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Review Article

Current Pathology, Pharmacotherapy Insights and the Method of Awareness for Effective Management of Cervical Cancer

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ABSTRACT

The primary motto of the review is to analyze the current pathology and pharmacotherapy of cervical tumors; in addition to that, we focus on creating awareness for early detection and vaccination to diminish the incidence of disease and death in developing countries. Cervical tumor occupied a second place among the malignancies in women, with the primary contributor to morbidity and mortality. Approximately 500,000 females are diagnosed with cervical tumors annually, leading to 300,000 fatalities globally. The disease is largely preventable. HPV types 16 and 18 are the primary etiological agents of cervical tumors. Accurate and early detection of abnormal cytologic changes prevents the progression of the disease. Standard treatment involves either radical surgery or radiotherapy. Childbearing is therefore impossible after the treatments. The intensity-modulated radiotherapy, one of the advance radiotherapy technologies, aids in reducing medication effects for women with locally advanced diseases. Cervical dysplastic lesions are prevented in eligible women who have not previously contracted the vaccine-specific HPV strains by receiving an HPV vaccination. Treatment decisions are primarily based on the stage determined by clinical FIGO staging. In wealthier nations, the utilize of pap smears has substantially decreased the occurrence of cervical cancer in low- and middle-income nations without examination and HPV vaccination programs. Approximately 90% of cervical cancer occurrences arise. Additionally, it emphasizes how important it is to prioritize efforts, especially in low- and middle-income nations. Its main goal is to raise awareness among women to lower the incidence of cervical tumors.

Introduction

Cervical tumor has become the second prevalent neoplasm in women and promotes higher morbidity and mortality. [1] The incidence of cervical tumors among women has exceeded half a million women in a year and causes about 300,000 deaths worldwide.[2] The disease is largely preventable. HPV subtypes 16 and 18 are the primary etiological agents of cancer of the cervical cavity, which is the fourth leading neoplasm among females globally, and continues to represent a significant hazard to public health. Cervical dysplastic lesions are prevented in eligible women who have not previously contracted the vaccine-specific HPV strains by receiving an HPV vaccination.[3] Treatment decisions are primarily based on the stage determined by clinical FIGO staging.[4] Given that high-risk human papillomavirus (HPV) strains are the principal etiological agents of the disease, it is critical to comprehend the pathophysiology and risk factors associated with it. [5] Variations in the availability of preventative measures, especially in low- and middle-income nation-states, lead to tenacious morbidity and death despite advances in screening and vaccination. [6] In addition to highlighting risk factors, epidemiology, etiology, and the most recent advancements in screening and treatment options, this chapter attempts to present a thorough review of cervical tumors.

Epidemiology of cervical cancer

Tumor of the cervical cavity is the predominant etiology of cancer-related fatalities among females in impoverished

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countries. [7] As 86% of cervical tumor deaths occur in developing, low- and middle-income nations, the mortality rate of this disease also reflects health disparities.

Worldwide Distribution of Cervical Cancer

Cervical cancer disproportionately affects developing countries. Age-standardized incidence rates in Southern Africa, South America, and South-Central Asia surpass 25 per 100,000 women, highlighting the higher prevalence in these regions. Notably, Haiti has an exceptionally high rate of 64 per 100,000 women, followed by Lesotho at 46 and Bolivia at 42. India contributes significantly to the global burden, accounting for more than 25% of all new cases with 132,000 diagnoses annually. In sharp contrast, wealthy countries exhibit an age-standardized incidence rate of around 0.0103% women, which is about half the rate seen in underdeveloped nations. In Europe, Finland, 0.0062% women, Malta 0.0071% women, and Ireland, 0.0084% women demonstrate the lowest incidence rates. Screening practices exert influence on trends in the prevalence of cervical tumors. [8] Age-adjusted rates of cervical cancer occurrence, for occurrence, have been declining in Nordic nations since the 1960s; from 21.2 per 100,000 in 1966 to 7.6 per 100,000 in 2006, the rates have decreased. However, a few sub-Saharan African locations have seen a rise in occurrence in recent years.

Cervical Cancer Distribution in India

Over the past two decades, cervical tumors have been the leading tumor impacting females in India. According to the latest findings from the National Cancer Registry Program (NCRP), the most commonly diagnosed cancers among women are breast and cervical cancers. Based on NCRP data from 2009 to 2011, the Aizawl district in northeastern India recorded the highest age-standardized occurrence amount of cervical tumor at 0.0243% women, followed by Barshi Elaborated at 19.4 and Bangalore at 18.8.

Age-adjusted rates for certain conditions have declined in several Indian cities over various periods. For instance, Barshi saw a drop from 22.1 in 1988 to 14.1 in 2010, Chennai from 41 to 16.7 by 2009, Thiruvananthapuram from 9.2 in 2005 to 7.7 in 2011, and Bangalore from 32.4 in 1982 to 18.7 in 2009. The annual percentage decrease across these areas, between 1982 and 2010, ranged from 1.3% in Bhopal to 3.5% in Chennai. While the decline in Barshi's registry was limited to individuals up to 44 years old, other, older population-based cancer registries (PBCRs) demonstrated a significant reduction in age-adjusted rates for age groups ranging from 25 to 34 up to 54 years. (Figure 1).

Agents for HPV in India

It's understood that HPV is an essential, though not by itself adequate, factor in the development of cervical cancer. Of the several HPV strains, eighteen are recognized as highly risky, while the rest are considered at low risk. The general prevalence of HPV infection in females without cervical tumors ranges from 7.6 to 16.8%, which mirrors the global average of 9 to 13%. Hospital-based studies have shown that 9.9 to 16.6% of women with normal cervical cells carry HPV. Higher rates of HPV infection are observed in specific vulnerable populations, including 25% of commercial sex workers, 32.3% of women in Mumbai's urban slums, and 41.7 to 56% of HIV-positive women. Furthermore, an examination by Bhatla *et al*. concluded that there's no noticeable regional differentiation in HPV frequency between northern and southern parts of India per an analysis conducted by Bhatla *et al*.

While the general frequency of HPV doesn't differ much between North and South India, specific high-risk types show regional variations: HPV-35 appears more common in South India, whereas HPV-16 and HPV-45 are significantly more widespread in Northern India. Research conducted in Delhi also revealed that high-risk HPV varieties exhibit a greater propensity for persistence, with types 16, 45, 67, 31, 51, and 59 demonstrating the highest rates of chronic infection. Among these high-risk types, HPV-16 infections persisted for an average of 12.5 months.

Patient survival rate (Worldwide)

In countries that are developing, less than 50% of females diagnosed with cervical tumors recover beyond five years; in industrialized nations, this figure is roughly 66%. Significant gains in cervix cancer survival were seen in the initial half of the twentieth century (Table 1), partly as a consequence of improved detection stages and improved treatment outcomes, especially as a result of advancements in radiation therapy.

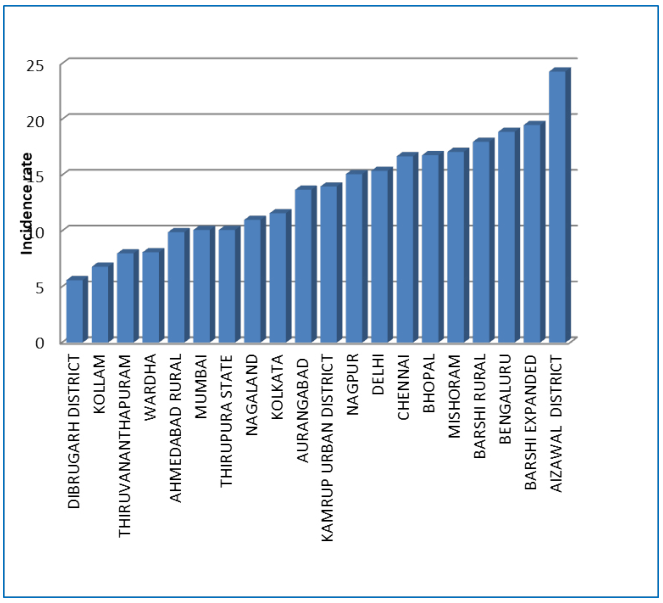


Fig. 1: Cervical cancer distribution in India

Table 1: Worldwide patient survival rate

Sl. No.	*Country*	*Confidential Interval*
1	Austria	64.7
2	Belgium	65.1
3	Czech Republic	63.7
4	Denmark	64.0
5	Europe	62.6
6	Finland	65.0
7	France	66.9
8	Germany	60.5
9	Iceland	63.5
10	Ireland	59.7
11	Italy	64.7
12	Malta	68.2
13	Netherland	66.5
14	Norway	66.7
15	Poland	51.5
16	Portugal	56.4
17	Slovenia	63.6
18	Spain	62.9
19	Sweden	66.2
20	Swetzerland	68.2
21	UK-England	59.1
22	UK-Northern Ireland	58.9
23	UK-Scotland	58.8
24	UK-Wales	54.7

Cervical Cancer Mortality (Worldwide)

Cervical cancer disproportionately impacts less developed countries, where it is responsible for about 80% of global cases and deaths (Fig. 2). This malignancy constitutes 15% of all cancers affecting women in these nations, with a large portion (around 40%) of cervical tumor fatalities in developing nations concentrated in a densely inhabited area of South-Central Asia. The countries facing the highest mortality burden include Lesotho (0.038% deaths of women), Haiti 0.035%, and Tanzania 0.033%. When adjusted for age, the death rate from cervical cancer in less developed nations stands at 0.0112% women, approximately three times higher than that in developed countries.

Distribution of HPV by PAP-test

Data on the study populations for the years 2005 and 2016 (annual population minus exclusions) were calculated. The prevalence rates of screening across three and five years (Pap testing and Pap-HPV co-testing) were computed as a percentage of the research cohort. A Pap test conducted during the past two years or at least one in the current year was deemed to contribute to the rate of Pap testing. The minimum number of co-tests— articulated as Pap and HPV tests conducted in the same week—during the current passing year or the prior four years was utilized to ascertain the Pap-HPV co-testing rate.

A graphic summary of the average percentages of Pap testing and Pap-HPV co-testing per age category was presented. In the 2016 population, variants that may be linked to finishing Pap or Pap-HPV co-testing, compared

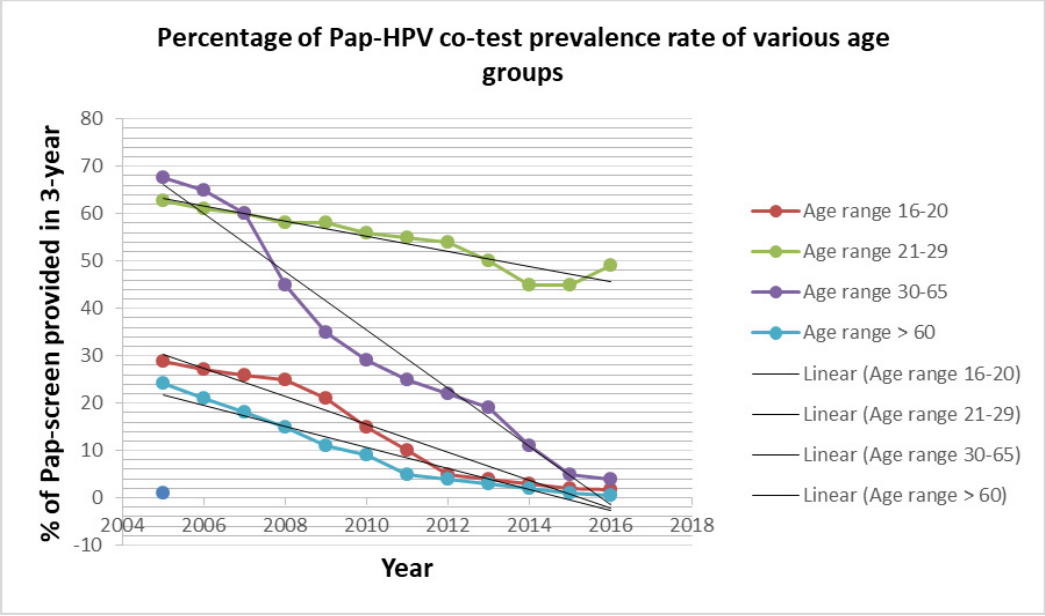


Fig. 2: Percentage Prevalence of Pap-HPV co-test

to not doing either Pap testing or Pap-HPV co-testing, were evaluated using multinomial logistic regression. The Charlson Co-morbidity Index, age, race, ethnicity, and smoking status were among the evaluated variables. 95% confidence intervals (CIs) and odds ratios (ORs) are used to report the results. The *p-values* below 0.05 were regarded to be statistically significant (Figures and 3).

64.6% of research-qualified females (aged 30–65) in the population in 2016 had undergone cervical cancer screening during the last five years, 60.8% had undergone Pap-HPV co-test screening within the same time frame, and 3.9% had undergone Pap testing within the same time frame. The screening protocols were adhered to by 53.8% of evaluation-eligible females between the ages of 21 & 29, with the preponderance being screened appropriately with Pap tests (47.4%) rather than Pap-HPV co-tests (6.6%). In 2016, the rates of total Pap and Pap-HPV co-test checkups for teenager females, women aged 16 to 21, and women over 65 years were 2.1% and 8.8%, respectively. These rates were reasonably low and in line with recommendations not to screen women in those age categories.

The historical trends in pap testing every three years are broken down by age group. In every age group, there were notable decreases in Pap test rates between 2005 and 2016 (p <0.01). [9]Pap screening rates among teenage girls and women aged 16 to 21 dropped from 28.8% in 2005 to 1.8% in 2016. The percentage of women aged 21 to 29 who had Pap tests fell from 62.8% in 2005 to 47.3% in 2016. Pap test statistics for females aged 30 to 65 dropped from 67.5% in 2005 to 3.9% in 2016. In 2016, the percentage of women over 65 who had Pap tests dropped from 24.2% to 0.6%.

Pathogenesis of HPV

The human papillomavirus (HPV) is responsible for the predominant form of tumor in females, cervical cancer, attributed to non-enveloped double-stranded DNA. These viruses fall within the categories of cutaneous and mucosal human papillomavirus. HPV at high-risk categories 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, and 59 can result in mucosal infection. Sections 43, 44, 56, 58, 59, 66, 68, and 70 are low-risk. The aforementioned low-risk categories are the ones that cause cervical lesions. 70% of these lesions result from HPV-16 and HPV-18.[10] Only 8 proteins, including E1, E2, E4, E5, E6, E7, L1, and L2, are encoded by the HPV genome and are involved in the conversion of healthy cells into malignant ones. The most susceptible location for HPV invasion is the squamocolumnar junction of the cervix, at the junction of the epithelia that constitute the endocervix and exocervix. After that, it replicates the virus, causing cervical dysplasia and the advancement of a tumor known as cervical intraepithelial neoplasia (CIN). [11] The cellular dysplasia is due to an alteration in the cells of squamous epithelium by a process called koilocytosis and the altered cells are termed Koilocytes, which are darker, larger, asymmetrically outlined nuclei, causing carcinogenic lesions in severe instances. Viral replication is initiated when basal cells undergo mitotic cell division,

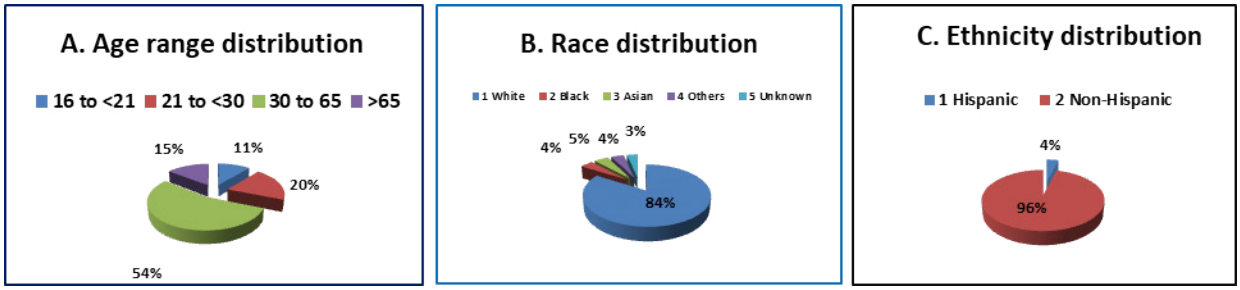


Fig. 3A: Distribution of HPV Virus by PAP-test on year-2005

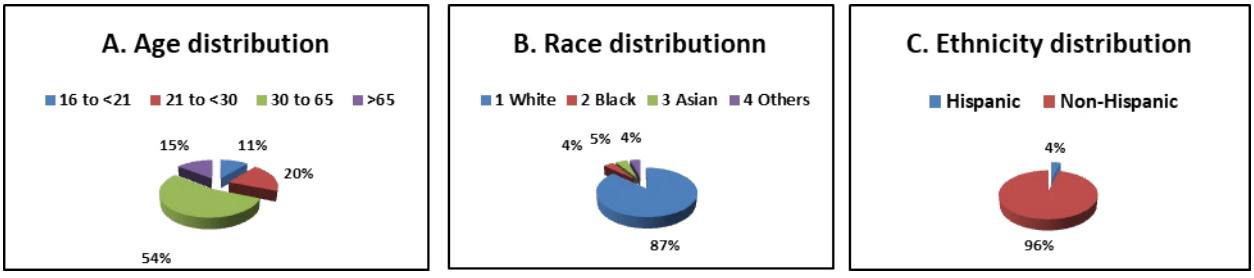


Fig. 3B: Distribution of HPV Virus by PAP-test on year-2016

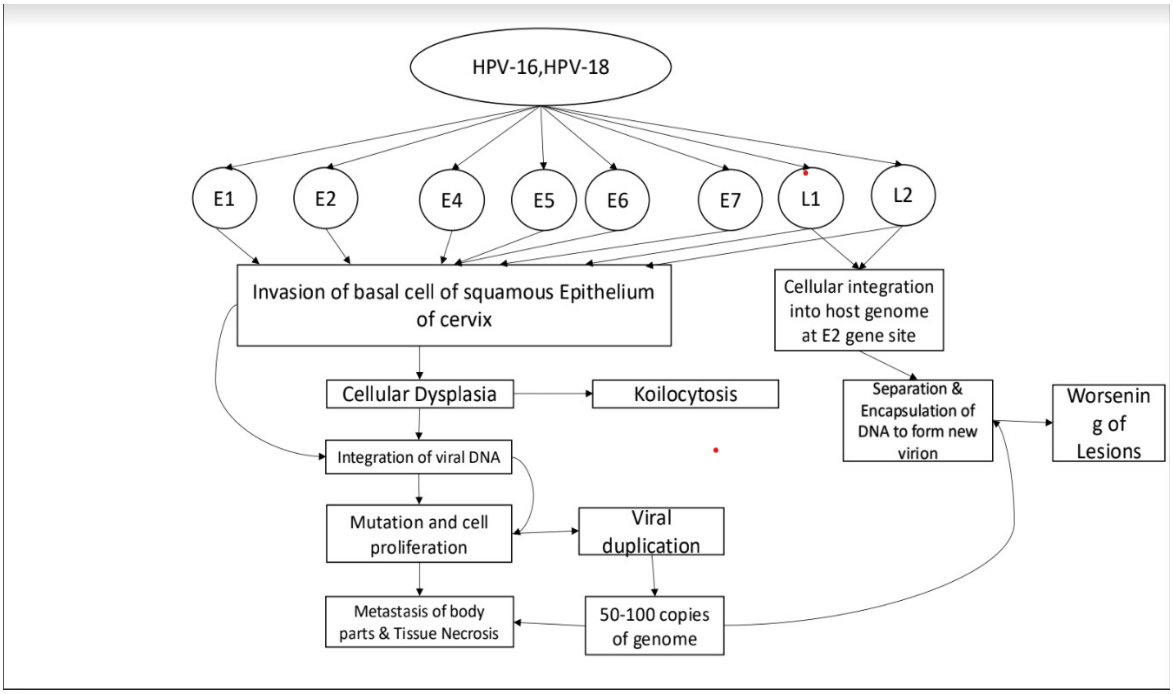


Fig. 4: Pathogenesis of Cervical Cancer

resulting in the formation of two daughter cells. One of these daughter cells is destined to become the terminally differentiated cell, whilst the other persists in the basal layer. Initially, this HPV infiltrates the basal cell of the epithelium via engagement with receptors such as alpha 6 integrin (HPV-16) through micro incisions. Each cell contains 50–100 copies of the genome as a result of the replication of HPV-16 and the E1 and E2 proteins. The E1 and E2 proteins are also needed for the separation of the produced DNA. The L1 and L2 genes are copies of during the vegetative phase of the life cycle, subsequent to the migration and development of the infected basal cells. The life cycle is repeated as the newly manufactured DNA is encapsulated to form new virions, which are then released, resulting in increased severity of the lesions. (Figure 4).

Cervical cancer in pregnant women

Cervical tumor is the most commonly diagnosed gynecological malignancy during pregnancy. Cervical tumors associated with pregnancy are rather uncommon. Cervical cancer constitutes 71.6% of gynecological malignancies during pregnancy, and ovarian malignancies represent 7.0%. Cervical tumor in pregnancy is quite uncommon, and its symptoms may be confused with other pregnancy-related conditions. Gynecological examinations are infrequent during pregnancy, which prompts Cervical cancer to be identified during the current pregnancy or within six to twelve months post-delivery, is classified as pregnancy complicated by cervical cancer. Complications during pregnancy associated with cervical carcinoma are rare. Approximately 1% to 3% of females diagnosed with cervical tumors are either postpartum or pregnant. Roughly 50% of these cases are discovered during pregnancy, with the remaining 50% being detected within a year following delivery. One of the most frequent cancers to occur during pregnancy is cervical cancer, which is thought to affect 0.8 to 1.5 instances for every 10,000 newborns. [12] Research has demonstrated a notable association between infections of human papillomavirus (HPV) 16 and HPV 18 alongside the concentrations of progesterone, estrogen, and human chorionic gonadotropin during gestation. This discovery suggests that maternity may expedite the progression of cervical tumor. Cervical cancer progresses more rapidly when a woman has a compromised immune system during early pregnancy and postpartum, alongside heightened lymphatic circulation and blood flow, as well as other factors that may facilitate tumor spread.

Screening for cervical cancer

Cervical tumor rates have been lowered by 50 to 80% thanks to systematic screening programs at the population level. The majority of malignancies in environments with strong screening systems occur in people who are either newly diagnosed or infrequently tested. One of the primary reasons of the stark differences between cervical tumor occurrence & death in high- and low-asset nations, as well as between individuals who are socially privileged and those who are disadvantaged in the United States, is unequal access to screening. To diagnose and treat women with precancerous lesions before cancer occurs,

Screening programs for cervical cancer identify individuals who are asymptomatic but have these lesions. Screening tests need to be easy for primary care physicians to administer and maintain, sensitive, and reproducible. [13] The cornerstone of screening for many years was cervical cytology, or Pap testing. However, the significance of HPV testing has increased as the body of knowledge regarding the association between HPV infection and the onset of cervical tumors has broadened.

Methods of Cervical Cancer Screening

HPV primary screening, HPV testing, and cervical cytology (Pap) testing are all components of cervical cancer screening, which significantly reduces the incidence and mortality of cervical cancer.

Cheapness in Cervical Cancer Screening

HPV testing is the most economical screening technique for cervical cancer. Although HPV testing usually predominates in Pap testing, co-testing is more affordable.

HPV primary screening

The advancement of HPV diagnostics and immunizations was significantly accelerated by the persistent infection, which revealed that the tumor-causing human papillomavirus (HPV) was the root cause of the malignancy. [14] The sensitivity of HPV assays was determined to be higher than that of cytology (96.1 vs. 53.0%). The recent molecular technology facilitated the diagnosis of human papillomavirus infection-related cancer by detecting pieces of their DNA in cervical cells. HPV testing is advised by the American Cancer Society (ACS) as a component of a cervical cancer screening regimen. Every five years, Individuals aged 25 to 65 are advised to have a basic HPV test, according to ACS recommendations. If primary HPV testing is unavailable, a Pap test conducted separately every three years or a co-test that incorporates an HPV test and a Pap test every five years may be employed for screening. Even those who have had an HPV vaccination should adhere to these recommendations for their age groups. Cervical HPV infection is more likely to progress to cervical tumors and precancerous lesions, and can be identified and detected in the very early stage by an HPV test. It identifies high-risk HPV strains that are. However, an HPV test is unable to identify cancer or precancer. High-risk HPV strains have the proteins E6 and E7. Certain HPV tests function by looking for mRNA E6/E7, which are the instructions the virus utilizes to make these proteins. [15] An HPV test is considered positive if the findings indicate that mRNA E6/E7 was found. These proteins are not found in every HPV test. Certain tests search for the DNA of particular highly risk HPV strains.

Cervical cytology (PAP TEST)

The speculum is examined by a physician in cervical cytology, and a sample of cervical cells is obtained. The cells are subsequently immersed in a liquid solution (liquid-based cytology) or spread onto a slide (traditional cytology) and submitted to a lab for cytopathologist analysis. When the cells are examined, they may show low-grade anomalies and high-grade anomalies, or cells that appear normal. Low-grade abnormalities, including atypical squamous cells of uncertain significance (ASC-US) and low-grade squamous intraepithelial lesions (LSIL), generally demonstrate evidence of HPV infection; yet, they do not invariably signify a precancerous lesion. HSIL, atypical squamous cells suggestive of high-grade lesions, and atypical glandular cells are strongly correlated with high-grade histological results, warranting excisional intervention to prevent the progression to invasive malignancy. A high-grade abnormality detected by cytology is a specialized test that indicates a high probability of precancer. It is not a sensitive test, though; every screening round misses between 30 and 50% of precancers. The limited sensitivity necessitates decades of regular cytology testing to avoid cancer, and cytology in general lowers the prevalence and mortality rates of cervical tumors.

Co-Testing

For females between 30 and 65 years old, the American Society for Colposcopy and Cervical Pathology (ASCCP), the American College of Obstetricians and Gynecologists (ACOG), and the American Cancer Society (ACS). [16] All recommend Pap-HPV co-testing as the preferred method for cervical cancer screening. This involves conducting both a Pap test and a human papillomavirus (HPV) test..

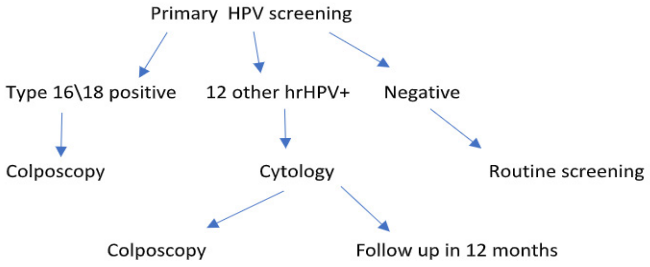
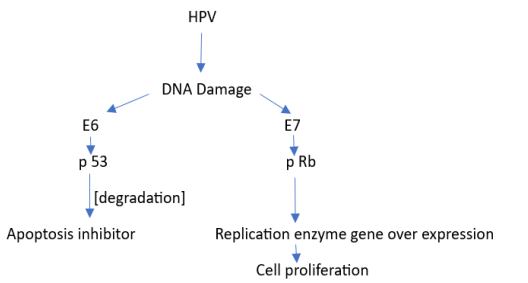


Figure 5: Sequence of HPV screening for cervical tumor



[E6 oncoproteins bind to cellular tumour -suppressor protein p53 and E7 proteins binds to p Rb proteins.]

Figure 6: Protein synthesis of mRNA E6/E7 of HPV for diagnosis

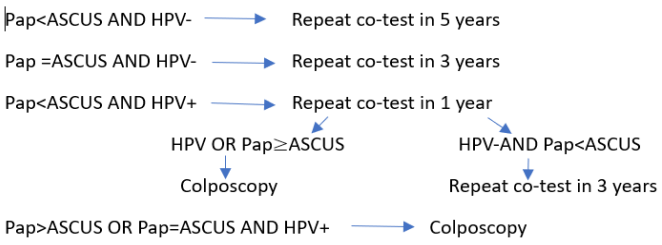


Figure 7: Co-testing for cervical cancer diagnosis

Screening for cervical cancer during pregnancy

The 'three-step paradigm' for screening for pregnancy in cases of cervical cancer consists of Cervical cytology, colposcopy, and cervical biopsy. Cervical cytology is the principal technique for the swift diagnosis of cervical tumors. The test presents no risk to either mothers or children during gestation. However, recent research suggests that cervical mucosal glandular hyperplasia, squamous-columnar junction migration, active basal cell proliferation that is active, irregular cell morphology, and nuclei enlargement are all caused by variations in the degrees of maternal estrogen and progesterone. These conditions are susceptible to being misdiagnosed as severe squamous intraepithelial lesions or even aggressive carcinoma. Detecting the cervical image obtained during a colposcopy is frequently challenging to interpret. Due to the fluctuations in the mother's hormone levels during pregnancy. Consequently, colposcopy should be implemented during the initial and second phases of gestation. If the initial colposcopy is inadequate, a subsequent one may be performed after twenty weeks of gestation. Performing a colposcopy is recommended in the following scenarios: 1. uterine rupture or interaction bleed (not associated with pregnancy); 2. conspicuous cervix abnormalities observed during the gynecological examination; 3. lesions suspected to be invasive malignancy; 4. cervical cytology screening conducted colposcopy referral criteria: Cervical cytology was employed to identify atypical squamous cells of unknown significance (ASC-US). If both ASC-US and HPV results are negative, patients who test HPV-positive may undergo re-evaluation six months postpartum. Patients with low-grade squamous intraepithelial lesions (LSIL), atypical squamous cells of undetermined significance (ASC-US), and high-grade squamous intraepithelial lesions (ASC-H) cannot be excluded. Pregnant women diagnosed with high-grade squamous intraepithelial lesions (HSIL), atypical glandular cells (AGC), and higher classifications are also qualified for re-evaluation. In cases of suspected cancers or high-grade lesions in the cervical area, a cervical biopsy may be performed for pathological examination via colposcopy or visual inspection. A cervical biopsy will not elevate the incidence of pregnancy-related complications, abortion rates, or preterm deliveries; conversely, curettage of the cervical canal during pregnancy will heighten the rates of abortion and early birth. As a result, this operation is prohibited when a woman is pregnant. Maternal age, fetal development, and the stage at which the tumor is malignant are just a few of the variables that affect the comprehensive treatment of a pregnancy affected by cervical cancer.

Various treatment methods for cervical cancer

Surgery

Surgery is a commonly utilized and efficacious method for treating several forms of nascent cancer, as it physically excises the cancerous cells. [17] The surgical techniques employed to treat cervical cancer include conization, trachelectomy, electrosurgical excision, radical hysterectomy, total hysterectomy, and cryosurgery. Individuals with precancerous lesions, especially those identified with CIN2 and CIN3, may undergo treatment options such as thermal ablation, cryotherapy, laser excision, or loop electrosurgical excision, contingent upon the severity of their illness. [18] Precancerous lesions are excised using thermal ablation, cryosurgery, and laser surgery, employing a heated probe powered by electricity or liquid nitrogen, along with a laser beam. Fertility-preserving surgeries including trachelectomy, conization, and LEEP. Gynecologic oncologists have extensively employed minimally invasive surgery (MIS), encompassing robotic and laparoscopic procedures, for the management of cervical carcinoma. [19] These recommendations were derived from limited observational studies, and their meta-analyses indicated that, in people with early cervical tumors, minimally invasive surgery (MIS) was linked to expedited recovery, reduced postoperative complications, and comparable survival rates relative to open surgery. The recommended therapeutic approach for females who have completed childbearing remains total hysterectomy, with or without salpingo-oophorectomy. In the initial phases of cervical tumor, a radical hysterectomy is generally conducted for lesions measuring up to 4 cm. It entails the total excision of the uterus, cervix, parametria, and the upper vaginal cuff. A Radical hysterectomy is commonly classified based on the number of parametria; class II hysterectomy is primarily offered to patients with class IA2 disease, and class III hysterectomy is typically performed in class IB or IIA disease. Conization is recommended for early-stage tumors, involving the excision of a cone-shaped tumor mass from the cervix with a fine wire during LEEP, which may be conducted under local anesthesia. In females with early-stage cervical tumors, minimally invasive (laparoscopic or robotic) radical hysterectomy was initially compared against open radical hysterectomy in the LACC, a phase III randomized controlled trial (RCT). The primary aim of the trial was to ascertain whether minimally invasive surgery (MIS) was not inferior to open surgical methods, with the

principal endpoint being disease-free survival (DFS) at 4.5 years. Within the MIS cohort, 84% of women received treatment with traditional laparoscopy, whereas 16% underwent surgery with a robot. Comprehensive studies have been performed on sentinel lymph node biopsy (SLNB) in individuals with initial-stage cervical tumors, demonstrating promising outcomes. [20] By identifying micro-metastases and lymph nodes in unexpected places, the sentinel lymph node approach may also improve the identification of nodal metastasis. Tumors in stages IA1–IB1 received an SLN biopsy and then a full pelvic lymphadenectomy.

Radiotherapy

High-energy X-rays are utilized in radiotherapy and are essential in the therapy of cervical tumors. Currently, external beam radiation therapy (EBRT), intensity-modulated radiotherapy (IMRT), and brachytherapy (internal radiation therapy) are the three modalities employed to treat cervical cancer. Advanced diagnostic technologies, including magnetic resonance imaging (MRI) and computed tomography (CT) scans, have enhanced the assessment of the original tumor. External beam radiation therapy (EBRT) is the predominant form of radiation therapy employed in cancer treatment, delivering high-energy radiation beams to the tumor from an external source. Intensity-modulated radiation therapy (IMRT), a more advanced kind of radiation therapy, is employed to target both malignant and benign tumors by calibrating photon and proton radiation beams to conform to the tumor's outlines. Brachytherapy avoids adjacent tissues by either implanting a radioactive source at the tumor location or administering a high dosage of radiation straight to the tumor. In 68.3% of patients with stage IIA-IIIB cervical tumors, a full response is noted; however, in 20 to 50% of females, radiation fails to impede the course of locally advanced illness.

Conventional radiation therapy

3D-CRT uses 3D imaging, such as a computed tomography (CT) scan simulation, to identify target volumes and organs at risk (OARs). This anatomic information can be enhanced by image registration using MRI, PET/CT, or magnetic resonance imaging [MRI]. Towards the last of the 20th century, 3D-conformal radiation therapy (CRT) was the accepted standard for EBRT. Intensity-modulated radiation therapy: In recent years, IMRT has grown significantly.[21] IMRT makes use of tiny beamlets that can change in strength to better fit 3D target volumes and reduce the amount of radiation that reaches nearby vital structures. In addition to being increasingly often utilized in the oligometastatic context, Positron emission tomography (PET)-adoptive IMRT enables the delivery of a highly conformal beam at a dose enough for achieving enduring local control.[22] When patients with cervical cancer undergo pelvic RT alone, the incidence of anemia and thrombocytopenia is much lower when there is a large reduction in pelvic bone marrow (BM) irradiation. IMRT can be administered in the form of volumetric intensity-modulated arc radiotherapy treatment (VMAT) or multiple static fields. Faster treatment times and fewer monitor units are two benefits of VMAT. A current meta-analysis of dosimetric research found that VMAT is superior to the rectum V40 (the irradiation volume of the rectum is 40 Gy). The availability of proton therapy treatment for various cancers, including cervical tumors, has increased. Since 1903, brachytherapy has been used to treat cervical tumors. For locally advanced cervical cancer (LACC), brachytherapy (BT) boost after radiochemotherapy (RCT) is the standard of care.

Immunotherapy

Immunotherapy for cancer improves the immune system by stimulating antitumor effects in patients, with the added benefit of especially targeting dysplastic precancerous and malignant cervical epithelial cells that contain HPV oncoproteins. It comprises vaccination, immune checkpoint inhibitors/blockades (ICI), and adoptive T cell therapy for cervical tumors and immune checkpoint inhibitors. By activating T cells against cancer cells, the ICIs significantly enhanced the clinical outcomes of numerous malignancies. The ICIs act on both Programmed Death Ligand-1 (PD-L1) and PD-L2, as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), to mediate the release of immune-suppressing inhibitors, including the Programmed Death-1 (PD-1). The expression of PD-L1 in cervical cancer tissues was reported to be approximately 96%.

PD-L1 is selectively expressed on the outermost layer of antigen-presenting cells (APCs) and tumor-infiltrating lymphocytes (TILs), and may significantly contribute to the onset and duration of HPV infection by decreasing regulation T-cell activity. However, it is infrequently seen in typical cervical cells, even when present next to CIN or tumor tissues. Given the strong correlation between HIV infection and cervical tumors, PD-1 and its ligands represent viable targets; their blockage may impede the PD-1/PD-L1 interaction and reinstate T cell-mediated cytotoxicity. The FDA-approved ICI drug pembrolizumab evidences it demonstrated an efficient inhibitory effect on the target PD-1/PD-L1 in PD-L1-positive cervical cancer solid tumors. The similar drug nivolumab is also used to treat metastatic and recurrent cervical tumors. Another important target called Checkpoint Protein Receptor CTLA-4 may also be useful by downregulating the immune system, inhibiting the target may inhibit activation of T-cells in reaction to tumor cells and demonstrate antitumor protection.

Vaccines

A vaccination that precisely targets the oncoproteins E6 and E7 of HPV-16 and HPV-18 utilizes live vectors.

It encompasses peptides or protein-based viral and bacterial vectors. Live vector-based vaccines employ bacterial or viral vectors and can provoke strong cellular and humoral immune responses with a single administration. Bacterial vector systems comprise *Listeria monocytogenes, Lactococcus lactis, Lactobacillus plantarum*, and *Lactobacillus casei*. Live viral vector vaccines administer target antigens by infecting cells and utilizing the translation mechanism. Recently, vaccines were cultivated by targeting specific antigens, such as E6 and E7, against adeno-associated viruses, alphaviruses, adenoviruses, and vaccinia viruses. The dendritic cell-based vaccine (DCBV), a whole-cell vaccine, functions as an antigen-presenting cell (APC) and acts as a conduit in innate and adaptive immunity.[23] The advantages of peptide and protein-based vaccinations are safety, stability, and ease of large-scale production. HPV antigens are presented in dendritic cells on MHC Class I or II molecules. The drawback of the peptide/protein-based vaccines is that the immunogenicity property is weaker than live vector-based vaccines, thereby the delivery to the target site may be needed at present, multiple peptide-based vaccines exist, including the ISA101 vaccine, a lengthy peptide vaccine that targets HPV-16 E6 and E7, which has been utilized in a phase I/II clinical trial including recurrent and metastatic patients with HPV-associated malignancies.

Targeted therapy

Targeted therapies are designed to obstruct substances, primarily proteins, that are particularly expressed by cancer tissues and are crucial for regulating expansion, proliferation, and metastasis. These medicines improve effectiveness and reduce side effects relative to traditional chemotherapies. In cervical cancer, anti-angiogenic medicines that target vascular endothelial growth factor (VEGF) have been utilized, particularly Bevacizumab, which binds to VEGF receptors to inhibit ligand binding. Brivanib, an inhibitor of both VEGFR and fibroblast growth factor receptors, has shown significant efficacy. Cervical tumor demonstrates moderate to high expression levels of the epidermal growth factor receptor (EGFR) protein. [24] A recent study on the genetic characterization of cervical tumor samples and testing in patient-derived xenograft (PDX) models revealed that the co-administration of trastuzumab and lapatinib in HER2-overexpressing PDX significantly inhibited tumor growth relative to the control group.

Chemotherapy

Chemotherapy is a crucial component of the traditional cervical cancer treatment plan, usually used as an adjuvant therapy after surgery. The most effective monotherapy employed in the previous three decades for cervical tumor prevention is platinum-based chemotherapy, cisplatin. The conventional approach to treating locally advanced cervical tumors involves the simultaneous delivery of cisplatin chemotherapy and radiation therapy. Chemotherapy is considered a secondary treatment for recurring disease. Drug resistance generally means that second-line therapy may be less successful than first-line therapy. It may be more beneficial to use cisplatin in combination with other medications than as a stand-alone treatment.[25] Combination chemotherapy enhances response rates and potential survival by employing agents that demonstrate individual efficacy, exhibit nonoverlapping toxicity, and provide additive or synergistic effects without exacerbating toxicity.

Single-agent chemotherapy

In the 1980s,[26] 50 mg/m^2 of cisplatin administered once every three weeks became the accepted standard of therapy, with a 38% response rate. Other active ingredients include ifosfamide, capecitabine, gemcitabine, paclitaxel, irinotecan, topotecan, pemetrexed, vinorelbine, and others. [27]These medications cause cell cycle arrest, prevent replication, or intercalate with DNA, causing overly damaged cells to undergo apoptosis.

Combination chemotherapy

Combination treatment demonstrates superior response rates compared to monotherapy when a platinum analog is combined with ifosfamide, doxorubicin, docetaxel, etoposide, paclitaxel, decitabine, tirapazamine, 5-fluorouracil, irinotecan, mitomycin-C, pegylated doxorubicin, or vinorelbine.

Adjuvant chemotherapy

The adjunct platinum-based chemotherapy after chemotherapy and radiation therapy may enhance survival in females with early-stage cervical carcinoma (IA2–IIA) exhibiting recurrence associated with risk. [28] Supplementary chemotherapy subsequent to the first surgical or radiotherapeutic intervention can enhance outcomes.

Neoadjuvant chemotherapy:[29]

In these investigations, a cisplatin-based combination was used, based on the theory that chemotherapy may decrease the initial tumor, making malignant cells susceptible to following radiation.

Vaccination

This type of cancer control includes early detection (HPV vaccination), secondary avoidance (screening and management of precancerous lesions), further prevention (identification and treatment of invasive cervical tumors), and palliative care.[30] Numerous nations have approved three preventive HPV vaccination varieties: quadrivalent, bivalent, and nonvalent strains. Between 2006 and 2014, four HPV vaccines were approved: Thirty-one Gardasil, a quadrivalent HPV [4vHPV] that targets HPV6, HPV11, HPV16, and HPV18; Cervarix, a bivalent HPV (2vHPV) that targets HPV16, HPV18; and Gardasil 9, a nonvalent

HPV (9vHPV) that targets HPV6, HPV11, HPV18, HPV16, HPV31, H PV33, HPV45, HPV52, and HPV58.

The L1 main capsid protein of HPV is expressed in yeast (*Saccharomyces cerevisiae*) by recombinant DNA technology. These particles, which assemble themselves to form empty casings that resemble viruses, are known as virus-like particles (VLPs). Though they lack genetic information, VLPs share the same outer sheath of L1 protein as HPV. [31] To generate a potent immune response, these VLPs serve as antigens in the vaccine. In the event of an exposure, the virus will be coated by the antibodies targeting the L1 protein in the vaccinated individual inhibit its release of genetic material.

The quadrivalent HPV vaccine was created by *Saccharomyces cerevisiae,* which produced the L1 gene, and the bivalent vaccine was developed by utilizing the Trichoplusia infected with baculovirus in insect cells. To enhance the effectiveness of immune responses over an extended period, The quadrivalent vaccine contained 225 mg of amorphous aluminium hydroxy phosphate sulfate as an adjuvant, while the bivalent vaccine contained the proprietary adjuvant ASO4, which is composed of 500 mg of aluminum hydroxide and 50 mg of 3-O-de-sacyl-4'monophosphoryl lipid A, a toll-like receptor 4 agonist, as an additional immune stimulator. A second iteration of prophylactic anti-HPV vaccination is the human papillomavirus 9-valent recombinant vaccine. *Escherichia coli* is one of the bacteria that have been utilized to create the HPV L1 VLP vaccine, which protects against HPV16, HPV18, HPV6, and HPV1. Preclinical and clinical trials are presently being conducted on methylotrophic yeasts, Hansenula polymorpha-based HPV6, HPV11, HPV16, and HPV18 VLPs, as well as Pichia pastoris-based HPV16 and HPV18 VLPs.

On the other hand, L2-based vaccinations produce fewer neutralizing antibody levels than VLPs based on L1 proteins. If chimeric L1-L2 virus-like particles were developed, the therapeutic potential of current HPV vaccines would be enhanced due to the extensive cross-protection of L1 and the robust immunogenicity of the L1-based vaccination. In comparison to L1 VLP, L2 VLP is less immunogenic and can generate a long-lasting neutralizing response, in addition to safeguarding a variety of HPV strains.

When paired with viral oncoproteins E6, E7, and L2, vaccines can provide both therapeutic and preventative immunity. On their own, however, they do not have any therapeutic promise. It is also possible to reduce the incidence of cutaneous squamous cell cancers with an L2-based immunization. Vaccination should begin between the ages of 9 and 12; however, vaccination is allowed up until age 26. For Gardasil, a minimum of four weeks should elapse between the initial and next dose, 12 weeks should elapse between the subsequent and final dose, and 24 weeks should elapse between the initial and final dose. For cervarix, a minimum of 1 and 6 months should elapse between the first and second doses.

Treatment of cervical cancer in pregnant women

The fundamental objective of suitable treatment for a pregnant female with a complicated cervical tumor is to safeguard the health of both the mother and the fetus. These women are difficult to detect and treat since they are pregnant, and doctor treatments are limited in these situations. Notwithstanding, it is imperative to adhere to fundamental therapeutic tenets, including the FIGO clinical phase of cervical carcinoma, lymph node involvement, pertaining to histology characteristics of the disease, gestational age, imaging assessment (magnetic resonance imaging), and the patient's and family's aspiration for conception. The direct impact of cervical tumor on the maternity uterus complicates treatment throughout gestation. The pertaining to histology subtype, disease stage, nodal status, gestational age, and obstetric complications, given the mother's choices about maintaining or discontinuation of childbearing, are all critical factors in the administration of a pregnant lady with a cervical tumor. Prior to selecting a treatment plan, these elements must be considered and deliberated with the patient and her partner within a multidisciplinary team framework. Therapeutic interventions for cervical cancer were historically contraindicated during pregnancy. The recommended course of action was to either terminate the pregnancy during the first two trimesters or postpone therapy until the third trimester, when the fetus had reached full maturity. Pregnancy preservation and treatment have increased in popularity during the past ten years.

Choice of delivery mode and complications in pregnancy

The best way to deliver a fetus with big cervical tumors is through cesarean section. Risks associated with vaginal birth include tumor metastasis, severe bleeding at the scar incision, and vaginal laceration. Transverse cesarean sections should be avoided when cancers have locally progressed due to the possibility of the tumors being sliced or torn. Traditional vertical incision helps lessen bleeding and prevent tumor blood vessels from being harmed. To check for metastases, the postoperative placenta needs to be sent for pathological investigation. The International Association of Gynecological Oncology released its second worldwide consensus in 2014, stating that while delivery could be delayed until a full-term pregnancy (>37 weeks), some patients would unavoidably experience premature delivery due to tumor progression or the need for radiation therapy.

Cervical cancer in HIV-positive women

Due to their impaired immune systems, women with HIV in low- and middle-income nation-states are more likely

to acquire cervical tumors. In the end, screening lowers the high rates of cervical incidence and is a very effective preventive technique for early detection. Nonetheless, there is still a low screening rate for cervical tumors in this population. Treatment for cervical cancer is much the same for females with and without HIV. At the moment of HIV cancer detection, a combination of antiretroviral medications must be prescribed. To maximize the course of treatment, the oncologist and the infectiousologist must work closely together. With the same safety and efficacy profile as people in general, HPV vaccination is also advised.[32] The Institute for Disease Control and Prevention advised HIV-positive individuals. Women to have two pap smears within the first year of their diagnosis, and after that, they should get one every year.[33] Conventional doses of radical chemotherapy and radiation can be successfully tolerated by HIV-positive cervical cancer patients who have been meticulously selected and are receiving HAART. There were no significant disparities in the GIT system, skin, hemopoietic system, or Genitourinary system in HIV-positive versus HIV-negative patients. In two sites in Africa, the safety, tolerability, and practicality of concurrent chemo-radiotherapy were evaluated in research involving 38 HIV patients who had locally advanced cervical cancer. The findings showed that 85% of HIV-positive women who follow ART guidelines can tolerate and finish concurrently with HIV-negative women. Comparing HIV-positive and HIV-negative individuals, the former had an advanced cervical tumor and were younger. It has been discovered that placing HIV-positive individuals on lifelong ART and facilitating their enrollment is crucial and improves their response to cervical tumor treatment. Investigating precancerous lesions and administering cervical tumor treatment in HIV-positive people, focusing on the beneficiaries of treatment and their standard of living. [34] It is necessary to evaluate the therapeutic regimen's efficacy in light of the C4 count and ART.

The occurrence of [35] cervical tumors in females living with HIV is six times greater. HIV infection reduces immunity by causing CD4 cells to be destroyed. The patient's HIV viral load is correlated with the level of destruction. As the CD4 cell population gradually declines, the body's defenses against infectious agents are weakened, which increases the risk of opportunistic infections in HIV-positive people. Infections that have lain dormant might potentially resurface in the presence of immune suppression. These opportunistic infections worsen the clinical conditions of HIV-positive individuals, which hurts their prognosis. Should the CD4 cell counts be less than 200 cells/μL, opportunistic infections are likely. Surgery, radiation therapy, and chemotherapy are the three treatments available for cervical cancer, either separately or in combination. Most cervical cancer patients in high-prevalence areas receive chemotherapy and radiation therapy, which might compromise their immune systems. The use of highly active antiretroviral therapy (HAART) has been able to manage the increase in viral load and enhance immune function in HIV-positive individuals.[36,37] Because chemo-radiotherapy alters the immune status of patients, people with weakened immune systems typically have more side effects following treatment. Since CD4 cells are thymus-dependent, their recovery is contingent upon the health of the thymus gland. Adults experience thymus gland involution, which results in CD4 cell recovery. Counting people with involute thymus glands is typically quite slow. In research evaluating the thymus gland activity following chemotherapy, it was shown that three months after treatment, 63% of participants in the younger patient group, aged 18 to 49, showed signs of thymus function, compared to 0% of the individuals in the older patient group, aged 70 to 91.[36] The fact that the same cytochrome p450 enzyme pathway processes several chemotherapy and HAART medications should also be taken into account in HIV-positive cancer patients. This could have an impact on chemotherapy medications; clearance, increasing their toxicity, or ineffectiveness. Patients with cervical cancer who are HIV-positive have benefited from a variety of therapy approaches and adjustments. [38]Still, the management result is subpar. It is imperative to investigate methods for enhancing therapeutic efficacy and minimizing potential side effects. As of right now, the best consistent therapy approaches are not yet known.

Prevention

Primary, secondary, and tertiary prevention can all be applied to the prevention of cervical lesions. In addition to focusing on the entire population free of symptoms, the major objective entails lowering the incidence of lesions. Vaccinations against diseases and nutritional supplements, such as eating a diet high in fruits, vegetables, and other nutrients, are also advised.[39] The secondary focus is early detection and screening preventive programs that may try to increase the disease pervasiveness by bringing it into the asymptomatic phase and advancing early treatment plans, including HPV detection, Papanicolaou smears, and technological advancements.[40] The tertiary strategies, which may include therapeutic vaccinations that serve as guiding principles for the expanding field of tumor antigen immunotherapy to eradicate the existing papillomavirus infection, are focused on minimizing the recurrence or early detection of recurrence.

Cervical cancer awareness – Attitude among women (worldwide)

If detected early on, Cervical cancer is extremely avoidable and highly treatable. Nevertheless, in countries with low and middle incomes, there is a greater incidence and fatality rate due to inadequate awareness. A substantial increase in survival rates is achieved with early detection and treatment. Ninety percent of cases of cervical cancer

can be avoided with vaccination. Death rates can be lowered by 70% with routine screening. Education and awareness campaigns can save lives. Therefore, measuring women's awareness levels is crucial and helps to substantially decrease the frequency of cervical tumor.

Women in Malta's knowledge, awareness, and attitudes toward cervical cancer and screening

The objective is to assess females' perceptions of screening and their knowledge of cervical tumor among individuals aged 25 to 64. A quantitative, cross-sectional telephone survey was done in 2017. Interviews were conducted with 407 women, with an 85% response rate. Women with elevated educational attainment had significantly enhanced awareness of cervical tumor symptoms and risk determinants (p <0.001). Sixty-nine percent of responders underwent cervical screening every three years. Frequent participants had higher odds of being between the ages of 35–44 and 45–54 (p <0.001), procreation (p = 0.001), and experiencing a close relative with tumors (p = 0.002). Embarrassment, test anxiety, and result anxiety were the major excuses for missing class. [41] The augmentation of literacy on health and improving our efforts to promote health will increase the identification of early symptoms, the awareness of risk factors, and the frequency of screenings.

Students' knowledge of the prevention of cervical cancer in Poland

The study included 995 students, possessing a mean age of 21.9 years. Eighty-six percent of the students were female, 19% were male, and 0.4% had no data. The major risk factor for cervical cancer is infection with human papillomavirus (HPV), which was recognized by the majority of students (82% of all respondents; 86% of medical students, 73% of non-medical students; p < 0.001). Merely 40% of the students recognized that the Population Prevention and Early Diagnosis Program is executed every three years in Poland for women aged 25 to 59. The majority of students correctly identified that cervical cytology is employed in Poland to detect cervical cancer, and they were cognizant of the fundamentals of cytology. Cervical cancer does not exhibit any specific early warning indicators, as only 57% of students were aware. Seventy-eight percent of the participants were cognizant of the fact that the HPV vaccination diminishes the likelihood of cervical cancer. Medical pupils and pupils engaged in sexual activity demonstrated a more comprehensive comprehension of cervical cancer.

The pupils from Poland knew a little bit about primary and secondary prevention as well as cervical cancer risk factors. Medical trainees displayed noticeably greater knowledge.[42,43] To lower the overall incidence and increase the rates of early diagnosis, certain measures should be made to guarantee that young people who are not connected to the medical field receive better education on cervical cancer. Name, gender, age, degree of education, occupation, and any further medical issues or histories are all included in the questionnaire. The question for the symptomatic analysis comprises,

- Bleeding in the vagina after menopause
- Continuous pelvic discomfort
- Unexpected weight loss
- Vaginal bleeding during or after intercourse,
- Inter-menstrual bleeding, discomfort or pain experienced during sexual activity
- Persistent vaginal discharge with an unpleasant odor
- Unusually long or heavy periods
- Blood in the feces (or) pee
- Enduring lower back pain

Among the obstacles to people's routine screening include, embarrassment test anxiety Fear of an unfavorable outcome, not believing I am in danger, wanting to attend but didn't schedule a time to go Overly hectic way of life, making date at your earliest convenience is difficult, Have had a negative screening experience in the past, are too immature to be screened, or do not believe that screening is necessary. It is a perfect opportunity for WHO and its partners to persuade the world about awareness of cervical tumor and the significance of Human Papillomavirus vaccine, which is The main reason of cervical tumor, during Cervical Tumor Consciousness Month in January might support the education and awareness initiatives intended to decrease the likelihood of cervical tumor by urging women to schedule routine screenings for the disease and encouraging eligible individuals to get vaccinated against the HPV virus.

Discussion and conclusion

Cervical tumor is the second most prevalent disease among females and a primary contributor to morbidity and mortality. Cervical tumor is mainly caused by HPV strains 16 and 18. The prevention of disease progression from pre-invasive to invasive stages involves accurate and timely diagnosis of aberrant cytological alterations. Therefore, cervical examination by initial HPV screening, followed by intervention for detected precancerous tumors by the Human papillomavirus (HPV) vaccine, is the two essential strategies that might be the most effective way for the avoidance and effective management of cervical tumors. It was evidenced that the prevalence of cervical tumors in the US has been reduced by half as a result of the establishment of HPV vaccination protocols and routine screening initiatives. [44] However, roughly 90% of cases of cervical tumors arise in nations with low or middle income, lacking access to HPV immunization programs or screening.

In nation-states with low and middle revenue, raising awareness among the younger population, securing adequate financing for cervical examinations, and organizing Oncological therapies and palliative care for

females diagnosed with cervical tumors are significant challenges to successful expansion. It is expected that the WHO eradication campaign will spur coordinated efforts to deal with these problems. However, the authors strongly believe and emphasize that, the government initiative to create awareness through health professionals, and paramedical forces as well as by increasing the active screening and vaccination program with financial assistance in teenage population may result in a decrease in cervical cancer incidence in India and another low and low-middle country, Furthermore, the swift expansion of vaccination and the regularity of cervical screening throughout all nations might potentially avert approximately 13.4 million instances of cervical tumor anticipated over the next fifty years, and may result in incidence rates of fewer than 4 per 100,000 women annually by the century's conclusion.

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