



An Overview of Pathophysiology and Management of Cervical Cancer

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ABSTRACT

Cervical cancer is a persistent health problem worldwide, especially in developing countries where getting good health care facilities, treatment and screening is a dream. This review paper gives an inclusive overview of pathophysiology and management strategies for cervical cancer. Beginning with the discussing normal physiology of those parts which are involved in cervical cancer such as vagina, cervix, and the pathophysiology of cervical cancer which include HPV infection. The paper explores the stepwise progression from normal cervical tissue to invasive carcinoma and shedding light on the complication occur in the cervical cancer. This article gives proper information about the clinical feature or symptom which helps to identifies the Undiagnosed cervical dysplasia, then can be treated in more efficient way and also provide info about the FIGO (International Federation of Gynecology and Obstetrics) staging approach in cervical cancer for the clinical evaluation. Furthermore, the review highlights ongoing research efforts to improve screening facilities, prevention programs, treatment tactics and supportive care for cervical cancer patients. Emerging technologies like nano technology and advancements in chemotherapy. Overall, this review Can be a great asset for healthcare professionals, Scholars & policymakers working at avoiding, screening & Approaches to treating cervical cancer. By elucidating the complex pathophysiology and outlining current management approaches, it aims to contribute to the global efforts towards reducing the burden of this devastating disease.

Keywords: Cervical cancer-1, mortality-2, worldwide-3, pathophysiology-4, HPV-5, Cervix-6.

INTRODUCTION

One of the top four cancers diagnosed in women worldwide is Cancer of the cervix. A certain form of Neoplasm that starts in the cervix, or lower Portion of the uterus, and travels to the vaginal opening is called cervical cancer.¹ This human virus is the main reason of this type of disease which is intimately transmit and approx. 80% of women infected by the HPV infection². This type of infection are very often in the time of adolescence and early adulthood³ but Women of all ages are affected by cervical cancer because it may take 10 to 15 years to exhibit any changes in cervix, which is why it's a very serious global health issue because access to adequate screening and healthcare resources is restricted in middle and lower wages brackets nations **expected** Shortage in facilities, technology, & awareness⁴.

The two most common histological types of cervical cancer are adenocarcinoma and squamous cell carcinoma. Adenocarcinoma accounts for approximately 70% of cases, while squamous cell carcinoma makes up around 25% of cervical cancer diagnoses. Respectively, the Precancerous abnormalities usually mark the beginning of the progression of cervical cancer in the cervical cell and there are exceeding 200 forms of HPV point out found on DNA series and if treatment is not received at the right time, then these changes will eventually grow into an invasive malignancy. It is possible to discover it early and take action with routine screening techniques like HPV tests and Pap smears because cervical cancer develops slowly.⁵

While Cancer of the cervix rates have fallen in wealthy countries, it remains a major health problem in underdeveloped and poor nations. despite improvements in preventive methods like HPV immunization and surgical treatment. Over Seventeen out of twenty mortality rate came from cervical cancer occur in nations with middle & low incomes.⁶ Global takes action to prevent and control the risk factor of cervical cancer. It must cover advanced infrastructure, drilling on risk factors, strengthen the healthcare facilities and awareness campaigns. This introduction set the foundation for the more thorough examination of cervical cancer's causes, risk factors, symptoms, diagnosis, available treatments, and preventative measures.⁷

PATHOPHYSIOLOGY

Normal Physiology

Vagina

In female reproductive system vagina perform a significant part in several important functions like menstruation, child birth or in pregnancy and in sexual intercourse. The human vagina is generally referred to as a slightly thick-walled S-shaped fibromuscular collapsible tube. Vagina connects or joins the vulva which is external genitals with the cervix (lower part of uterus).

The vagina is 6 to 10 cm (about 3.94 in) in length extending from cervix to uterus. It contains a unique microbiome, mostly composed of Lactobacillus bacteria (shaped like rods, non-spore-forming, gram-positive microbes). This



microbiome helps to keep the vagina atmosphere slightly acidic, thus it protects from pathogens. Despite not having a gland, the vagina secretes a large amount of fluid.⁸ When compared to the other part of female reproductive system, vagina is relatively thin and only consists of only three tunics: Mucosa is the deepest layer, muscularis is the intermediate layer, and adventitia is the uppermost layer. The lamina propria and a non-keratinized stratified squamous epithelium make up the mucosa, sometimes referred to as the mucous membrane or epithelium, this stratified squamous epithelium is similar to the lining of human mouth and this layer helps to protect the deeper tissues from friction, infection and irritation. Lamina propria is highly vascularized which means it contains blood vessels, lymphatic vessels and nerves. Two layers of smooth muscle comprise the muscularis, or middle layer, of the vagina, the inner circular muscle layer surrounds & helps to constrict or restrict the vaginal opening. The outer longitudinal muscle layer helps during childbirth or intercourse by stretching and expanding the vagina. The adventitia consists of areolar connective tissue on the outside and interior fibers that are elastic.⁹

Cervix

The uterus's bottom region contains the cervix, which has a muscular canal. Cervical canal which is 2 to 3 long and approximately 3mm (about 0.12 in) in diameter it forms a link between the vagina and the uterine lumen cervix have many roles, but the major function is to provide passage for the fluids to pass between the uterus and vagina and cervix cell shows the cell changes that can indicate the malignancy.¹⁰ The superior orifice (the opening) is commonly referred as internal os, inferior opening of cervix into the lumen commonly referred as external os.¹¹

There are several structures that support the cervix. First *Pubocervical fascias* a dense connective tissue that surrounds the lower part of the cervix and uterus.

second cardinal ligaments: These are two broad ligaments which extend from a cervix attaches to the pelvis structure and provides support for its cervix and uterus.

third Uterosacral ligaments: the back of cervix and the sacrum, the triangular bone at the base of the spine is joined together by two strong bands of tissue known as Uterosacral ligaments.¹²

The pathway between the internal and external ostia is referred as cervical canal. The portion of uterine cervix extending the ectocervix is the part that enters female reproductive tract. The ectocervix is lined by stratified squamous epithelia cells form the lining of outer surface of the cervix, the major function of these types of cells is to provide protection and support. The cervical canal is lined by columnar epithelial mucosal glands that secrete thick, mucous, acidic secretions. These secretions fill and seal the cervical canal and form a mucous plug, which prevents the penetration of pathogens to the uterus and the last type of cell is goblet cells which produces mucus in cervical canal and helps to protect the cervix from infection.¹³

Human Papilloma Virus (HPV)

It has been known since the 1970s that we came to know about the HPV (humanpapilloma virus) infection, which is one is among the primary reasons for cervical carcinoma. And there are varieties of Papillomavirus that can induce the malignancy of the cervix epithelium.¹⁴ Human papilloma virus is rapidly evolving into a global issue, mainly to developing countries, HPV triggering malignancy and the most significant and common of which is cervical cancer.¹⁵ Most people consider HPV infection can only spread through sexual activity, still, HPV can also spread by non-sexual routes such as vertical transmission during pregnancy and casual physical contact.¹⁶

Human papillomavirus (HPV) has double stranded DNA viruses, they belong to the papova virus family, comparing to the other virus HPV does not have any envelope to surround its capsid, the diameter of the PV virion is 55 nm, its DNA can replicate within the nucleus and has more than 7900 base pair genome and they are further divided into three groups 1. Early (E1, E2, E3, E4, E5, E6, E7), 2. Late (L1, L2), and 3. Control. These genomes' main functions are to encode viral proteins which are crucial for capsid formation. The outer shell of PVs is called capsid. This capsid possesses different types of symmetry called as icosahedral means it 'have 20 equilateral triangular faces with roughly spherical shape, they also have subunits called as capsomers approximately 72 capsomers join themselves to create a capsid structure and capsid main function is to provide protection to genetic material.¹⁷

Over 200 kinds of HPV virus are recognized for mankind but not all of them cause any serious health issue or development of any kind cancerous cell, however HPV virus divided into five genera: nu (ν), mu (μ), alpha (α), beta (β) and gamma (γ), additionally alpha and beta are thoroughly researched. The alpha papilloma virus group members cause infection in mucosal epithelia, furthermore according to the tendency to induce cancer the alpha papilloma virus separated into kinds that are high-risk (HR) and low-risk (LR). The low hazard virus causes viral infection such as benign tumors, and commonly caused by Ninety percent of genital warts are caused by HPV 6 and HPV 11. means they generally does not cause cancer but on the other hand HPV 16 & HPV 18 are the major reason of the 80% cervix cancer.¹⁸

Recent studies show that Cervical cancer is primarily dependent on the E6 and E7 oncoproteins. The E6 disrupt the p53 enzyme activity, E6 binds with P53 cause the interferences with the cell cycle, E6 bind with AP(accessory protein) which has ubiquitin ligase activity, E6+E6+AP combined with the p53 degradation region, which inhibit all the function of p53, which increases the uncontrolled replication of cells with HPV 16 or HPV 18 infection, when E7 oncoproteins form complex with pRb releases free E2F and inhibit pRb function, this ultimately causes the cell loss its control over the cell cycle.¹⁹



Clinical feature

Another health threat is cervical cancer. care problem, as the time passes it becomes worsened, so the clinical features of Cancer of the cervix can vary Based on the progression of cervix carcinoma. The main desire of identifying clinical features is to spot the pre-malignancy changes so they can be treated before they become severe form of cancer.²⁰The most typical signs of cervical cancer include Abdominal and pelvic pain as malignancy spreads, ongoing pelvic pain or discomfort could develop. Lower back or pelvic discomfort may feel vague or acute, pain or discomfort during sexual intercourse (dyspareunia) can be a symptom of advanced cervical cancer.²¹Foul-smelling vaginal discharge, particularly it happens in between menstrual cycles or after menopause, may indicate cervical cancer. The discharge may be watery which might be red in colour with foul smell. Changes in menstrual patterns, such as heavier or longer periods than usual, can be an indication of cervical cancer.²²Some other clinical features are painful intercourse, Vagina appears tight or narrow, Dryness and discomfort in the vagina and smell coming from the genitals.²³

Complication in cervical cancer

Many difficulties may arise from cervical cancer, especially if the disease is not identified and not treated in its early stages. Some common complications associated with cervical cancer include; 1st is metastasis in which cervical cancer can spread to nearby tissues and organs, including the bladder, uterus, pelvic wall and rectum. Pelvic pain can be caused by the tumor or by the cancer spreading to other tissues in the pelvis. Pregnancy with late cervical cancer typically shows pain due to tumor.²⁴Those patients who are suffering from cervical cancer for longer period may experience lower back pain or pelvic pain that can radiate to the lower extremities in the posterior side, swelling in the legs or leg edema, is not a direct sign of cervical cancer. However, several issues associated with cervical cancer, or its treatment can cause edema. Changes in the bowel or bladder, including Feeling pressure in the pelvis, along with blood in urine or stool, or unusual passage of these fluids, may indicate the advancement of disease.²⁵

ETIOLOGY

smoking

Smoking is a well-established hazard factor for Cancer of the cervix. Smoking tobacco heightens the likelihood of cervical cancer. They can ease the defense mechanism because it is making harder for the body to fight the HPV infection.²⁶Smoking also directly harms the cervical cells, the risk for the current various investigations, a higher dose of ingested tobacco corresponded to a greater response (negative outcome). The ORS was higher in more advanced pre-invasive neoplasms (order 1-3).²⁷ There are several mechanisms which Might raise the danger factor of cervix cancer. There is a Tobacco derivatives cause immunized deficiency Cigarettes include compounds, particularly nicotine and its catabolite, which can induce

harm the DNA in cells called squamous cells.²⁸ They may produce epigenomic alterations in the mucosa of the cervix, resulting to the pathogenesis of cancer in the cervix and in numerous areas of the body. The link between smoking and cancer of cervix has been recognized since the 1970s. This connection was observed through the correlation between the rates of cervical cancer and other cancers associated with tobacco use. The potential causal relationship between cigarette smoking and the development of cervical cancer deserves further independent investigation and analysis, separate from its interaction with HPV infection.³⁰

HPV

Cervical cancer is primarily caused by a persistent infection with high-risk strains of HPV, which are transmitted through sexual contact that are restricted by the barrier contraceptives and metaplastic of cervical squamous epithelium of transformation zone. HPV (human papillomavirus) is identified as the predominant causative agent in the steps involved in cervical cancer development. It is a type of virus which is transmitted through sexual contact.³¹ HPV is the most prevalent cause of pre-cancerous and malignant genital infections. In cervical cancer, there are most cases that occur due to the infection of HPV, with the type 16 and type 18. HPV, particularly HPV 16, has been discovered to be relatively frequent in the world.³² 99.7% of all cervical carcinomas bear high-risk HPV when the correction is made for the non-reproductive tissues and inadequate DNA. 75% HPV strains, specifically types 16 and 18, are recognized as the primary etiological agents responsible for the development of cervical cancer.³³

The C. trachomatis

C. trachomatis contributes to the higher incidence of cervix squamous cell carcinoma, they enhance the probabilities of tumours of squamous cells by raising the sensitivity to HPV or enhancing HPV effects.³⁴ It is common sexually transmitted infection that can increased the hazard of cervical cancer, particularly when they combined by means of the HPV infection, women with chlamydia may have debilitate ability to clear the HPV infection. Chlamydia infection can cause the inflammation in the cervix then they develop the cervical cancer.³⁵

HIV

They weaken the immune system. HPV is transmitted by sexual copulation and the primary cause of cervical cancer, The immune system of an HIV-positive person is less able to combat HPV infection, and there may be a higher incidence of persistent HPV infection among those with HIV who also have cervical cancer.³⁶ HIV and cervical cancer are linked that indicates women having with HIV have a higher chance of having high-risk HPV infections and persistent HPV infections.³⁷



Sexual partner

Multiple sexual partners may increase the danger of cervical malignancy. That's because the exposure towards different sexual partner increases the likelihood of on countering and enhances the strains risk of HPV, the threat aspect for cancer related to cervical is the early age of copulation.³⁸ It has been proposed that having sex when older is linked to a lower diagnostic age.³⁹

PATHOGENESIS

The FIGO staging approach is commonly involved for the female reproductive organ's tumor, specifically cancer related to cervical. FIGO staging relied on clinical evaluation, taking into account the high prevalence of cervical cancer in low-income areas with limited access to modern technologies, so that all the procedure or test related to the cancer is done in low cost, Staging is clinically assessed by tumor size and the degree of pelvic extension. The current FIGO staging system for cervical cancer relies on clinical examinations such as colposcopy, barium enema or lower gastrointestinal endoscopy, Physical examination intravenous pyelography, cervical or cone biopsy, and chest radiography are all acceptable for staging, as are a few other tests performed in select situations, like proctoscopy and cystoscopy. It is not predicated on findings made during surgery.⁴⁰ Surgical vs clinical staging which is most effective treatment approaches for different stages of cervical cancer? This has been a significant issue for several decades. Clinical staging is not as accurate as surgical staging, despite advancements in imaging modalities and tumor size measurement. The FIGO staging classifies cervical cancer as a local illness which affecting the pelvis so, Surgical staging cannot be used globally, particularly in countries with inadequate resources or less advancement in technology where late stages is widespread because of less awareness and surgical facilities are limited.⁴¹ One the basis of FIGO staging, the cervical cancer is mainly divided into 4 stages, and then treatment plan is based on these stages:

Stage I: In this stage cancer is still so small that it can only be visible with a microscope, and it has not spread deeply into the cervical tissues. Stage I carcinoma should be ignored if it is only present in the cervix and has not spread to the uterine corpus. Stage 1: subdivided into stage IA and stage IB.

stage IA: This invasive cancer can only be diagnosed through microscopic examination. During this stage, all visible lesions, regardless of size, are identified. According to FIGO staging criteria the stage IA tumor have maximum stromal invasion of 5 mm and lateral spread of 7 mm, the depth of invasion should not exceed 5mm and the measurement is from the epithelium's base to the original tissue, surface, or glandular.

IA1: These tumors exhibit stromal penetration not deeper than 3mm (≤ 3 mm), and horizontal spread not more than 7mm (≤ 7 mm) and they are associated with having very

low incidence of lymph node involvement. The fact that the presence of LVSI (lymphovascular space invasion) in stage IA1 cervical carcinoma raises the probability of lymph node metastases and cancer recurrence by about 5%.

IA2: Cervical cancer is detected only through microscopic examination, with a Strome's depth of invasion greater than 3 mm (> 3 mm) or less than 5 mm (≤ 5 mm), and a horizontal spread of less than 7 mm (≤ 7 mm).

IB: In this stage clinically specific lesion which are clinically noticeable or a microscopic lesion larger than A2. IB Also have 2 subpart which are IB1 and IB2

IB1: Invasive cancer stromal invasive depth of ≥ 5 mm and maximum size of < 2 cm

IB2: Clinical evident lesion with a maximum diameter of more than 4 cm⁴²

Stage II: Tumors spread beyond cervix but not through the wall of the pelvis. The cancer extends to the vagina but does not reach the bottom third.

Stage IIA1: Clinically noticeable or visible lesion 4cm or less (~ 4 cm), , involving less than the vagina's top two thirds

stage IIA2: Noticeable lesion in a clinical setting 4 cm with involvement in less than the vaginal upper two thirds

Stage IIB: Not into the pelvic side wall, but clearly involved in the parametrial involvement⁴³

Stage III: Cancer impacts the pelvic barrier, the lower component of the genitals hydronephrosis or a non-functioning kidney, and/or the pelvic and/or para-aortic lymph nodes.

stage IIIA The cancer only affects the vagina's bottom part; it does not extend to the pelvic wall.

stage IIIB: Extension to the pelvic wall and hydronephrosis or renal failure (unless an underlying cause is identified)

stage IIIC: Tumor involvement, regardless of size and extent, involving pelvic and/or para-aortic lymph nodes (with r and p notations) c

stage IIIC1: Only metastases from pelvic lymph nodes.

stage IIIC2: Metastasis of para-aortic lymph nodes.⁴⁴

Stage IV: Carcinoma has spread beyond the pelvis and impacted the bladder or rectum mucosa, as shown by a biopsy. Bullous edoema is not considered Stage IV.

In Stage IVA: Rectal, bladder, or upper urethral mucosa can be infiltrated by tumors.

In stage IVB: Spread to the remote body parts including pelvic nodes.⁴⁵

Risk factors

Parity

The rising number of full-term gestations holds significance concerning HPV and cancer of cervix. Females who have experienced multiple pregnancies face an elevated hazard



of contracting HPV or developing cervical cancer. The most plausible explanation for this phenomenon is the local tissue trauma during vaginal delivery or the cellular oxidative stress, which can lead to enhanced DNA damage and facilitation of HPV integration.⁴⁶ Women with the more pregnancy have greater susceptibility to cervical cancer as compared to do they have fewer pregnancy. The possible mechanism for this proposed the increase the hormone level and the impaired the immune system of the pregnancy, Due to the hormonal change during the pregnancy they affect the growth of cervical cells and the increase the susceptibility to the HPV. In the multipurpose Female transition zones extends longer on the ectocervix, facilitating direct contact to the virus.⁴⁷

Geographical region changes

Cervical cancer one of the most persistent malignity influencing the women in the world after the breast cancer and lung cancer. In the geographical changes the migration pattern and the urbanization can influence the cervical cancer incident and mortality rates. According to the Global cancer statics (GCST), they are more than half million new cases are diagnosed every year and then the claim the lives more than a quarter million women.⁴⁸ Social economic factor and the environmental exposure difference between the regions and the affecting the cervical cancer while the cervical screening and the HPV vaccination are helping to reduce the invasion developed country, but the burden of cervical cancer disproportionately affects developing nations. countries where they lack the basic healthcare⁴⁹

Oral contraceptives

Oral contraceptive the use of oral contraceptive or other hormonal contraceptive are increase the Peril of the cervix cancer. Oral contraceptives including oestrogen and progesterone may affect the prevalence of cervical cancer through raising HPV infection & raising the advancement of pre-cancerous lesions.⁵⁰ Synergistic effect and interaction in between HPV & Oral contraceptive Augmentation the peril for cervical cancer, conducted a meta-analysis by JARC.⁵¹ Overall increase in the with the old contraceptive is small especially when we compared to the other risk factor like HPV infection as the risk decreases after the discontinuation of the oral contraceptive administration⁵²

Nutrition and Dietary

Poor diet quality, low in takes of fruits and vegetables in daily life, low intake of vitamin E, overweight and obesity, high intake of salt preserve food, alcohol conception can lead to the growth of the cervical cancer. Vitamin B12, thiamine, riboflavin, folate, and folate may protect the cervix against precancerous lesions.⁵³

Recent years have seen a renewed focus on the importance of dietary variables in the development of cervical cancer has received a lot of attention, and multiple

research projects have analyzed this issue via inconsistent data derived from diverse sources.⁵⁴

A balanced diet and increased α - and γ -tocopherol levels have been linked to a 50% reduction in cervical cancer. Maintaining a healthy lifestyle can lead to elevated levels of free-radical fighters, which can play a crucial role in avoiding cervical tumour.⁵⁵

Prevention

Cervical malignancy prevention is a critical aspect of public health aimed at reducing Frequency rate and Fatality rate associated with this disease and Prevention of the cervical cancer are classified into two stages primary prevention, secondary prevention.⁵⁶

major prevention: This step focuses on preventing HPV, which is the major cause of cervical malignancy, by vaccination. The vaccination is highly successful strategy to stop cervical malignancy before it starts against the HPV types.⁵⁷

The first HPV vaccine to be approved was Gardasil, which was licensed in 2006. Gardasil provides protection against HPV subtypes 6, 11, 16, and 18. Subsequently, Cervarix was licensed in 2009 and confers immunity against HPV strains 16 and 18.⁵⁸

The placebo control trials of three difference HPV vaccine have come with hope and energy to fight against the cervical cancer⁵⁷

Consuming enough whole vegetables and fruits, seafood, and nuts can dramatically reduce the incidence of cervical intraepithelial neoplasia. The aforementioned foods include antioxidants that include vitamin C, E, carotene, lutein, and lycopene, as well as vitamin A, calcium, and polyunsaturated fatty acids.⁵⁶

Secondary prevention this stage focuses on the prevention of early detection through regular screening such as pap smear and HPV test. These tests can detect the precancerous changes in the service. There are no randomized trials to evaluate the importance of screening on cervical cancer, prevalence and mortality⁵⁹ and all the data of the screening effect came from the group and case control studies. the reduction in the cervical cancer conducted by the international agency for research in Cancer published in 1986 they show that the well-organized programs very effective and good for the reducing the cervical cancer family medication and treatment can easily prevent the medicine of the cervical cancer⁶⁰

Screening

Cervical cancer is a major cause of illness and death for women globally concerning globe; however, it is a curable disease and many programs have helped a lot to reduce the death rate., with advancements of technology specially in health sector, and in medical science, example screening methods have emerged serves as an effective tools and powerful way to fight against cervical cancer.⁶¹



Since routine screening is the most impactful population health interventions. strategy for lowering mortality and rates of new cervical cancer cases. Early-stage cervical cancer or precancerous lesions can be easily detectable by different kinds of screening programs, which facilitates immediate intervention and treatment, therefore screening greatly helps to improve public health.

There are two most popular screening methods which are profound to be most effective and useful techniques among the variety of tests and these two techniques able to detect abnormal changes in the cervix that may indicate the development precancerous conditions, are 1st is Papanicolaou (Pap) smear and 2nd is HPV testing.⁶²

1. Pap smear test: For early detection of cervical cancer, Pap smears are the most economical screening method. Sometime used with combination of HPV testing for better result. In the 1940s Dr. George Papanicolaou was the 1st who developed the Papanicolaou test and hence since then became a staple of cervical cancer preventive programs worldwide. Whenever this test is used in all populations and adequately examined, there is a clear correlation between increased cervical cancer screening rates and a corresponding reduction in both the incidence and mortality rates of cervical cancer.⁶³

A Pap smear involves a medical professional who collects the sample of the cervix cells gently with the help of a brush or a small spatula. The collection process is often quick and painless, although some women might feel minor discomfort. The collected cells are then placed on a glass slide or in a liquid media for analysis.⁶⁴

The frequency of Pap smear screening varies depending on sexual history, age and previous screening results. Women should start pap smear screening at the of 21 and also recommended to continue until the age of 65. The screening frequencies can differ, with some guidelines advising screening in every three years for women aged 21 to 29 and every three to five years for the women aged between 30 to 65.⁶¹

Those women with abnormal test result, such as A Colposcopy test was recommended for ASCUS (atypical squamous cells of unknown significance), HSIL (high grade squamous intraepithelial lesion), and LSIL (low grade squamous intraepithelial lesion).⁶⁴

Limit of pap test; The Pap test easily detects the high-grade squamous intraepithelial lesions (HSIL) with a sensitivity of 70.80%. Although pap test is a screening tool, Its false-negative frequency for cervical cancer ranges from 15% to 25% cancer. These False-positive reports can result in unneeded procedures and additional therapies and patient anxiety.⁶³

2. HPV testing: HPV DNA test is currently considered as the gold standard for identification of HPV virus. HPV DNA test is more reproducible than cytology and only detects high-risk HPV strains. There are numerous HPV tests that are available for screening such as: DNA-based tests and RNA-

based tests. In DNA-based tests cervical cell samples are tested from cervix for HPV DNA presence using these methods. With regard to high-risk HPV varieties, they are extremely sensitive and specific. In RNA-based tests few newer tests detect HPV mRNA, which is indicative of active HPV infection.⁶⁵

To increase the sensitivity and specificity of cervical cancer screening, HPV testing is often combined with Pap smear screening. This method is called co-testing, that enables the detection of high-risk HPV strains as well as abnormal cellular mutations. If women have both positive HPV test and negative cytology in that case Women should either retake the co-test in a year or receive urgent access to HPV genotype-specific testing for HPV 16 or HPV 16 and 18.⁶⁶

Treatment

The course of medication for cervical cancer is determined by the stage or progression of the disease, patient health and other factors such as age. There are many treatments options for cervical carcinoma. One popular method of treating cancer is surgery, in this they remove the cancerous tissue, there are different types of surgical procedure used depending upon the stage or severity and location of the cancer. Conization is a type of surgery which involves removing a Cone-shaped cervical tissue. In hysterectomy uterus is removed along with the nearby organs. Simple, modified radical, or radical hysterectomy are also possible options. Pelvic exenteration involves removing the cervix and in more severe cases the rectum, bladder, and a portion of vagina is removed last is radial trachelectomy in which uterus is intact, but cervix is removed.⁶⁷

Nano technology shows significant development in the past few years which increases the effectiveness of nanotechnology for treatment or medication of cancer, with very less harmful effect. Nano technology increased the bioavailability of particular drug, with specific targeted distribution of drug in the site of action. There are different types of nano carriers, such as liposomes, solid lipid nano particles (SLNs), polymer nano particles (PNPs), and nano emulsions, that have shown interest in treating cervix cancer. These systems can encapsulate and release proteins, genes, vaccinations, and medications etc.⁶⁸

Chemotherapy: Drugs are used to either eradicate or inhibit the growth of cancer cells. Radiation therapy is often given alongside chemotherapy, a combined treatment known as chemoradiation. When cervical cancer has progressed to later stages or has spread outside the cervix, it is frequently used. One of the most often prescribed chemotherapeutic agents for cervical cancer is cisplatin. It shows its mechanism of action by damaging the DNA of virus. cisplatin is widely utilized in the traditional procedure of metastatic cancer of cervix and non-metastatic cervical cancer with local progression; it can also be used in conjunction with other chemotherapeutic medications.⁶⁹



5-FU is a pyrimidine analog, 5-fluorouracil (5-FU)-FU resembles the building blocks of DNA and RNA. After 5-FU enters cancer cells, it is transformed into active metabolites that obstruct DNA and RNA synthesis of cancer cells, hence inhibiting cancer cell development and leading to cell death. The most popular regimens for chemotherapy and the standard concurrent chemotherapy regimen used in combination with radiation therapy for cervical cancer typically involves the administration of cisplatin at a dose of either 40 mg/m² or 50 mg/m², followed by a continuous intravenous infusion of fluorouracil (4 g/m² over 96 hours) on days 1 and 29 of the radiation treatment course.⁷⁰

natural products are found in nature or from living species such as herbs-shrubs & animals, have APIs are said to provide appealing substitutes for chemotherapy medicines or to be useful in conjunction with them for example - Purified flaxseed hydrolysate, for instance, which is isolated from Lignan, inhibits the growth of angiogenesis and the spread of HeLa (immortal) cells, while inducing death. In SiHa and CaSki cells, nigella sativa thymoquinone also demonstrated an apoptotic effect and an anti-proliferative effect. Praeruptorin-B, ethanol extracts from Bauhinia variegata candida, and popular tea are examples of such natural compounds.⁷¹

CONCLUSION

Cervical cancer remains a significant global health concern. Through this review, we have explored several facets of the illness, such as hazard factor, techniques for screening, types of therapy, and preventative measures. The review underscores the importance of understanding the identification of clinical feature, etiology, risk factors connected to cervical carcinoma, notably persistent Early sexual debut age, smoking, parity, and HPV infection, emphasizes the need of comprehensive prevention strategies. While HPV vaccination has demonstrated efficacy in reducing the incidence in cervical neoplasm, for expanded vaccination programs there is critical need to reach vulnerable populations worldwide. Improved version of screening methods, HPV DNA testing and Pap smear tests, greatly increased accuracy of cervical carcinoma early detection but the main issue is poor infrastructure for screening, restricted access to screening services for poor people and last sociocultural barriers continue to exist and impede the efficacy of screening initiatives. Efforts should be taken from the individual country governments to make it possible better health and necessary requirement for women and to increase awareness, lessen stigma, and support sexual and reproductive health education Governments, medical professionals and researchers must work together to reduce cervical cancer's effects and eventually eradicate this preventable illness.

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