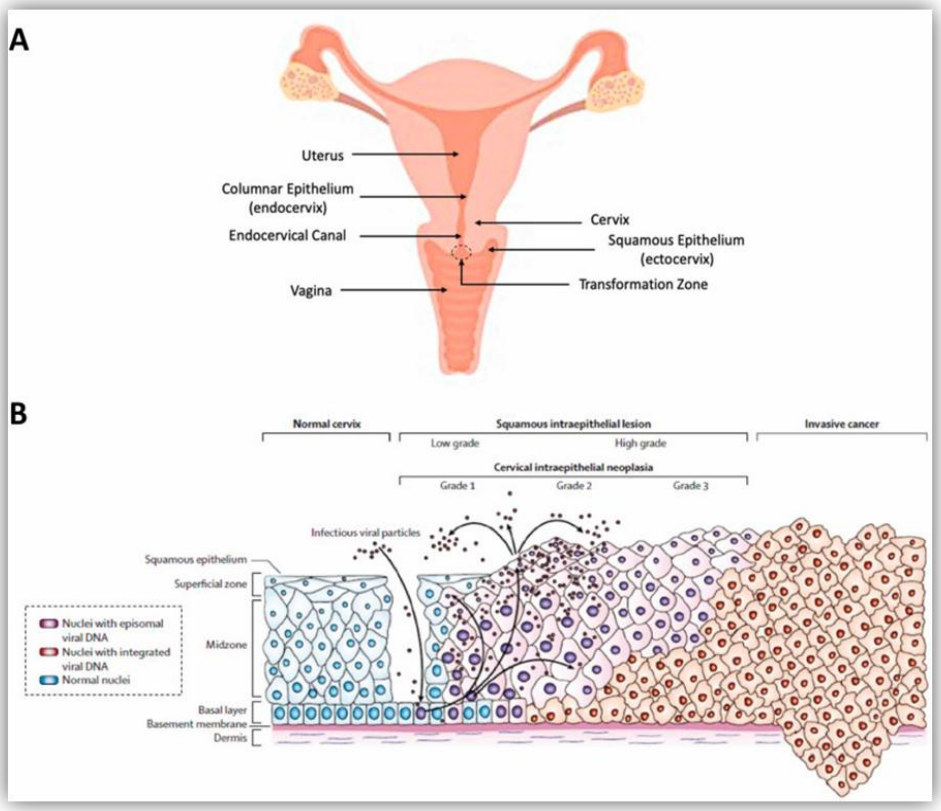

Fig. (1). Anatomical location of cervical cancer origin and progression from a normal cervix to invasive squamous cell carcinoma mediated by HPV.

Cervical cancer disease management

Primary and secondary strategies to prevent cervical cancer remain key in reducing the burden of the disease and much has been written about this.[3] The focus of this review is, therefore, on treatment options for cervical cancer.

Early-stage cervical cancer is often asymptomatic and may be diagnosed during a routine screening or pelvic examination. The most common symptoms include heavy or abnormal vaginal bleeding, in particular following intercourse.[4], [5] Some women may present with a vaginal discharge that may be watery, mucoid, or purulent and malodorous, however it is rarely seen in isolation of other symptoms.[6] In advanced disease, patients may experience lower limb oedema, flank pain, as well as pelvic or lower back pain. Additionally, bowel and/or bladder related complaints such as changes in pressure or the passage of urine and/or faeces through the vagina indicate invasion of the bladder and rectum respectively.[7]

Treatment of cervical cancer

As indicated above, the stage and extent of cervical cancer progression determines the treatment strategy needed and may include one or a combination of surgery, radiation and chemotherapy (fig 2).

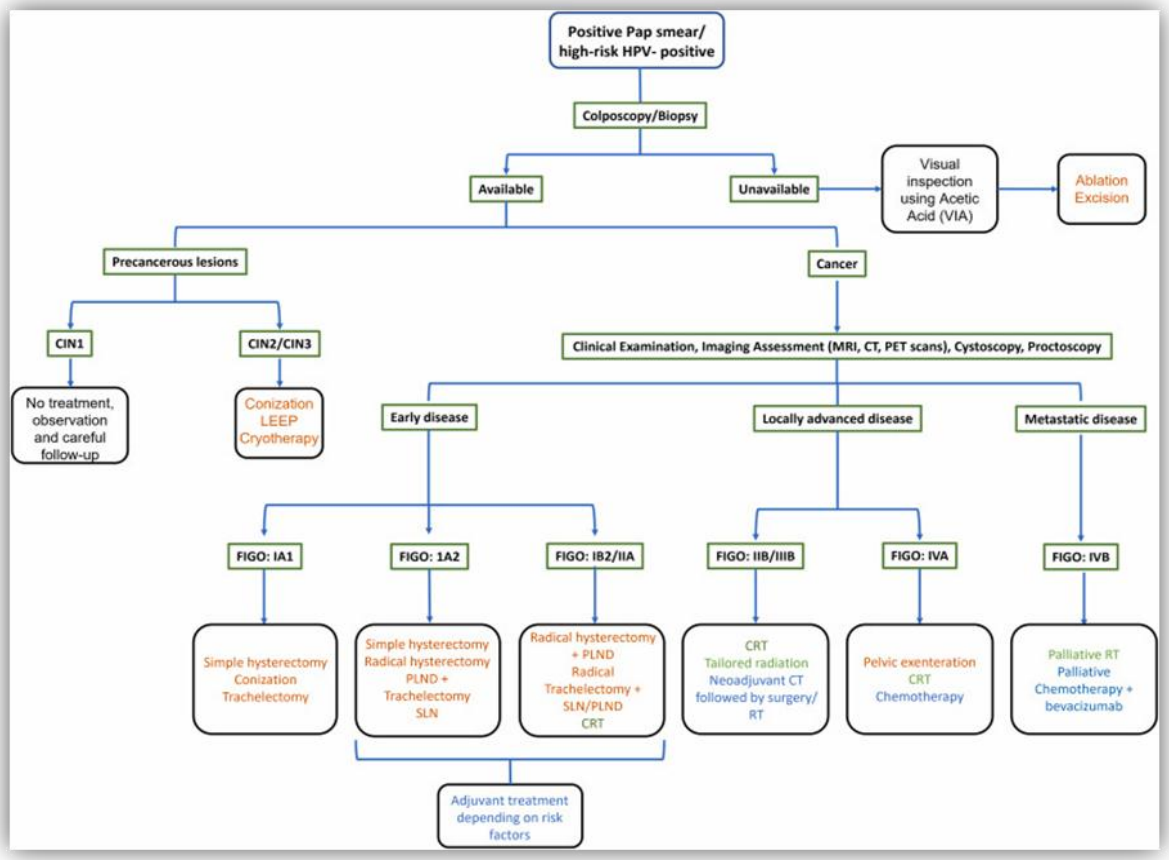

Fig 2: Overview of the management and treatment of cervical cancer based on stage of disease. Interventions written in orange refer to surgical, green refer to radiotherapy and blue refer to chemotherapy based treatment options. PLND, pelvic lymph node dissection; SLN, sentinel lymph node biopsy; CRT, chemoradiotherapy; RT,

radiotherapy. Adapted from Marth et al. (2017).[5] (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Surgery

Surgery is a commonly used and successful technique in combatting various early-stage cancers as it involves the physical removal of cancerous tissue. It can, however, also be used to remove metastatic tissue.[8]

Currently, the types of surgery performed to treat cervical cancer include total hysterectomy, radical hysterectomy, loop electrosurgical excision procedure (LEEP), conization, trachelectomy, and cryosurgery.[9]

he choice of surgical procedure is highly dependent on the disease stage and extent of spread (Fig. 2).[10] otal hysterectomy with or without salpingo-oophorectomy (the removal of one or both ovaries), remains the treatment of choice for women who have completed childbearing. Radical hysterectomy is most commonly used for larger cervical cancer lesions (up to 4 cm in size) and involves complete resection of the uterus, cervix, parametria, and cuff of the upper vagina.[11]

The findings of the Laparoscopic Approach to Cervical Cancer (LACC) trial revealed that radical hysterectomy performed using laparoscopy was associated with an increased rate of recurrence, loss of fertility and potential urinary dysfunction in the long-term.[12]

Radiotheraphy

Radiotherapy is a crucial treatment for cervical cancer, utilizing high-energy x-rays to target and shrink tumors. There are three main types of radiation therapy used: External Beam Radiation Therapy (EBRT), Intensity-Modulated Radiotherapy (IMRT), and Brachytherapy (internal RT), EBRT directs radiation beams from outside the body towards the tumor, and it's the most common form of radiotherapy. IMRT is a more advanced technique, tailoring radiation beams to match the tumor's shape, suitable for both cancerous and non-cancerous tumors. Brachytherapy involves either delivering a high dose of radiation directly to the tumor or placing a radioactive implant at the tumor site, sparing nearby tissues.[13], [14]

Improved diagnostic tools like CT scans and MRI aid in evaluating the tumor, its invasion extent, and metastasis, which further refines radiotherapy planning. However, radiotherapy can lead to adverse effects such as diarrhea, abdominal cramps, pelvic pain, skin problems,

lymphedema, and sexual dysfunction. Despite advancements, radiotherapy alone may not effectively control locally advanced disease in 20–50% of cases.To enhance its efficacy, radiotherapy is often combined with chemotherapy, especially for larger cervical cancer lesions (greater than 4 cm wide). This combined approach improves outcomes and is particularly beneficial for managing advanced stages of the disease.[15], [16],[17],[18]

Chemotherphy

Chemotherapy is an integral part of the standard cervical cancer treatment regimen and is typically administered as an adjuvant therapy following surgery when poor prognostic tumour features increase the risk of recurrent disease, in combination with radiotherapy as previously mentioned, and as a standalone treatment for locally advanced disease (Fig. 2). The most effective single agent which has been used for the last three decades to treat cervical cancer is the platinum-based chemotherapeutic, cisplatin.[19] However, despite initial patient response to cisplatin, increased resistance during the course of the treatment is often reported and this reduces the efficacy of additional second-line platinum-based chemotherapeutics.[20] Subsequently, studies have found that combining cisplatin with other agents is potentially more effective than single drug treatment.[19], [21] Indeed, a study by Long et al. (2005) showed that while the response rate of cisplatin alone was 20%, combined with topotecan, the response rate increased to 39%. [Another study reported similar results when cisplatin was combined with paclitaxel. Currently, topotecan, paclitaxel and other non-platinum-based chemotherapeutics such as 5-fluorouracil and bleomycin, are therefore commonly used in combination with cisplatin for treating cervical cancer. This results in significant and clinically meaningful improvement in median survival duration.[19], [22], [23]

Chemotherapy, when combined with radiotherapy (called chemoradiotherapy), is commonly used for treating locally advanced cervical cancer. The goal of this treatment approach is to lower the chances of cancer coming back, but it can lead to side effects and long-term health issues. Research that looked at many studies found that chemoradiotherapy can increase overall survival and time without the cancer progressing. It also reduces the risks of the cancer returning in the cervix or spreading to other parts of the body. Sometimes, when the cancer is advanced and can't be cured, chemotherapy is used to make the patient feel better and ease symptoms, like pain. However, it might not always shrink the tumor. It's crucial to keep finding and improving treatments because cancer cells can become resistant to drugs, making chemotherapy less effective.[23]–[26]

The cell cycle

The cell cycle, which is the process by which cells divide and replicate, is divided into four main phases, each with its own checkpoints to ensure that the cell's genetic material is accurately copied and distributed.

G1phase: This is the first phase where cells decide whether conditions are suitable for DNA replication. If conditions are not favorable, cells may enter a resting state called quiescence or senescence (G0 phase).

Sphase: During this phase, DNA replication occurs, ensuring that each daughter cell receives a complete set of genetic material.

G2phase: In this phase, cells check that DNA replication has been completed accurately before proceeding to cell division.

M phase (mitosis): This is the phase where cells divide into two identical daughter cells.

The progression through these phases is tightly regulated by proteins like cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors, and other enzymes. Cyclin-CDK (fig 3)complexes are activated under favorable conditions and help cells move through the cell cycle by phosphorylating specific targets.

However, when conditions are not favorable or when there is DNA damage, cell cycle progression is inhibited. CDK inhibitors block the action of proto-oncogenes and activate tumor suppressor genes, which trigger cell cycle checkpoints to halt cell division and allow for repair of damaged DNA.

Mutations in genes involved in these processes can lead to uncontrolled cell division, a hallmark of cancer. In cervical cancer, for example, the tumor suppressor gene p53 is often lost or inactivated, disrupting the G1/S checkpoint and allowing cancer cells to exploit the G2/M checkpoint for DNA repair.

One such target in cervical cancer is the protein Wee1, which normally acts as a tumor suppressor by preventing cells from entering mitosis when DNA is damaged. However, in cancer cells with mutations in p53, Wee1 becomes overactive, allowing cancer cells to survive and repair DNA damage caused by treatments like radiotherapy. Inhibitors of Wee1,

such as MK-1775, have shown promise as they selectively target cancer cells relying on the G2 checkpoint for survival. Inhibition of Wee1 can induce cell death in cancer cells and make them more sensitive to chemotherapy and radiotherapy, offering a potential treatment strategy for cervical cancer (fig 4, fig 5).[27]–[29], [29]–[33]

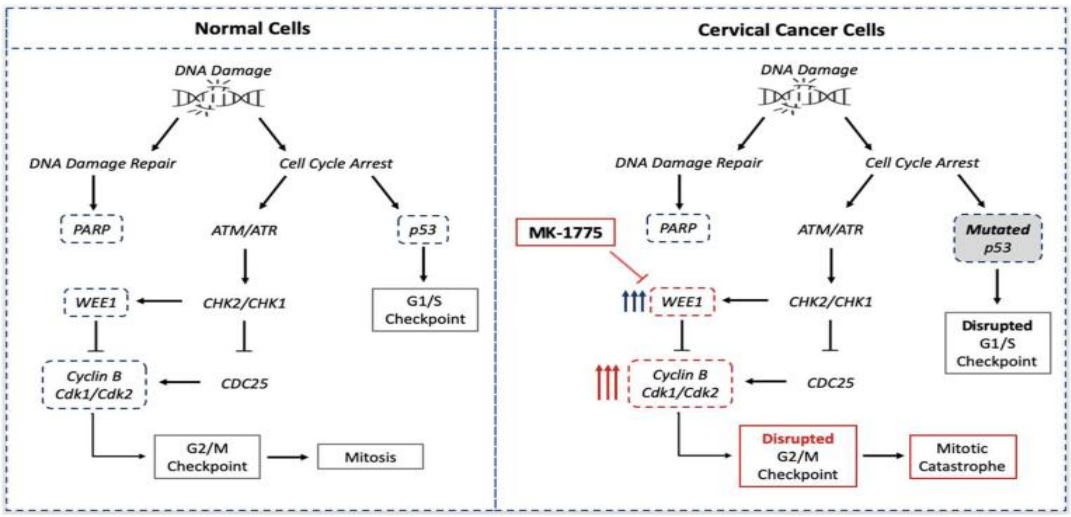

Fig 3: Simplified Diagram of the role of Wee1 and the Wee1 inhibitor, MK-1775, in the cell cycle. WEE1 is overexpressed in various tumour cells with replication stress DNA damage, including cervical cancer tumours. Wee1 inhibitors, for example MK-1775, abrogate G2 arrest by increasing the activity of Cyclin B/Cdk1/Cdk 2, leading to cells with unrepaired DNA damage to enter into mitosis and undergo mitotic catastrophe. Processes shown in red are as a result of/affected by MK-1775.[29], [33] (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

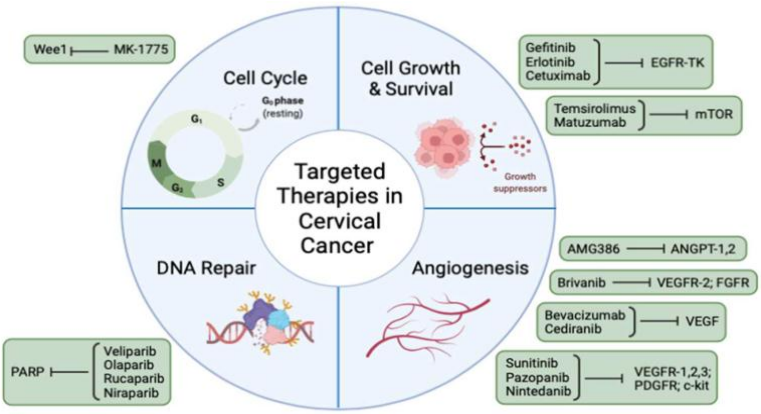

Fig 4: Therapeutic agents targeting biological pathways and their main molecular targets in various stages of cervical cancer.

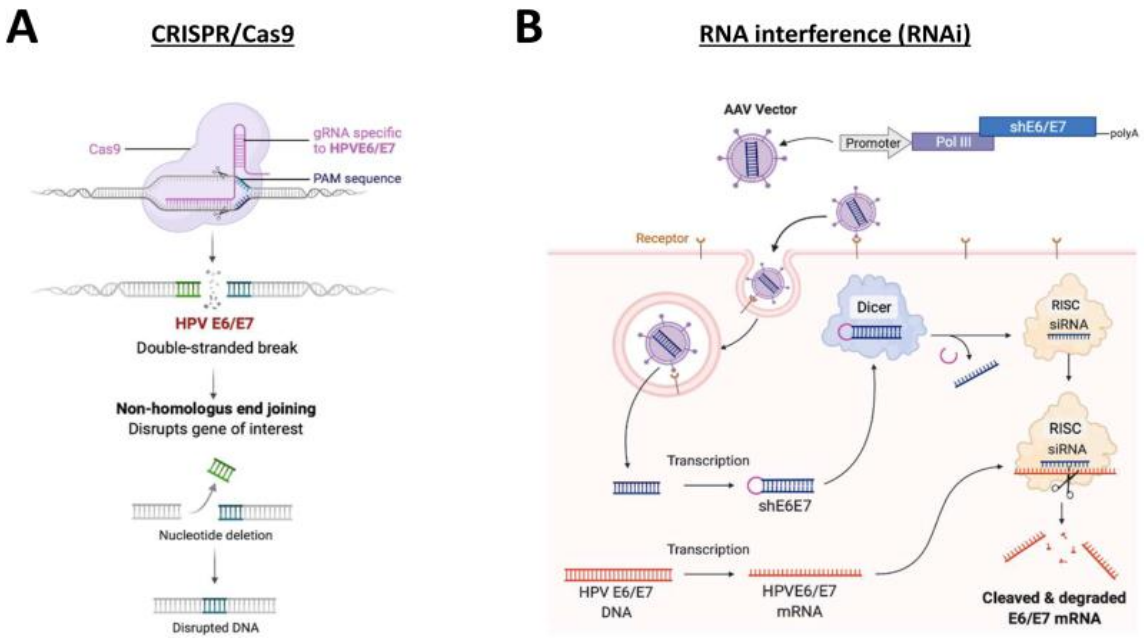

Fig 5: Schematic diagram showing mechanisms by which HPV E6 and E7 can be targeted in cervical cancer by A) **CRISPR/Cas9 and** B) **RNA interference (RNAi). PAM, protospacer-adjacent motif; AAV, adeno-associated virus.**

Histopathology

It is essential that all cancers must be confirmed by microscopic examination. Cases are classified as carcinomas of the cervix if the primary growth is in the cervix. All histologic types must be included. The histopathologic types, as described in the WHO Classification of Female Genital Tumours[34] are as follows.

Squamous epithelial tumors

- Squamous cell carcinoma, HPV-associated
- Squamous cell carcinoma, HPV-independent
- Squamous cell carcinoma NOS

Glandular tumors

- Adenocarcinoma NOS
- Adenocarcinoma, HPV-associated
- Adenocarcinoma, HPV-independent, gastric type
- Adenocarcinoma, HPV-independent, clear cell type
- Adenocarcinoma, HPV-independent, mesonephric type
- Adenocarcinoma, HPV-independent, NOS
- Endometrioid adenocarcinoma NOS

- Carcinosarcoma NOS
- Adenosquamous carcinoma
- Mucoepidermoid carcinoma
- Adenoid basal carcinoma
- Carcinoma, undifferentiated, NOS

Mixed epithelial and mesenchymal tumors

- Adenosarcoma

Germ cell tumors

- Endodermal sinus tumor
- Yolk sac tumor NOS
- Choriocarcinoma NOS

Diagnosis And Evaluation Of Cervical Cancer

1. Microinvasive Disease

Diagnosis of Stages IA1 and IA2 is made on microscopic examination of a cone biopsy specimen, obtained by LEEP or cold knife conization, which includes the entire lesion. It can also be made on a trachelectomy or hysterectomy specimen. The depth of invasion should not be greater than 3 or 5 mm, respectively, from the base of the epithelium. The horizontal dimension is no longer considered in the 2018 revision as it has not been shown to impact survival. Note must be made of lymphovascular space involvement, which does not alter the stage, but may affect the treatment plan. The margins should be reported to be negative for disease. If the margins of the cone biopsy are positive for invasive cancer, the patient is allocated to Stage IB1.[35]

2. Invasive Disease

n the case of visible lesions, a punch biopsy may generally suffice for diagnosis, but if not satisfactory, a small loop biopsy or cone may be required. Clinical assessment is the first step in allocation of staging. FIGO 2018 staging permits the use of any of the imaging modalities according to available resources, i.e. ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), to provide additional information on tumor size, nodal status, and local or systemic spread. MRI is the best method of radiologic assessment of primary tumors greater than 10 mm. However, ultrasound has also been shown to have good diagnostic accuracy in expert hands. The modality used in

assigning staging should be noted for future evaluation. Imaging can identify additional prognostic factors that can guide the choice of the most appropriate treatment modality.[36], [37]

Symptoms

1. Blood spots or light bleeding occurs during menstrual cycle.
2. Menstrual bleeding that is longer and heavier than typical.
3. Bleeding after intercourse, douching or a pelvic assessment.
4. Increased vaginal release.
5. Pain occurs during sexual intercourse.
6. Blood loss after menopause.
7. Mysterious constant pelvic and or back pain.[38]

Causes

1. The majority cervical cancer cases are cause by the sexually transmitted human papilloma virus (HPV).
2. HPV is the same virus that causes genital warts. There are about 100 different strains of HPV. Only definite type's causes cervical cancer, these 2 types that most commonly caused cancer are HPV- 16 & HPV-18. Being infected with a cancer causing strains of HPV.

HPV can also cause other cancers in women and men this include.

1. Vulvar cancer
2. Vaginal cancer
3. Penile cancer
4. Alal cancer
5. Rectal cancer
6. Troat cancer

HPV is a very common infection in sexually active adult and may acquire it at some point in their life time.[39]

Prevention

1. Avoid smoking and avoid using oral contraceptive for long time
2. It is also can be prohibited by avoiding hazard factor and by getting regular pap test (papnicolaou test) also known as Pap smear.
3. A vaccine is a most important avoidance for cervical cancer.

4. Avoid many sexual partners during sex.

5. Change in life style or eating habbits.

6. Avoiding other risk factors like early marriage/ child bearing and smoking.[40]

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.

1. 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.

2. Radiation Therapy

It may also used in treatment of cervical cancer frequently in conjunction with surgery. If the cancer is enveloping and spread away from the surface of the cervix.

3. 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.[41]

CONCLUSION

Cervical cancer is a significant global issue, particularly in low- and middle-income countries (LMICs) where resources and access to treatment are limited. In 2020, the World Health Assembly passed a resolution aiming to eliminate cervical cancer by 2030. This involves achieving three key targets: (1) vaccinating 90% of girls against HPV by age 15, (2) screening 70% of women at ages 35 and 45 using high-performance tests, and (3) treating 90% of precancerous lesions and managing 90% of invasive cancer cases.[3]

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