Scholars Academic Journal of Pharmacy (SAJP)
Abbreviated Key Title: Sch. Acad. J. Pharm.
©Scholars Academic and Scientific Publisher
A Unit of Scholars Academic and Scientific Society, India
www.saspublisher.com

ISSN 2347-9531 (Print)
ISSN 2320-4206 (Online)

Pharmacology

Cervical Cancer- A Disease Affecting Millions

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Review Article

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Article History
Received: 15.02.2018
Accepted: 21.02.2018
Published:28.02.2018

DOI:
10.21276/sajp.2018.7.2.6

Abstract: Cervical cancer is one of the primary cancers affecting women worldwide. It is another term used for malignant neoplasm originating from the cells of cervix uteri. Cervical cancer is the 2nd most frequent cancer among women globally, among a predictable 528,000 latest cases along with 266,000 deaths between women every year. The culprit behind this disease is Human papillomavirus. About 70% of cervical cancers are caused by type 16 and 18 HPV. The occurrence of HPV is greater in countries where cervical cancer burden is high. Its prevalence depends upon genetic and non-genetic factors. The latter include diet, exercise, lifestyle etc. The treatment for cervical cancer varies among countries due to lack of expertise in radical pelvic surgery. Many times, radiotherapy is combined with chemotherapy for effective cure. Recent advances in the areas of surgery, radiotherapy, and chemotherapy for the treatment of cervical cancer have significantly reduced patient fatality rate with better quality of life. The development and implementation of a combination of CT/RT have escalated survival rates in many cases. Bevacizumab in chemotherapy has also improved survival rates. But despite so much progress made in recent years, there is still no sure shot treatment available and prevention of cervical cancer is still a long way to go. Early stage screening can prove to be beneficial for early detection and treatment. There is still need of targeted drugs for treating cervical cancer. A lot of research work is being carried out in this direction.
Keywords: HPV, Radiotherapy, Bevacizumab, Screening, Chemotherapy.

INTRODUCTION

The human body consists of a number of cells. Typical body cells mature, separate into a new cell and die in a systematic manner.

Normal cells segregate faster to permit the human being to grow. When cells in the body start to develop out of control then cancer begins. The growth of cancer cells is unusual from the standard growth of cells. These cells continue to multiply and form a new abnormal cell instead of dead of these cells [1]. Worldwide, uterine cervix cancer is primary cancer among women which is known as cervical cancer. The lower part of the uterus is known as the cervix. It is cylindrical in shape and connects the vagina and the uterus [2]. Cervix cancer may initiate from the mucosal surface of the cervix. Uterine cervix cancer grows locally and can expand in a link to the uterus, par cervical tissues, and pelvic organs. Uterus cervix cancer is separated into cervix squamous cell cancer and Cervix adenocancer. In the case of cervical cancer cervix squamous cell cancer are more common than adenocancer [1]. Abnormal vaginal bleeding is a common symptom of cervical cancer, but in several cases, there can be no noticeable symptoms until the carcinoma has progressed to a complex phase**.** Human papillomavirus (HPV) appears to be a basic cause in the expansion of about all cases of cervix cancer [3].

Human papillomavirus is tiny, nonenveloped double-stranded DNA tumor virus which infects squamous epithelium, as well as skin and mucosa of the upper respiratory and anogenital tract. The genome is wrapped in a capsid case involving focal and small structural proteins. It is primarily multiplied during sexual contact. Human papillomavirus is more than 120 subtypes and their structure has common including three main section such as early section (E), late section (L) and genome regulatory section. Genital HPV is acquired during close skin contact, not immediately penetrative sexual activity and has a lifespan possibility of disease up to 80% in bare persons. The incidence of Human papillomavirus in women decreases with age but increase by increasing the statistics of sexual cohorts. The majority of HPV infections are asymptomatic and self-preventive. 10–15% of women are infected with determined HPV and is related to a different form of cancer. More than 70% of uterus cervix cancers are caused by type 16 and 18 human papillomaviruses. Typically, four phases are explained the growth of cancer from HPV. Phase 1 is defined with HPV possession, which can be followed by a determination (phase 2). Phase 3 is a premalignant infection and the final phase is attacked primary to

cancer (phase 4). Once incorporated into the genome of the host cell, HPV can reason of hereditary rearrangement include deletion, translocations, and establishment of proto-oncogenes. Although HPV is essential for alteration of the contaminated cell, it is not adequate on its own and requires supplementary epigenetic actions, as well as inflammation, distorted immune action or contact to ecological factor. It is obvious that HPV disease is causally associated to uterus cervix cancer and its pioneer lesion. While HPV has a high incidence, the frequency of uterus cervix cancer is low, so another factor is probably to influence infection development. Cervix cancer can also be related with vaginal liberation, dyspareunia or pelvic ache [4].

Epidemiology

Human papillomavirus disease is the most frequent sexually transmitted disease globally and most sexually energetic persons of mutual sexes will get it at several points in their existence. On the source of a meta-study of 1 million women through typical cervical cytology, about 291 million women globally are expected to enclose human papillomavirus disease of the cervix at a certain position, equivalent to a standard incidence of 10·4%, although predominance (16·9%) is advanced in women less than 25 years. Approximately 70% of cervix cancers are due to type 16 and 18 HPV. Approximately 24% of women have been identified with type 16 human papillomavirus disease; type 18 has been identified in approx.9 % [5]. Cervical cancer is the 2nd most frequent cancer among women globally, among a predictable 528,000 latest cases along with 266,000 deaths between women every year. An inconsistent figure of these reports (85 %) and deaths (87 %) happen between women livelihood in developing countries. Women livelihoods with HIV are at enlarged risk of emergent cervix cancer and incident more fast development of the infection [6]. It is greatly less frequent in the US as of the usual utilize of Pap smears [3]. HPV is one of the most frequently sexually communicated infection in the world and the most sexually active people get affected by it at some stage of their life. About 70% of cervical cancer cases happen because of HPV type 16 and type 18. The occurrence of HPV is generally higher in countries where the burden of cervical cancer is high like Latin America, Sub-Saharan Africa and India. Exceptions are China and Mongolia where the disease burden is unknown but the still, occurrence is high. HPV occurrence is maximum in young women and slows down after 35 years. The second jump in prevalence is observed after 55 years in some Latin American countries [5]. The HPV infection diagnosed in women above 30 years of age is likely to be more persistent and longer lasting. The scenario in the US is quite different. The prevalence of cervical cancer has significantly reduced. African- American women endure 72% higher frequency of cervical cancer and 13% of the lesser rate of survival than Caucasian women [7].

86% of the deaths due to cervical cancer occur in low to medium income countries. In India, about 122,844 women are detected with cervical cancer and almost 67,477 do not make through. Women who are older than 15 years are at risk. India also ranks highest in the age-standardized occurrence of cervical cancer in South Asia. The age group at which the incidence of cervical cancer is highest is 15-44 years. According to the survey conducted between 2009 and 2011, Aizwal was declared as the place with the highest incidence of cervical cancer in India [8].

Signs and symptoms

The premature phase of cervical cancer can be entirely asymptomatic. The occurrence of the tumor is designated by vaginal hemorrhage, contact hemorrhage, or (seldom) a vaginal accumulation. Moreover, temperate pain in sexual activity and vaginal liberation are a sign of cervix cancer. In sophisticated infection, metastases can be available in the stomach, lungs. Sign of complex cervix cancer can comprise a failure of enthusiasm, weight loss, weakness, pelvic ache, backache, legacy, inflamed legs, serious hemorrhage from the vagina, bone rupture, and (seldom) outflow of urine from the vagina [1]**.**

Causes of cervical cancer

Cervical cancers begin on the surface of the cervix. There are two kinds of cells are present on the surface of the cervix: squamous and columnar. Squamous cells are mainly responsible for cervical cancer. All cervical cancers are mainly caused by HPV (human papillomavirus). HPV is a common virus that enhances during sexual intercourse. There are many different types of HPV [3]. Women having multiple sexual partners leads to a higher risk of cancer. Genital warts are the condition of benign cancer of epithelial cells, are caused by different strains of HPV.

The occurrence of growing cancer depends equally on genetic and non-genetic factors. A genetic factor is hereditary, consistent feature and a non-genetic factor is variable and can be changed frequently. Non-genetic factors may consist of diet, exercise, or exposure to other substances in the environment. Other factors which are responsible for cervix cancer are as follows

- **Cigarette smoking:** it is one of the major reasons for a higher risk of developing cervical cancer. Smoking also increases the risk of squamous cell cancer by exposing the body to cancer-causing chemicals and also by weakening the immune system. Women who smoke suffer from a greater risk of cervix cancer.
- **Reproductive factors:** Most common route of spread of HPV infection is through sexual contact, especially early onset sexual activity, multiple partners, high- risk sexual partners.

- **Immunosuppression:** Women who are taking immunosuppressive medications leads to a greater risk of developing cervical cells deformity.
- **Lower socioeconomic status:** The occurrence of cervical cancer is superior to poor and uneducated women living in rural areas as compared to women living in of higher urban areas.
- **Long-term mental stress:** high levels of stress in women over a constant period are at increased risk of developing cervical cancer [1]**.**
- **Immune system:** A weak immune system, due to HIV or immunosuppressive drugs, leads to women at increased risk of cervical cancer.
- **Multiple pregnancies:** Women with 3 or more pregnancies are at a higher chance of developing cervix cancer due to hormonal changes.
- **Dietary habits:** A diet deficient in fruits, vegetables, or an overweight person, leads to higher risk of cervical cancer
- **Diethylstilbestrol (DES)**: DES increases the risk of adenocarcinoma in the cervix, especially in women during pregnancy [9]**.**

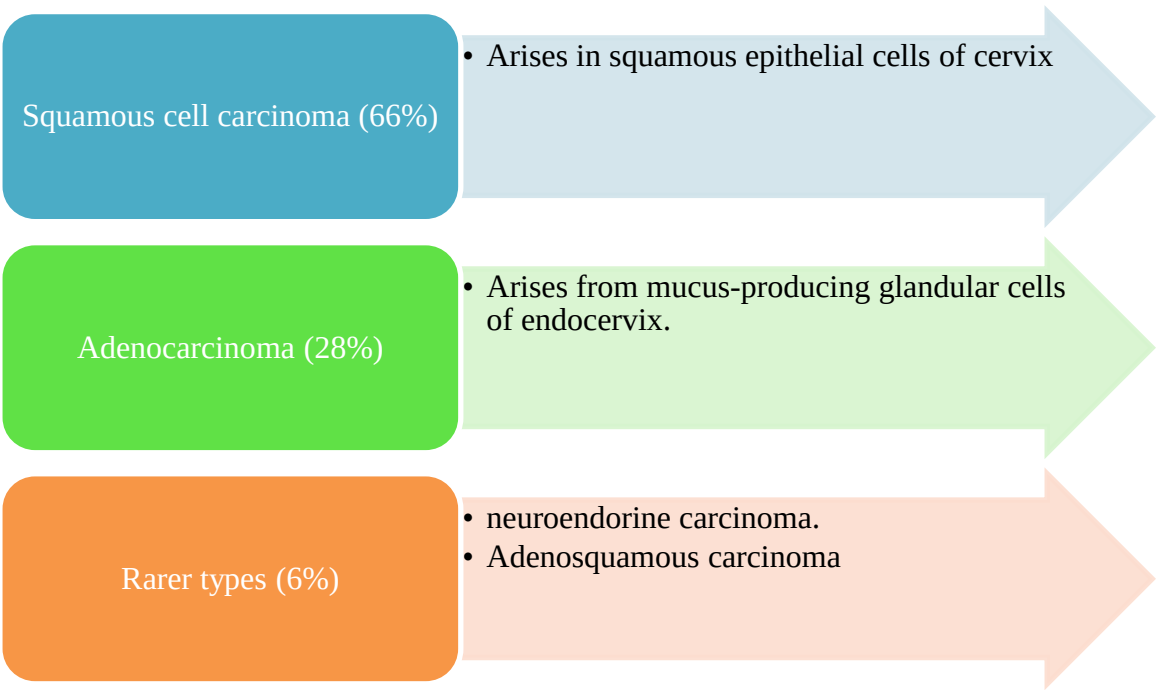

Fig-1: Pathologic types of cervical cancer [9]

Diagnosis of cervical cancer

Visual inspections

Visual inspection with acetic acid (VIA) or visual examination with Lugol's iodine (VILI) are the major screening techniques in most countries due to their low price and use of less equipments. In VIA test, the cervix is washed with an acetic acid solution, and as a result, abnormal cells become white and they are easily visible to the eyes. And in VILI test, the cervix is cleaned with Lugol's iodine, and as a result of it, higher lesion on the cervix gets stained with it.

Papanicolaou (Pap) Smear

In a Pap smear, a sample of cells from the cervix is taken with a small wooden spatula or brush and examined under the microscope. Due to the higher requirement of equipment and advanced trained personnel, the results are not easily available. It can be insensitive due to condition of the cervix at the time of taking that's why need to be done at regular intervals to avoid the unwanted results [10]**.**

Colposcopy A

Speculum is inserted into the vagina and the cervix is visualized in the microscope. Colposcope is used for the examination of cervix

Biopsy

precancer and cancer confirmation is done by biopsy. It is done by colposcopy. The cervix is stained with acetic acid and then iodine which stains any abnormal epithelium. a biopsy is done by the help of following medical devices mainly include punch forceps or Spira Brush CX, loop electrical excision procedure (LEEP) and conization techniques are used for further treatments in which inner lining is removed and examined carefully.

Examination under anesthetic (EUA)

General anesthetic is used for the examination of cervix and vagina. Cystoscopy is used for the detection of bladder or/and the colon and rectum with a procto-sigmoidoscope to detect cancer.

CT (computerized tomography) scans

A sequence of narrow beams is emitted through the CT scanner from the human body. The x-ray detector is present inside the CT scanner which detects hundreds of stages of different density. Barium drink is given to patients before the procedure. The barium appears white on the scan. A tampon may be placed into the vagina before the scanning, and barium liquid may be placed into the rectum. The whole procedure takes from 10 to 30 minutes.

MRI (magnetic resonance imaging scan)

In this technique magnetic and radio waves are produced. Researchers may possibly be able to detect cervical cancer in its early phase with the help of the vaginal coil.

Pelvic ultrasound

High-frequency sound waves are used to generate an image on a monitor [1]**.**

Stages of cervical cancer

Cervical cancer is staged by the International Federation of Gynecology and Obstetrics (FIGO) staging system, which is based on clinical examination. Following diagnostic tests are used to detect the stages: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, an X-ray examination of the lungs and skeleton, and cervical conization.

Stage I: Invasive cancer identified only microscopically. All gross lesions even with superficial invasion are Stage IB cancers.
Stage I is subdivided as takes after:

IA Invasive carcinoma which can be analyzed just by microscopy, with most profound attack <5 mm and the biggest expansion <7 mm

- **IA-1** Measured invasion attack of <3.0 mm top to bottom and expansion of <7.0 mm
- **IA-2** Measured invasion attack of >3.0 mm and not >5.0 mm with an expansion of not >7.0 mm

IB Clinical lesions confined to the cervix or preclinical lesions greater than IA

- **IB-1** Clinical lesions <4.0 cm in measurement
- **IB-2** Clinical lesions >4.0 cm in measurement

Stage II: The carcinoma extends beyond the cervix but has not extended to the pelvic wall. The carcinoma involves the vagina but not as far as the lower third.

- **IIA**-with no parametrial attack
- **IIB**- With clear parametrial attack

Stage III: The carcinoma has extended to the pelvic wall. The tumor involves the lower third of the vagina. All cases with a hydronephrosis or nonfunctioning kidney are included unless they are known to be due to other causes.

- **IIIA** No extension to the pelvic wall.
- **IIIB** Extension to the pelvic wall and/or hydronephrosis or non-working kidney

Stage IV: The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. Bullous edemas as such do not permit a case to be allotted to Stage IV.

- **IVA** Spread of the growth to adjacent organs.
- **IVB** Spread to distant organs [11]**.**

Treatment of cervical cancer

Cervical cancer is another term used for the malignant neoplasm originating from the cells of cervix uteri [3]. Its treatment varies between different countries because of lack of expertise in radical pelvic surgery [11]. Many factors influence the treatment for cervical cancer like its stage, location, type, age, and choice to have children [12]. The choice of treatment depends mainly on the size of the tumor and whether the cancer has spread. Surgery is an option for women with Stage I or II cervical cancer.

Radical hysterectomy

The whole uterus is removed including nearby tissues, lymph nodes and the upper third of the vagina. In few conditions, the ovaries, fallopian tubes, and lymph nodes are detached. It can be combined with chemotherapy or radiation therapy.

Pelvic exenteration

All the organs of the pelvis, including the bladder and rectum, are removed in the surgery.

Lymphadenectomy

It involves Surgical exclusion of the lymph nodes. It is known as lymph node dissection(LND), either bilateral or unilateral.

Radical Trachelectomy

This surgery involves removing the cervix, together with the top 2-3cms of the vagina and joining the top of the vagina to the lower segment of the uterus. It is used mainly to preserve the fertility with lymphadenectomy.

Radiation Therapy

Radiation therapy uses high-frequency rays to kill cancer cells.

Radiation therapy is either external or internal.

- Internal radiation therapy- a radioactive material is filled in the device which is used during the surgery and place inside the woman's vagina and the device is removable.

- External radiation therapy - A large machine directs radiation at your pelvis or other areas .with cancer.

Chemotherapy

The drugs are used to kill cancer for the treatment sometimes chemotherapy is combined with the radiation therapy. Drugs used for the treatment of cervical cancer chemotherapy include

- 5-FU,
- Cisplatin,
- Carboplatin,
- Ifosfamide,
- Paclitaxel,
- Cyclophosphamide(3)
- Bleomycin
- Hymactin

The side effects depend mostly on the dosage of the drugs given. Chemotherapy lowers the levels of blood cells, bruise occurs. It may lead to hair loss. It can lead to a condition like poor appetite, nausea and vomiting, diarrhea. And other side effects include skin rash, numbness in hands and feet, hearing aid problems, loss of balance, joint pain.

Cone Biopsy it involves removal of a cone-shaped segment of the cervix both ectocervical and endocervical tissue [1]**.**

Recent advances

Recent advances in the areas of surgery, radiotherapy, and chemotherapy for the treatment of cervical cancer have significantly reduced patient fatality rate with better quality of life. The primary reason behind greater fatality in developing countries is due to lack of awareness about cancer and limited quantity and low quality of resources available for treatment. The most recent advances include development and implementation of a combination of CT/RT which has escalated survival rates in many cases [13].

Recently, there has been the introduction of novelty in radiotherapy with the usage of external radiation therapy called teletherapy and brachytherapy guided by magnetic resonance imaging (MRI). But these therapies come with a disadvantage. With these therapies, too much time is spent on a single patient which makes the treatment overall a slow process and not accessible to everyone on time. Recently, the drug bevacizumab has gained a lot of appreciation. It is a monoclonal antibody directed against vascular endothelial growth factor. The use of bevacizumab in cervical cancer chemotherapy significantly improved survival rate with an increased overall response. Other similar agents are currently being explored for their potentials similar and beneficial use like sunitinib, lapatinib, pazopanib, and cediranib [14].

Most recently, two HPV vaccines namely, Gardasil and Cervarix, have been approved by FDA which are highly effective against HPV infection. Cervarix is mainly active against HPV type 16 and 18 (more prevalent in India) whereas, Gardisil has shown more activity against HPV type 6,11,16 and 18. Another drug which has proved efficacy recently is pazopanib which act by blocking certain growth factors in cancer cells. The growth promoters it blocks are mainly kinase proteins [9].

Detection and early diagnosis of cervical cancer are important as it saves many cases from worsening. Papanicolaou smear test was one such screening test which detected cancer at early stages for past five decades. Recent advances have occurred in screening area also with liquid-based cytology doing wonders. It is more effective with almost no sampling issues. Also, there has always been an issue with molecular test costs in low or medium income developing countries. Xpert HPV is one good solution to cost problems. It is the low-cost point of care test which has recently shown efficacy in a trial in Papua New Guinea. Topical immune response modulators like imiquimod and Yallaferon have been developed to deal with chronic and recurrent HPV- induced lesions. These are recombinant interferon alpha-2b gel. But still, the recurrence rate is high. Currently, lopinavir and cidofovir are being tested for their efficacy in treating precancerous lesions. Recently, T- cell therapy has also gained attention as a novel treatment for metastatic cervical cancer. This therapy involves the infusion of E6 and E7 specific tumor infiltrating T lymphocytes to cause shrinking of the tumor. But such therapies offer challenges when it comes to delivery [15]. Despite so many discoveries and research, prevention of cervical cancer is still a long way to go. Early stage screening can be beneficial for early detection and treatment of cervical cancer [9].

Future prospects

Despite so much progress made in recent years, there is still no sure shot treatment available for cervical cancer. In future, development in technology should be made with significant upgradation in software technology to facilitate a better understanding of the patient's case. High definition images of cancer cells give a better idea of the cancer stage [16].

There is still utmost need of targeted drugs for treating cervical cancer. Future research in this field should address to molecular pathways involved, functional consequences of alterations, identification of potential biomarkers. The associated biological pathways should be explored and molecular targets identified. Moreover, there is no second line therapy available for metastatic cervical cancer so significant research and clinical studies can be conducted in this direction in future [17].

The area offering immense research in cervical cancer is targeting. Targeting the molecules involved in virus-host interactions which are critical to the thriving of HPV could be interrupted. Specific drug delivery systems need to be developed to target the better conserved cellular proteins with minimal side effects [18].

CONCLUSION

Although the condition of women suffering from cervical cancer in developed countries has improved over the years women in countries with limited resources still suffer. It is important to identify and provide the most important resources required for treatment. More work should be done on prophylaxis of cervical cancer like vaccination. Also, the treatment should be individualized based on the condition of a patient like age, stage, lifestyle etc. There should be more focus on prevention, early detection and timely therapy and fertility preservation. Efforts must be made to improve the quality of life of patients by catering to health needs. As is always said that "Prevention is better than cure", more efforts should be diverted in prophylaxis as it is also cost-effective. So, diagnosis tests like HPV tests and Pap smear tests should be made cheaper and available to the public.

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