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SCREENING AND PREVENTION OF CARCINOMA CERVIX: A REVIEW

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ABSTRACT

Globally, the primary cause of cancer-related mortality in women is Carcinoma of the Cervix, and it is most caused by persistent human papillomavirus infection. The World Health Organization has set a goal to eradicate Cervical Cancer by 2030; In accordance with the plan, vaccination should be received by 90% of girls of age below 15years, women between the ages of 35 and 45 will undergo screening with an extremely sensitive test, and women who are diagnosed with cervical cancer or cervical dysplasia will receive the necessary care from qualified professionals. Because of the demonstrated effectiveness of intervention tactics including immunization against the most carcinogenic HPV strains and screening, particularly using HPV-based approaches, cervical cancer is mostly preventable. A combination of HPV genotyping and cervical cytology (Papanicolaou testing) can determine the precancer risk in individuals with a positive HPV test result. Presently, there are three HPV vaccines that can be used as prophylactic measures: the quadrivalent, bivalent, and a newly created nonvalent vaccine. In this review, we elaborate on the Human Papillomavirus, Symptoms, and Risk factors, methods of transmission, and discuss in depth about the screening techniques and the vaccination available for the prevention of Carcinoma of the Cervix.

KEYWORDS: Vaccination, Papanicolaou, Carcinogenic, Quadrivalent, Professionals, adenocarcinoma.

INTRODUCTION

Despite being a preventable disease, 36 low- and middle-income countries (LMICs) still see women dying from carcinoma of the cervix as the principal causative agent of cancer.[1] Globally, Cancer is the most important barrier to the expectancy of life and the leading cause of death.[2] Among females, Carcinoma of the Cervix (CC) continues to be one of the most prevalent malignancies worldwide. According to the estimation of GLOBOCAN 2020, approximately, it showed 6,04,000 newly reported cases and 3,42,000 deaths of cervical cancer annually. Eighty five percent of new cases and Ninety percent of fatalities take place in low- and middle-income nations.[3]

The lowermost part where, the Uterus that connects the vagina is the Cervix; composed of epithelium and stroma with a cylindrical structure. Most of the cases of cervical cancer originate from the ectocervical or endocervical mucosa.[3] About 75% of instances of invasive cervical carcinoma are squamous cell carcinomas, which are the most common kinds of tumors that arise in the ectocervix. On the other hand, adenocarcinomas are more common in tumors that originate from the endocervix. Less frequent histological subtypes of cervical carcinomas include adenosquamous, clear cell, serous papillary, small cell or neuroendocrine, and others.[4]

Symptoms and Risk Factors: - It can take up to 15–20 years for cervical cancer to manifest without any symptoms, and in later stages, abnormal vaginal bleeding, pelvic discomfort, pain during sexual activity, and vaginal masses that could be malignant can all be markers of the disease.[5]

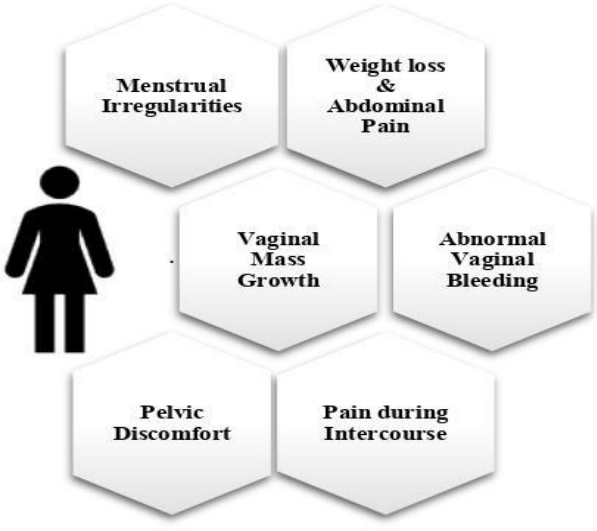

Fig. 1: Symptoms of Cervical Cancer.

The primary risk factor for cervical cancer development is infection with the human papillomavirus (HPV), followed by having several partners who engage in dangerous oral sex and regular non-protected sex, as well as having other multiple partners who may be contaminated with STDs like HPV, age, frequent childbirth, continuous use of combined oral contraceptives for 5 years, smoking and diet.[5]

Fig. 2: Risk factors of Cervical Cancer.

Human Papillomavirus: The Papillomaviridae family of viruses includes the deoxyribonucleic acid (DNA) viruses that cause human papillomaviruses (HPVs). They can hide from immunological reactions and are specially adapted to their host organisms.[6] The double-stranded, circular DNA molecule that makes up the human papillomavirus (HPV) genome has about 8000 base pairs.

The HPV viral oncogenes E6 and E7 have been identified as the main drivers of HPV-induced cervical cancer. The integration of viral DNA into the host cell genome is most likely the cause of the increased expression of these oncogenes observed in invasive malignancies and a fraction of high-grade lesions. The inactivation of retinoblastoma protein (pRb) and/or the tumor suppressor p53 is a typical occurrence for the human cell carcinogenesis. The HPV oncogenes E6 and E7 interact with these tumor suppressors and block their functions.[7] There are currently 216 HPV subtypes that have been found and classified as low, medium, or high risk.5 The 13 so-called "high-risk" HPV genotypes, which include HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, are highly associated with the risk of cervical cancer among the more than 200 HPV genotypes that have been identified. In contrast, the "low-risk" (LR-HPV) genotypes 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, and 81 frequently result in benign lesions.[8] Cervical malignancies, lesions, and preneoplastic dysplasia have all been related to HPV types 18 and 16, which also mediate uterine cervix cancer. HPV 16 accounts for around 50% of infections, while HPV 16 and 18 accounts for over 70% of cervical cancer occurrences globally.[6] While HPV18 is more frequently discovered in adenosquamous and adenocarcinomas carcinoma, HPV16 is mostly found in squamous cell carcinoma.[8]

High-risk HPV (hrHPV) infection is a major contributing component in the progression of low- and high-grade cervical intraepithelial lesions that eventually lead to cervical cancer from normal cervical epithelium. The host genome is altered as a result of the hrHPV infection of the cervical epithelium. This causes abnormal functioning of different tumor-promoting proteins as well as the silence of several tumor suppressor factors. Over the years, the advancement of neoplastic growth has been driven by the imbalance and instability that are brought about by different oncogenic factors originating from hrHPV into the host genome of cervical epithelial cells. However, the individual HPV subtypes determine how serious the consequences are for the development of cervical cancer.[5]

No matter how far we've come in primary and secondary cervical cancer prevention, a large number of population still suffer from or acquire metastatic illness, frequently during the first two years of concluding the first course of treatment. In certain cases, radiation therapy and/or surgical excision can treat limited recurrent local metastases. But, palliative chemotherapy is the only available treatment for the great majority of patients. Nonetheless, there is a substantial unmet clinical demand for efficient backup plans. Proteomics technologies, including mass spectrometry and protein array analysis, have made progress in understanding the molecular signalling pathways that underlie gynaecological oncology. Additionally, proteomics study of cervical cancer might identify novel targets for treatment, therefore reducing the establishment of medication resistance and enhancing prognosis.[9]

Transmission:- The primary method of HPV transmission is direct contact between the skin and the mucosa or skin. Sexual contact with an HPV-positive individual, whether by vaginal, anal, or oral means, is the most common way for the virus to spread.[9] The majority of people who engage in sexual activities, at some point during their lives become infected with HPV, the most prevalent virus that affects reproductive systems.[10] Semen, sperm cells, ovaries, endometrium, and other parts of the male reproductive system have all been confirmed to have HPV DNA. This suggests that HPV is often spread during or right after egg fertilization. HPV- induced lesions in babies were identified; this included laryngeal and anogenital lesions, and there was a possibility that HPV was transmitted intrauterine. The placenta, amniotic fluid, and umbilical cord were found to contain HPV DNA.[8]

The HPV infection spreading horizontally involves

contact of the skin (other than sexual), mouth and the fingers. Research has indicated that self-inoculation might be a channel for HPV transmission because it has been proven effective in female virgins and in children with low- risk HPV (genital warts) who do not have a history of sexual abuse. Another route of HPV transmission is vertical from mother to kid. Numerous research works have highlighted the potential for infection from the placenta, the amniotic fluid, or contact with the mother's vaginal mucosa during a normal delivery. Although there has never been proof of HPV transmission through the water, HPV DNA has been found in aquatic habitats. According to studies that have examined HPV samples on contaminated medical equipment (even after conventional disinfection), routine hygiene practices are ineffective in preventing the spread of HPV.[11]

SCREENING OF CARCINOMA CERVIX

The incidence and death of cervical cancer have significantly decreased as a result of the widespread use of population-based screening.[12] The majority of HPV infections are promptly eradicated by the body's immune system; however, a small percentage continue to manifest for longer than two years following cervical epithelial infection. The chance of getting a cervical precancer rises when HPV infections last for several years. If treatment is not received for years or decades, a small percentage of cervical precancers will spread. The longer time lag between HPV infection and cervical cancer is essential for the effectiveness of screening programs because it enables early treatment of cancer precursors to stop the spread of invasive cervical cancer.[13]

The main purpose of CC screening is early detection and diagnosis of the disease.[14] Because cervical cancer has a protracted premalignant phase, screening and treatment can be done before the cancer spreads and becomes invasive.[15] In contrast to the modest effort shown in most low- and middle-income countries, affluent countries have paid significant attention to cervical cancer prevention and the influence of screening programs on fatalities attributable to the disease. It has been demonstrated that awareness of cervical cancer and screening programs, in addition to other variables including partner attitude and individual perception, beliefs, and attitudes, affect the rate of screening uptake.[16]

Population-based screening for cervical cancer using Pap smears or cytology is a crucial secondary preventative intervention that increases the rate of cure for those who get the disease. When effective screening systems are in place, early identification and treatment through screening can prevent up to 80% of cervical cancer cases in wealthy nations.[15]

For millions of women who are no longer eligible for HPV vaccination, secondary prevention utilizing pelvic examinations with Pap tests and pelvic examinations with visual inspection and acetic acid (VIA) will remain an integral element of a complete cancer control plan. Examining the relationship between cervical cancer screening and all aspects of healthcare access is crucial.[17]

According to the American Cancer Society's cervical cancer screening guidelines (Fig. 3), primary HPV testing every five years is the recommended method for routine screening. Screening for cervical cancer should start in average-risk persons with a cervix at age 25 and stop at age 65.[18]

Various Screening Techniques

Pap Smear Examination (Cervical Cytology)

Earlier, Smears of the vagina and cervix, both normal and pathological, might be properly diagnosed by seeing them under a microscope. Nowadays, this process is commonly referred to as the Papanicolaou smear. With its low cost, high repeatability, and convenience of use, the Papanicolaou smear swiftly rose to the top of the cervical cancer screening field. Products based on liquid-based cytology (LBC) were developed in the 1990s as a result of cytotechnology advancements. Liquid-based test collection entails sampling and cell transfer to a liquid media, followed by automated processing, as opposed to the traditional Papanicolaou smear method of applying a fixative after a cervical sample is spread onto a slide.[19] Although the compensation for liquid-based cytology (LBC), also known as thin-layer cytology, is not more than that for traditional cytology tests, LBC techniques are now expressly approved alongside conventional cytology procedures.[20]

Hpv Test:- A cervical or vaginal sample is taken as part of HPV primary screening to look for the existence of an oncogenic HPV infection. Cervical samples are taken by a doctor using a speculum examination. But utilizing a self-collected vaginal swab or a sample acquired by a doctor may both identify an oncogenic HPV infection, suggesting that self-sampling may be a viable alternative in the future.[21]

In clinical practice, the use of HPV testing and genotyping to assess the risk of cervical cancer and precancerous lesions has increased.[22]

Hpv And Cytology Co-Testing

Co-testing entails obtaining an HPV test and a cervical cytology sample. During a speculum examination, a practitioner gathers samples. Cytology and HPV tests can be obtained independently or from a single liquid-based cytology sample, depending on which assays are employed.[21] In clinical practice, the use of HPV testing and genotyping to assess the risk of cervical cancer and precancerous lesions has increased. When it comes to detecting precancers, an HPV test—which looks for the nucleic acids of carcinogenic HPV strains in a cervicovaginal specimen—has a higher sensitivity than cervical cytology, which looks at exfoliated cells under a microscope.[22]

The recommendations apply to all asymptomatic individuals with a cervix, regardless of their sexual history or human papillomavirus (HPV) vaccination status, including those who have undergone supracervical hysterectomy and transgender men who retain their cervix.

These recommendations represent guidance from the American Cancer Society (ACS) for persons who are initiating cervical cancer screening or have had all normal cervical cancer screening results in the past, or have been returned to routine cervical cancer screening based on follow-up recommendations from the Risk-Based Management Consensus Guidelines. The recommendations do not apply to individuals at increased risk for cervical cancer due to solid organ or stem cell transplantation, human immunodeficiency virus infection or immunosuppression from other causes, or in utero exposure to diethylstilbestrol.

Recommendations[a]

The ACS recommends that individuals with a cervix initiate cervical cancer screening at age 25 y and undergo primary HPV testing every 5 y through age 65 y (preferred). If primary HPV testing is not available, individuals aged 25-65 y should be screened with cotesting (HPV testing in combination with cytology) every 5 y or cytology alone every 3 y (acceptable) (strong recommendation).[a]

Cotesting or cytology testing alone are included as acceptable options for cervical cancer screening because access to primary HPV testing with a test approved by the FDA for primary screening may be limited in some settings. As the United States makes the transition to primary HPV testing, the use of cotesting or cytology alone for cervical cancer screening will be eliminated from future guidelines.

The ACS recommends that individuals with a cervix who are older than age 65 y, who have no history of cervical intraepithelial neoplasia grade 2 or a more severe diagnosis within the past 25 y, and who have documented adequate negative prior screening in the 10-y period before age 65 y discontinue cervical cancer screening with any modality (*qualified recommendation*).[a,b]

- Adequate negative prior screening is currently defined as 2 consecutive negative HPV tests, or 2 consecutive negative cotests, or 3 consecutive negative cytology tests within the past 10 y, with the most recent test occurring within the recommended interval for the test used. These criteria do not apply to individuals who are currently under surveillance for abnormal screening results.
- Individuals older than age 65 y without conditions limiting life expectancy for whom sufficient documentation of prior screening is not available should be screened until criteria for screening cessation are met.
- Cervical cancer screening may be discontinued in individuals of any age with limited life expectancy.

Abbreviation: FDA, US Food and Drug Administration.

- [a] A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening. Qualified recommendations indicate there is clear evidence of benefit of screening but less certainty about the balance of benefits and harms or about patients' values and preferences, which could lead to different decisions about screening.
- [b] Older than age 65 years means that cervical cancer screening is not recommended for individuals aged 66 years and older.

Fig. 3: American Cancer Society Recommendations for Cervical Cancer Screening, 2020.

Colposcopy

Cytology-based screening has been mostly successful due to its built-in simplicity, affordability, and extensive database of different cytological patterns associated with precancerous lesions. During a colposcopy operation, the cervix and vagina may be examined with a strong variable intensity light source and a changing magnification that can be adjusted from ×4 to ×30. It entails monitoring the alterations in the cervical epithelium following successive applications of Lugol's iodine, 5% diluted acetic acid, and normal saline. The integration of all the information gleaned during colposcopy forms the basis for disease classification. To confirm or rule out high-grade premalignant or malignant lesions, a guided biopsy from the most severe location must be performed if any abnormality is seen during colposcopy.[23]

Summary of Screening Tests

Reducing false-negative findings is the aim of a screening test. By these measures, HPV testing finds considerably more precancerous lesions per screen than cytology testing alone, making it the best screening method for cervical cancer. The number of cases detected when cytology is added to HPV testing alone (co-testing) is marginally increased, but at the expense of more invasive procedures (such as colposcopy with biopsy), more accurate results are detected.

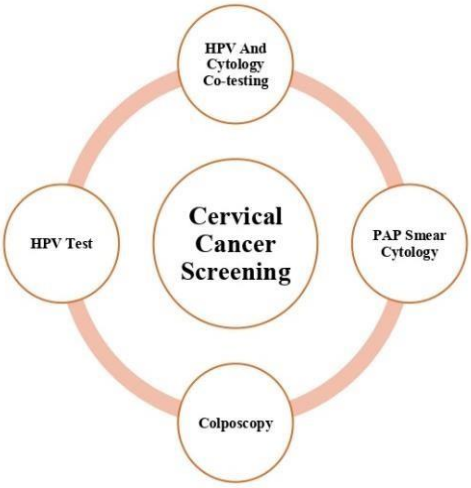

Fig. 4: Cervical Cancer Screening Techniques.

PREVENTION OF CERVICAL CANCER

Most cases of cervical cancer can be avoided by females receiving an HPV vaccination as a primary preventive measure, screening for precancerous lesions on the cervical mucosa as a secondary preventive measure, and early detection and treatment of cancer as a tertiary preventive measure.[24] The World Health Organization states that the majority of nations advise HPV vaccination to take place between the ages of 9 and 14, with young teenage females being the main target group. However, vaccination for adolescent boys and young adults who have not yet had their immunization is also frequently advised.[25] In many nations, especially Low Middle-Income Countries (LMICs), HPV immunization programs are still in their infancy. Currently, 122 countries and territories that make up the World Health Organization (WHO) and 27 non-member governments have HPV vaccinations listed on their national regular immunization schedules. Eight of the 29 (28%) low-income nations and 22 of the 51 (43%) lower-middle-income nations had HPV vaccination programs in place as of 2022. In the meanwhile, national immunization programs in 57% of lower-middle-income nations and 72% of low-income countries do not currently contain the HPV vaccine. An important consideration in a nation's capacity to launch and continue a program is cost.[26]

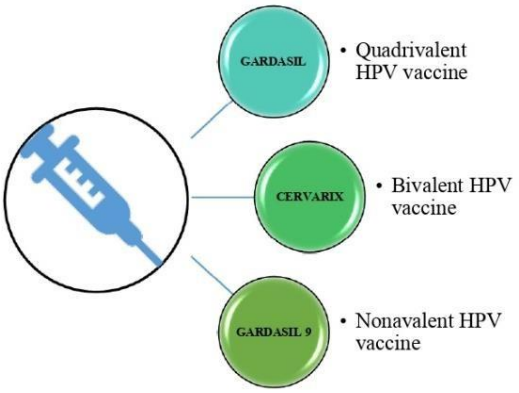

Fig. 5: Available HPV Vaccines.

Available Hpv Vaccines

Presently, there are three approved HPV vaccines (Table 1) for prophylaxis: Cervarix®, a bivalent HPV (2vHPV) vaccine that targets HPV16 and HPV18; Gardasil®, a quadrivalent HPV (4vHPV) vaccine that targets HPV6, HPV11, HPV16, and HPV18; and Gardasil 9®, a nonavalent HPV (9vHPV) vaccine that targets HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, and HPV58. The vaccines known as 4vHPV and 9vHPV were approved in 2006 and 2014, respectively. They are made using the amorphous aluminium hydroxy phosphate sulfate (AAHS) adjuvant in Saccharomyces cerevisiae (S. cerevisiae) expression systems. For both males and females aged 9 to 26, the 4vHPV vaccination is recommended as a preventive measure against cervical cancer, precancerous or dysplastic lesions, and genital warts.[27]

The quadrivalent HPV vaccine types 6,11,16, and 18 (HPV4; GARDASIL, Merck & Co. Inc.) was approved in June 2006 for use in girls aged 9 to 26 years to prevent cervical cancer precursors, vaginal and vulvar cancer precursors, anogenital warts, and cervical cancer associated with the HPV type.[28] Whereas it was approved for use in men in October 2009 for genital warts caused by HPV 6 and 11.[29]

	GARDASIL	CERVARIX	GARDASIL 9
Manufacturer	Merck & Co., Inc	GlaxoSmithKline Biologicals	Merck & Co., Inc
Antigen	L1 VLP of HPV – 6, 11, 16 and 18	L1 VLP of HPV - 16 and 18	L1 VLP of HPV – 6, 11, 16,18, 31, 33, 45, 52 and 58
Expression System	*S. cerevisiae*	Baculovirus expression vector system	*S. cerevisiae*
Indication	Females and Males, age between 9 – 26 years	Females, age between 9 – 25 years	Females and Males, age between 9 – 45 years

VLP: virus-like particle; *S. cerevisiae: Saccharomyces cerevisiae*;

Fig. 6: Various types of HPV Vaccine with Characteristics.

Carrageenan

Sulfated polysaccharides, such as heparin, cellulose sulfate, and dextran sulfate, have been demonstrated in earlier research to be able to prevent HPV infectivity. Initial virion attachment to cultivated cell lines is assumed to be primarily mediated by interactions between the virion and heparan sulfate, a kind of cell-surface glycosaminoglycan (GAG) for several virus types, including papillomaviruses. Sulfated polysaccharides are generally believed to inhibit viral infection by competitively competing with heparan sulfate chemically, which prevents the virus from adhering to the cell surface in the first place. Heparin, a highly sulfated form of heparan sulfate generated by mast cells, has been employed as a model inhibitor of HPV infectivity in several earlier investigations. When it comes to inhibiting the infectivity of genital HPV PsV in vitro, carrageenan, a kind of sulfated polysaccharide derived from marine red algae (seaweed), has about a thousand-fold better effectiveness than heparin.

Widespread commercial use of carrageenan as a thickening ingredient may be found in many foods and cosmetic items, including several lubricant brands for sexual purposes. Carrageenan may be helpful as an affordable topical microbicide to prevent the sexual transmission of HPV as premium formulations seem to have an excellent safety profile for long-term vaginal usage.[30]

Factors Related To Non-Vaccination

The adoption of the human papillomavirus (HPV) vaccine frequently falls short of that of other teenage vaccinations. In contrast to the adoption of the quadrivalent meningococcal conjugate vaccination (85%) and tetanus, diphtheria, and acellular pertussis vaccine (89%) in 2017, the uptake of a single HPV vaccine dosage was 66% and the completion of the HPV vaccine series was 49%.[31]

Numerous factors related to non-vaccination have drawn special attention, such as mistrust because of the perceived "newness" of HPV vaccinations, worries about vaccine safety, worries about sexual risk compensation, and insufficient vaccination recommendations from health care providers (HCPs).[32]

Vaccine Safety and Adverse Events Following Vaccination

Concerns and problems over the safety of vaccines have adversely influenced vaccination uptake worldwide, with HPV vaccine programs being particularly impacted. Pre-licensure clinical trials, post-marketing surveillance systems, and observational studies have all been used to assess the safety of the HPV vaccination globally. Although there have been prior identifications of potential signals linking the HPV vaccination to venous thromboembolism (VTE) and Guillain-Barré syndrome (GBS), these have been ruled out in follow-up observational studies. Case reports and media interest have focused on connections between the HPV vaccine and other specific conditions and syndromes, such as postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome (which is similar to POTS), complex regional pain syndrome (CRPS), and primary ovarian insufficiency (POI). Despite the lack of evidence from expert evaluations and observational research to show causal relationships, these theories are nonetheless put out.[33]

Fever, nausea, and dizziness were among the systemic adverse events following immunization (AEFI) that occurred within 15 days of vaccination among recipients of the quadrivalent (4vHPV) vaccinations. Pain, redness, and swelling at the injection site were far more common among vaccination recipients than in those receiving a placebo. Very few major adverse effects (<0.1%) were linked to the vaccination, and those that occurred were no more common than those who received a placebo. No patterns in the emergence of new medical disorders (including autoimmune illnesses) or safety issues were noted throughout the up to four-year follow-up. The bivalent (2vHPV) vaccine also showed a similar AEFI profile, with vaccinees experiencing considerably more local responses than placebo receivers and greater frequencies of some systemic AEFIs, such as headache, myalgia, and tiredness, occurring within 7 days following vaccination. Both vaccines show no pattern of newly identified autoimmune illnesses, chronic diseases, or medically severe conditions.[34]

CONCLUSION

Cervical cancer is a major worldwide burden and continues to provide a considerable therapeutic challenge, particularly in low- and middle-income countries (LMICs) where resources are scarce and available treatment choices are frequently out of reach. Therefore, all nations must support the 2020 World Health Assembly resolution calling for the "Elimination of Cervical Cancer" by 2030 through the accomplishment of the following three goals: (1) 90% of girls immunized against HPV by the age of 15; (2) high-performance test screening for 70% of women at 35 and 45 years old; and (3) 90% of precancerous lesions treated and 90% of invasive cancer cases managed.

The broad adoption of screening programs will play a major role in the fall in the incidence of cervical cancer and the mortality associated with it. Annual examination of the Cervix is no longer the "one size fits all" approach to cervical cancer prevention for all adult women. Adolescence is the first stage of primary prevention of cervical cancer, starting with universal vaccination to stave off future HPV infection. Since the majority of adults have been exposed to carcinogenic HPV, screening and secondary prevention are now the main methods of prevention for adults. Cervical cancer still tends to develop most commonly in unscreened and under-screened people. Ultimately, the greatest way to reduce the incidence of cervical cancer is to guarantee that all adults with a cervix receive screening and follow-

up and that all teenagers receive HPV vaccines.

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