IJFANS INTERNATIONAL JOURNAL OF FOOD AND NUTRITIONAL SCIENCES
ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 12, Iss 1, 2023

CURRENT CHALLENGES AND FUTURE DIRECTIONS IN CERVICAL CANCER THERAPY

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ABSTRACT
Cervical cancer ranks as the fourth most common cancer among women globally, resulting in over 300,000 deaths annually. It is primarily caused by persistent infection with high-risk types of human papillomavirus. Viral oncoproteins E5, E6, and E7, in conjunction with host factors, drive and sustain the malignant phenotype. Cervical cancer is largely preventable, and early detection significantly improves survival rates. In high-income countries with effective vaccination and screening programs, the disease incidence is low. Conversely, in low- and middle-income countries with limited resources, many women present with advanced, often untreatable disease, leading to high mortality rates. Treatment options include surgery, chemotherapy, and radiotherapy, administered singly or in combination.

KEYWORDS: Cervical cancer, E6/ E7 oncoproteins

INTRODUCTION
Cervical cancer ranks as the fourth most prevalent cancer in women worldwide and holds the fourth highest mortality rate among cancers affecting women. The majority of cervical cancer cases are preventable through regular screening and treatment of precancerous lesions. Consequently, most diagnoses occur in regions with inadequate screening protocols[1].
Incidence and Mortality

In 2024, estimated new cases and deaths from cervical cancer (uterine cervix) in the United States are as follows:

- New cases: 13,820
- Deaths: 4,360

INITIATION AND PROGRESSION OF CERVICAL CANCER
Cervical cancer originates in the cervix, the narrow opening into the uterus connected to the vagina via the endocervical canal[2]. The cervix comprises two main parts: the ectocervix covered with stratified squamous epithelial cells, and the endocervix lined with simple columnar epithelial cells. The squamocolumnar junction, where these epithelia meet in the endocervical canal, forms the transformation zone. This zone is crucial as it undergoes

metaplastic changes replacing columnar epithelium, making it susceptible to cervical cancer development through persistent HPV infection[3].

Cervical cancer primarily presents in two histological subtypes: squamous cell carcinoma (SCC) and adenocarcinoma. SCC, originating from squamous cells in the ectocervix, constitutes about 75% of cervical carcinoma cases. Adenocarcinoma arises from glandular cells producing mucus in the endocervix. Given its prevalence, this review focuses on the progression of SCC [4].

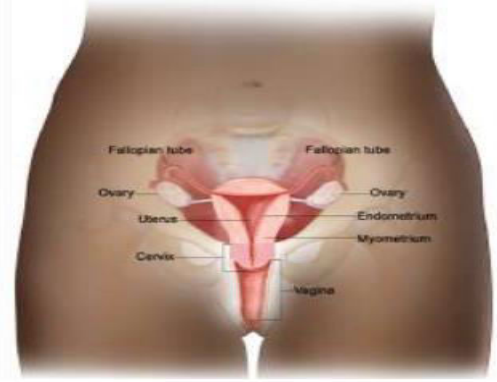

Figure 1: Female Reproductive System

A) Anatomical Diagram of Female Reproductive Organs

Cervical cancer begins with the growth of abnormal cells in the cervix, the lower part of the uterus that connects to the vagina. Most cervical cancers are caused by various strains of the human papillomavirus (HPV), a common infection transmitted through sexual contact. Normally, the body's immune system clears HPV infection without harm. However, in a small percentage of individuals, the virus can persist for years, leading to changes in cervical cells that can eventually develop into cancer[5].

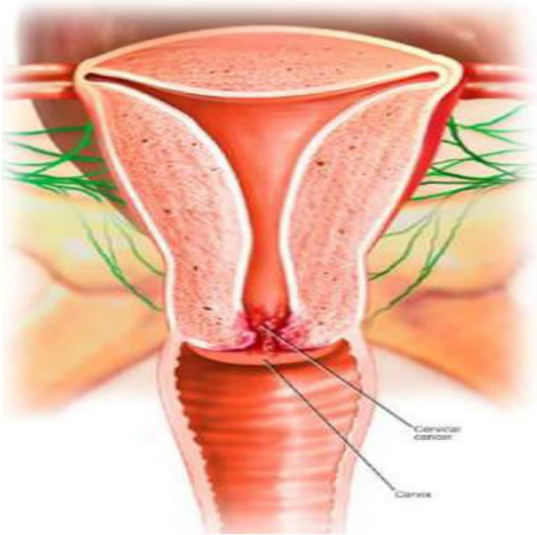

Figure 2: Anatomy of cervix

You can lower your risk of developing cervical cancer through regular screening tests and vaccination against HPV infection. If cervical cancer is diagnosed, initial treatment typically

involves surgery to remove the cancerous tissue[6]. Additional treatment options may include medications to target and eliminate cancer cells, such as chemotherapy and targeted therapies. Radiation therapy, using high-energy beams, may also be employed, sometimes in combination with low-dose chemotherapy [7].

SYMPTOMS

In its early stages, cervical cancer may not produce noticeable symptoms. As the cancer progresses, symptoms may include:

- Vaginal bleeding after intercourse, between periods, or after menopause.
- Heavier and longer menstrual bleeding than usual.
- Watery, foul-smelling vaginal discharge that may be heavy.
- Pelvic pain or pain during intercourse.

CAUSES

Cervical cancer begins when healthy cells in the cervix undergo changes in their DNA. DNA provides instructions for cell function, but these changes can prompt cells to multiply rapidly and continue living beyond their normal life cycle, resulting in an accumulation of cells that can form a tumor. These abnormal cells can invade and damage surrounding healthy tissue, and over time, may spread to other parts of the body[8].

Most cervical cancers are caused by HPV, a common virus transmitted through sexual contact. While HPV infection usually resolves without issues, in some cases, it can lead to cellular changes that increase the risk of cancer development [9].

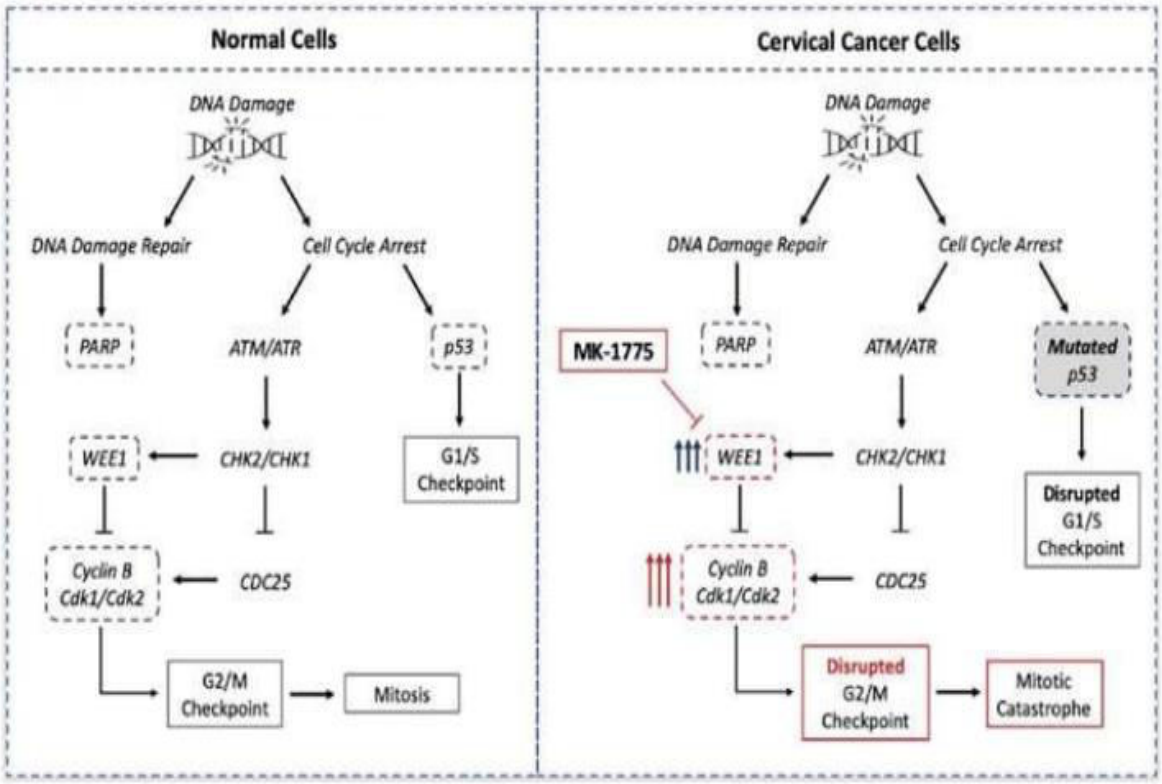

Figure 3: Differentiation between Normal and Cervical Cancer Cells

TYPES OF CERVICAL CANCER

Cervical cancer is classified into types based on the specific cells where the cancer originates. The primary types of cervical cancer include:

1. Squamous Cell Carcinoma: This type begins in thin, flat cells known as squamous cells, which line the outer part of the cervix. Squamous cell carcinoma accounts for the majority of cervical cancer cases.
2. Adenocarcinoma: This type starts in the column-shaped glandular cells that line the cervical canal.

DIAGNOSIS AND TREATMENT

Screening tests are essential for detecting cervical cancer and identifying precancerous cells that may develop into cervical cancer over time. Most medical guidelines recommend starting cervical cancer screening, including for precancerous changes, at age 21. These tests are typically repeated every few years[10].

Screening tests include:

1. Pap Test: During a Pap test, a healthcare provider collects cells from the cervix using a scraping or brushing method. These cells are then examined in a laboratory to detect any abnormal changes.

A Pap test can identify cervical cancer cells and detect precancerous cell changes that increase the risk of cervical cancer.

2. HPV DNA Test: The HPV DNA test involves testing cervical cells for infection with high-risk types of HPV that are most likely to lead to cervical cancer.

The type of treatment for cervical cancer depends on the cancer's stage at diagnosis. Advanced cancers often require a combination of treatments. Standard treatment options include:

- Surgery
- Radiation therapy
- Chemotherapy
- Other medications

1. SURGERY

Small cervical cancers that have not spread beyond the cervix are typically treated with surgery. The choice of surgical procedure depends on factors such as the cancer's size, stage, and whether future pregnancy is desired.

Options may include:

1. Surgery to remove the cancerous tissue only
2. Trachelectomy, which involves removing the cervix while preserving the uterus
3. Hysterectomy, which involves removing both the cervix and uterus

RADIATION THERAPY

Radiation therapy employs high-energy beams, such as X-rays or protons, to destroy cancer cells. It is commonly used alongside chemotherapy as the primary treatment for cervical

cancers that have spread beyond the cervix. Additionally, radiation therapy may follow surgery if there is an increased risk of cancer recurrence [11].

Radiation therapy can be administered in the following ways:

1. External Beam Radiation Therapy: Radiation is directed externally at the affected area of the body.
2. Brachytherapy: Radioactive material is placed inside the vagina temporarily, typically for a few minutes.
3. Combined External and Internal Radiation Therapy: Both external beam and brachytherapy are used in combination.

CHEMOTHERAPY

Chemotherapy involves powerful medications designed to kill cancer cells. For cervical cancer that has spread beyond the cervix, low-dose chemotherapy is often combined with radiation therapy to enhance treatment effectiveness. Higher doses of chemotherapy may be recommended to manage symptoms of advanced cancer.

Chemotherapy may also be used before surgery to shrink the size of the cancer.

TARGETED THERAPY

Targeted therapy uses medications that target specific molecules within cancer cells. By blocking these molecules, targeted therapies can cause cancer cells to die. Targeted therapy is typically used in conjunction with chemotherapy and may be considered for advanced cervical cancer cases [12].

IMMUNOTHERAPY

Immunotherapy utilizes medications that boost the immune system's ability to recognize and kill cancer cells. This treatment helps immune system cells locate and attack hidden cancer cells that evade detection. Immunotherapy may be an option for advanced cervical cancer when other treatments have not been effective.

PREVENTION

1. Primary Prevention:

Primary prevention strategies include adopting healthy lifestyles such as abstinence and safe sex practices, quitting smoking, and receiving HPV vaccination. Implementing changes in sexual practices, such as condom use, can reduce the transmission of both HIV and HPV, though this can be challenging to implement .

2. Secondary Prevention:

Secondary prevention aims to detect and treat preinvasive cervical lesions before they progress to invasive cancer. There are various modalities for secondary prevention.

FUTURE PROSPECTS

Cervical carcinoma remains a largely preventable disease, yet approximately 4,248 women in South Africa succumb to it annually. Research underscores that well-implemented, systematic national cervical screening programs can substantially reduce morbidity and mortality rates associated with cervical cancer. The World Health Organization (WHO) emphasizes that successful screening programs necessitate over 80% coverage, proper

follow-up and management of positive cases, seamless links between screening, diagnosis, and treatment services, high-quality care, and adequate resources. This applies across all screening methods including cytology, HPV testing, and VIA/VILI.

Currently, South Africa lacks an effective nationwide screening program. Partial screening efforts are underway in some regions, while opportunistic screening predominates in the private sector. A new cervical cancer control policy, integrating advanced technologies with existing screening strategies, is slated for release soon. Various cytologic modalities are available as alternatives to conventional cervical smears examined manually by technologists under a microscope.

Liquid-based cytology (LBC) represents a distinct approach to preparing cytologic specimens for microscopic evaluation. Despite being available for the past 15-20 years, LBC adoption has been limited in public sector laboratories due to its costliness. Some studies indicate improved specimen adequacy and abnormality detection with LBC, potentially justifying its expense. Plans are underway to introduce LBC in public sector laboratories. Additionally, computer-assisted screening of LBC smears is expected to aid cytotechnologists in their work

CONCLUSION

Cervical cancer prevention services should be integrated with treatment and palliative care services. Based on the experience of the ACCP, collaborators, and local partners, two overarching strategies can effectively reduce the burden of cervical cancer.

For countries lacking radiotherapy, radical surgery, or chemotherapy capabilities, the focus should be on:

- Establishing and enhancing cervical cancer prevention services to mitigate the future demand for resource-intensive treatments.
- Implementing and strengthening palliative care services across all levels of healthcare facilities, including community-based care.
- Initiating investments in centralized basic treatment services for cervical cancer.

For countries with limited cervical cancer treatment capacities, the strategy should encompass:

- Strengthening cervical cancer prevention services to reduce the future demand for intensive treatments.
- Enhancing palliative care services across all healthcare levels, including community settings.
- Reinforcing and expanding access to radical surgery, where feasible.
- Strengthening and improving access to existing radiotherapy services.

These strategies aim to enhance overall cervical cancer management by integrating prevention, treatment, and palliative care services effectively.

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