

A Brief Overview on Cervical Cancer and its Prevention

Ravina Dethe

Shri Shankaracharya College of Nursing Hudco Bhilai, (C.G.), India

Abstract: *Cervical cancer still remains the most common cancer affecting the Indian women. India alone contributes 25.41% and 26.48% of the global burden of cervical cancer cases and mortality, respectively. Ironically, unlike most other cancers, cervical cancer can be prevented through screening by identifying and treating the precancerous lesions, any time during the course of its long natural history, thus preventing the potential progression to cervical carcinoma. Several screening methods, both traditional and newer technologies, are available to screen women for cervical precancers and cancers. No screening test is perfect and hence the choice of screening test will depend on the setting where it is to be used. Similarly, various methods are available for treatment of cervical precancers and the selection will depend on the cost, morbidity, requirement of reliable biopsy specimens, resources available, etc. The recommendations of screening for cervical cancer in the Indian scenario are discussed.*

Keywords: cervical cancer, Human papilloma virus , HPV vaccine

1. Introduction

Cervical cancer is the uncontrolled growth of abnormal cells in the lining of the cervix. The cervix is part of the female reproductive system and is located in the lower part of the womb, forming the opening from the womb to the vagina. Cervical cancer remains one of the most common causes of death for women globally and ranks 4th of all cancers. Currently, every 2 minutes a life is lost to this disease. Importantly, it is the leading cause of cancer deaths in women.^[1]

This large-scale morbidity and mortality due to cervical cancer is totally unwarranted not only because the definitive cause of cervical cancer is now known, but also because the disease takes a long time to develop after initial infection with high-risk Human papillomavirus (HPV). Unlike most other types of cancer, it is preventable when precursor lesions are detected and treated. Screening can reduce both the incidence and mortality of cervical cancer. The mortality due to uterine cervix cancer has fallen dramatically in the developed countries since the advent and widespread application of cytology-based screening with Pap smear test. In India, to date, there is no organized cervical cancer screening program. Hence, a large proportion of these cancer cases present in advance stages at the time of diagnosis, when cure is not possible. Screening for cervical cancer is essential as the women often do not experience symptoms until the disease has advanced. Women with preinvasive lesions have a five-year survival rate of nearly 100%.^[2] Detection of CIN or precancerous lesions such as carcinoma-*in-situ* leads to a virtual cure with the use of current methods of treatment.^[3] In the absence of screening, nearly 70% of cervical cancer patients in India present in stages III and IV.^[4] Nearly 20% of women with cervical cancer die within the first year of diagnosis and the 5-year relative survival rate is 50%.^[5]

1.1 Risk Factors for Cervical Cancer

A risk factor is anything that increases your chance of getting a disease such as cancer. Different cancers have

different risk factors. But having a risk factor, or even several, does not mean that you will get the disease. Several risk factors can increase your chance of developing cervical cancer. Women without any of these risk factors rarely develop cervical cancer. When we think about risk factors, it helps to focus on those we can change or avoid (like smoking or human papillomavirus infection), rather than those we cannot (such as your age and family history). However, it is still important to know about risk factors that cannot be changed, because it's even more important for women who have these factors to get regular screening tests to find cervical cancer early.

1.2 Risk Factors Can Possibly Change

Human papillomavirus (HPV) infection

Infection by the human papillomavirus (HPV) is the most important risk factor for cervical cancer. HPV is a group of more than 150 related viruses. Some of them cause a type of growth called **papillomas**, which are more commonly known as warts.

- HPV can infect cells on the surface of the skin, and those lining the genitals, anus, mouth and throat, but not the blood or internal organs such as the heart or lungs.
- HPV can spread from one person to another during skin-to-skin contact. One way HPV spreads is through sexual activity, including vaginal, anal, and even oral sex.
- Different types of HPV cause warts on different parts of the body. Some cause common warts on the hands and feet; others tend to cause warts on the lips or tongue.

Sexual history

Several factors related to your sexual history can increase the risk of cervical cancer. The risk is most likely affected by increasing the chances of exposure to HPV.

- Becoming sexually active at a young age (especially younger than 18 years old).
- Having many sexual partners.
- Having one partner who is considered high risk (someone with HPV infection or who has many sexual

partners)

Smoking

When someone smokes, they and those around them are exposed to many cancer-causing chemicals that affect organs other than the lungs. These harmful substances are absorbed through the lungs and carried in the bloodstream throughout the body. Women who smoke are about twice as likely as those who don't smoke to get cervical cancer. Tobacco by-products have been found in the cervical mucus of women who smoke. Researchers believe that these substances damage the DNA of cervix cells and may contribute to the development of cervical cancer. Smoking also makes the immune system less effective in fighting HPV infections.^[6]

Having a weakened immune system

Human immunodeficiency virus (HIV), the virus that causes AIDS, weakens the immune system and puts people at higher risk for HPV infections. The immune system is important in destroying cancer cells and slowing their growth and spread. In women with HIV, a cervical pre-cancer might develop into an invasive cancer faster than it normally would. Another group of women at risk for cervical cancer are those taking drugs to suppress their immune response, such as those being treated for an autoimmune disease (in which the immune system sees the body's own tissues as foreign and attacks them, as it would a germ) or those who have had an organ transplant.

Chlamydia infection

Chlamydia is a relatively common kind of bacteria that can infect the reproductive system. It is spread by sexual contact. Women who are infected with chlamydia often have no symptoms and they may not know that they are infected at all unless they are tested during a pelvic exam. Chlamydia infection can cause pelvic inflammation, leading to infertility. Some studies have seen a higher risk of cervical cancer in women whose blood tests and cervical mucus showed evidence of past or current chlamydia infection.

Long-term use of oral contraceptives (birth control pills)

There is evidence that taking oral contraceptives (OCs) for a long time increases the risk of cancer of the cervix. Research suggests that the risk of cervical cancer goes up the longer a woman takes OCs, but the risk goes back down again after the OCs are stopped, and returns to normal many years after stopping. A woman and her doctor should discuss whether the benefits of using OCs outweigh the potential risks.^[7]

Having multiple full-term pregnancies

Women who have had 3 or more full-term pregnancies have an increased risk of developing cervical cancer. It is thought this is probably due to the increased exposure to HPV infection with sexual activity. Also, studies have pointed to hormonal changes during pregnancy as possibly making women more susceptible to HPV infection or cancer growth. Another thought is that pregnant women might have weaker immune systems, allowing for HPV infection and cancer growth.

Young age at first full-term pregnancy

Women who were younger than 20 years when they had

their first full-term pregnancy are more likely to get cervical cancer later in life than women who waited to get pregnant until they were 25 years or older.

Economic status

Many low-income women do not have easy access to adequate health care services, including cervical cancer screening with Pap tests and HPV tests. This means they may not get screened or treated for cervical pre-cancers.

A diet low in fruits and vegetables

Women whose diets don't include enough fruits and vegetables may be at increased risk for cervical cancer.

1.3 Risk factors that cannot be changed

Diethylstilbestrol (DES)

DES is a hormonal drug that was given to some women between 1938 and 1971 to prevent miscarriage. Women whose mothers took DES (when pregnant with them) develop clear-cell adenocarcinoma of the vagina or cervix more often than would normally be expected. DES-related clear cell adenocarcinoma is more common in the vagina than the cervix. The risk appears to be greatest in women whose mothers took the drug during their first 16 weeks of pregnancy. The average age of women diagnosed with DES-related clear-cell adenocarcinoma is 19 years.^[8]

Symptoms

Precancerous changes of the cervix usually do not cause pain or any other symptoms and are not detected unless a woman undergoes screening. Symptoms generally do not appear until abnormal cervical cells become cancerous and invade nearby tissue. The most common symptoms are copious foul-smelling vaginal discharge, abnormal bleeding or inter-menstrual bleeding, postcoital bleeding, postmenopausal bleeding or backache.^[9]

Different screening/diagnostic tests to detect cervical precancers and cancers

Several tests are available to screen women for cervical precancers and cancers. Each screening test has its own strengths and limitations and the choice of test will depend on the setting in which it is to be used.^[10]

Cytology-based screening

Cytology-based screening programs continue to be the mainstay of cervical cancer prevention. The different types of cytology are as follows:

Pap test with conventional cytology

Conventional cytology is being used for more than 50 years all across the globe. This test involves collection of cells lightly scraped from the ectocervix and endocervix, these are then examined under a microscope. This method is widely used for screening cervical cancers in most developed countries.^[11] The test is highly specific, but false-negative rates have always been an area of concern in cytology-based programs, wherein premalignant or malignant cells have been misdiagnosed as normal.

Pap test using liquid-based cytology

Liquid-based cervical cytology was developed to improve

the diagnostic reliability of Papanicolaou (Pap) smears. Conventional Pap smears can have false-negative and false-positive results because of inadequate sampling and slide preparation, and errors in laboratory detection and interpretation. Liquid-based Pap smears improve the diagnostic sensitivity of cervical cytology screening. They have the additional benefit of enabling easy testing for human papillomavirus (HPV).

Automated pap smears

Automated screening machines can potentially allow detection of abnormal cases that are missed with conventional screening, although they may substantially increase the cost of Pap smears. Automated Pap testing (AutoPap and AutoCyte Screen) attempts to reduce errors by using computerized analysis to evaluate Pap smear slides. With AutoPap, the material on the slide is reviewed and scored based on an algorithm, as to the likelihood of an abnormality being present. Typically, it does not show the cytotechnologist which of the cells are likely to be abnormal. Variety of visual characteristics, such as shape and optical density of the cells, are included in the algorithm.

In Auto Cyte Screen, various cell images are presented to a human reviewer, who then determines whether a manual review is required. The reviewer first needs to enter an opinion, after which the device reveals its determination based on a ranking as to whether manual review is warranted. When the findings of both the reviewer and the computer match and no review is needed, then, a diagnosis of “within normal limits” is given. Manual review is undertaken for cases which are designated by either the cytologist or the computer ranking as abnormal.^[12]

Visual examination of cervix

These methods are simple and can be performed by a trained health worker. The various visual examination methods are as follows:

- a) Unaided visual inspection
- b) Visual inspection after application of acetic acid (VIA)
- c) VIA with magnification (VIAM)
- d) Visual inspection after application of Lugol's iodine (VILI)

Unaided visual inspection or visual inspection or downstaging It is naked eye visualization of the cervix without acetic acid. This technique has been assessed in three studies from India and has been shown to perform poorly.^[13 14 15]

Visual inspection after application of 3 to 5% acetic acid It is naked eye visual inspection of the cervix after application of 3 to 5% acetic acid. When this test is done with the naked eye, it is also called cervicoscopy or direct visual inspection. Application of 3 to 5% acetic acid causes a reversible coagulation or precipitation of the cellular proteins. Areas with dysplasia or invasive cancer have large number of undifferentiated cells in the epithelium and hence undergo maximal coagulation because of higher content of nuclear protein and prevent light from passing through the epithelium, hence these areas appear acetowhite. The accuracy of VIA to detect cervical neoplasia has been

extensively studied and found to be satisfactory.^[16,17,18]

Visual inspection after application of 3 to 5% acetic acid and under magnification

This is performing VIA under low magnification using magnification devices. It is also called gynoscopy, aided VI, or VIAM. VIAM has similar sensitivity and specificity as compared with VIA and does not have any added benefit over VIA as noted in the Mumbai cervix cancer trial.^[19]

Visual inspection after application of Lugol's iodine

It is also known as Schiller's test and uses Lugol's iodine instead of acetic acid. Squamous epithelium contains glycogen, whereas precancerous cells and invasive cancer lack glycogen. Iodine is glycophilic and is taken up by the squamous epithelium, staining it mahogany brown or black. Precancerous lesions and invasive cancer do not take up iodine (because of absence of glycogen) and appear as well-defined, thick, mustard or saffron yellow areas.^[20]

Colposcopy

A colposcope is a low-power, stereoscopic, binocular field microscope containing a powerful light source, used for magnified visual examination of the uterine cervix to help in the diagnosis of cervical neoplasia. The most common indication of referral for colposcopy is positive screening tests (e.g., positive cytology, positive on VIA, etc.). Colposcopy allows the examiner to take tissue samples (biopsies) from specific areas that do not look normal. Endocervical curettage is usually obtained when the colposcopy is unsatisfactory, i.e., the squamolumnar junction cannot be visualized.^[21]

Cervicography

Cervicography consists of distant evaluation of photographs of the cervix “cervicograms,” taken with a specialized 35-mm camera, after application of acetic acid. However, cervicography cannot be recommended for universal screening, though it may have a role in the follow-up of patients with a mildly abnormal cervical smear.^[22]

Human papillomavirus DNA test

The etiopathological role of HPV as a causative agent of cervical cancer has been well established. However, most HPV infections in young women regress rapidly, without causing clinically significant disease. This test detects whether a person is infected with one or more of the 13 high-risk HPV viral types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). It is used as a routine screening test for women above 30 to 35 years in many regions and is especially useful to evaluate women with equivocal Pap test. The sensitivity of HPV testing for detecting CIN 2–3 lesions varied from 45.7 to 80.9% across different study sites in India the specificity varied from 91.7 to 94.6%.^[23]

Management of Cervical Precancers

Appropriate clinical management of screen-positive cases is pertinent to the success of cervical cancer screening program. Pre cancers are completely curable with appropriate treatment and regular follow-up. However, the survival is grossly affected for invasive cervical cancers. There is consensus agreement that cytology indicative of high-grade lesions (CIN2-3 or HSIL in the Bethesda system)

should engender immediate referral for colposcopy and biopsy. The management of women who have equivocal or borderline cytology of low-grade abnormalities (ASCUS/LSIL) is still under debate. It is generally agreed to have a HPV triage for women with equivocal cytology. Cervical pre cancers can be treated in different ways depending on the extent and nature of the disease. [24] The different modalities of managing pre cancers of the cervix are as follows:

Regular screening and follow-up

Low-grade cervical dysplasia (LSIL, CIN1) often spontaneously resolve without treatment, but careful monitoring and follow-up testing is required. Very early dysplasias are most likely to regress. Hence, the patient may be kept under observation and regular follow-up as very few of them may progress to high-grade dysplasias. Persistent CIN1 at 2 years warrants treatment.

Cryotherapy

Cryotherapy is a relatively simple and safe procedure that destroys the precancerous cells using compressed refrigerant gas like nitrous oxide or carbon dioxide to freeze the ectocervical tissue. The refrigerant gas is then made to flow, leading to destruction of abnormal cervical tissue because of extreme cold temperatures. Cryonecrosis is achieved by crystallization of intracellular water. The disadvantage of cryotherapy is that no tissue sample is available to confirm the histology and extent of involvement of the lesion. Cryotherapy is not appropriate for treating large lesions that cannot be covered by the probe or lesions located in the endocervical canal. [25]

Loop electrosurgical excision procedure

The loop electrosurgical excision procedure (LEEP) instrument is powered by an electrosurgical unit and consists of a wire loop electrode on the end of an insulated handle, which acts as a scalpel to excise the visible patches of abnormal cervical tissue. It is also known as large loop excision of the transformation zone. The current is adjusted to achieve cutting and coagulation effect simultaneously. The power used needs to be sufficient to excise the tissue without causing thermal artifact. The procedure can be performed under local analgesia and results in good cure rates. The cervical transformation zone and lesion are excised to an adequate depth, which in most cases is at least 8 mm, and extending 4 to 5 mm beyond the lesion. It can be performed as a single pass procedure or multiple pass procedure in the same sitting. There may be mild cramping during and after the procedure, and mild bleeding that may persist for some days. LEEP is most commonly used to treat high-grade cervical dysplasias. The major advantage of LEEP over cryotherapy is that it removes the affected epithelium rather than destroying it, thus allowing histological examination of the excised tissue. [26] Treatment success of LEEP varied between 91 and 98% in nonrandomized studies.

Cervical conization

This procedure which can be used for diagnostic or therapeutic purpose involves removal of a cone-shaped piece of tissue from the cervix. The base of the cone is formed by the ectocervix (outer part of the cervix), and the

endocervical canal forms the apex of the cone. Conization is performed under general anesthesia and can completely remove many precancers and very early cancers. After the procedure, cramping and some bleeding may persist for a few weeks. Rare complication is cervical stenosis. The treatment success of knife cone biopsy is reported as 90 to 94% in nonrandomized studies. [27]

Laser ablation

A laser beam is used to destroy abnormal cervical tissue at the transformation zone, the destruction of tissue being controlled by the length of exposure. It is usually performed under local anesthesia. Treatment success of laser ablation is reported as 95 to 96%. [28]

2. Recommendations for Cervical Cancer Prevention

Cervical cancer does not develop suddenly. It is the normal cells of cervix that develop precancerous changes that then turn to cervical cancer. Hence, there are two ways of reducing the burden of cervical cancers. One is to detect and treat cervical precancers before they become true cancers, and the second is to prevent the development of precancers itself.

Regular screening and timely follow-up is necessary

Despite the fact that early detection and treatment is one of the priorities of the National Cancer Control Programme in India, yet there is no organized cervical cancer screening program in the country; hence, screening mainly remains opportunistic. National consultations on cervical cancer control have concluded that cytology screening is not feasible in view of the technical and financial constraints in India. Visual examination and HPV testing have been evaluated as alternatives to cytology in India. However, with the high cost of HPV testing, VIA seems to be a feasible alternative for triaging, followed by appropriate interventions (depending on the level of expertise available at referral centers) in reducing the incidence and mortality of cervical cancer. [29]

According to American Cancer Society (ACS) guidelines, cervical cancer screening should ideally begin three years after the initiation of sexual intercourse. The women may be screened annually for the first three years, after which if three consecutive screening test results are normal, then once in two to three years screening suffices. The same recommendations apply for women with subtotal hysterectomy. Women above 70 years with an intact cervix who have had three or more documented, consecutive, technically satisfactory normal cervical cytology tests and no abnormal or positive cytology tests within the 10-year period prior to age 70 years may elect to cease cervical cancer screening. Women who are immunocompromised (including HIV-positive women) should undergo screening twice in the first year after diagnosis of HIV infection and if the results are normal, then continue with annual screening.

Women with total hysterectomy should be screened only if there is history of cervical precancer or cancer or when it is not possible to document the absence of cervical precancer or cancer as the indication for the hysterectomy. Women

with a history of cervical precancer should be screened until there is a 10-year history of no abnormal/positive cytology tests, including documentation of three consecutive, technically satisfactory, normal or negative cervical cytology tests. Women with a history of *in utero* DES exposure and/or a history of cervical carcinoma should continue screening after hysterectomy, as also immunocompromised women with intact uterus, for as long as they are in reasonably good health and do not have a life-limiting chronic condition.

Other recommendations for prevention of cervical precancers and cancers are to avoid use of tobacco, practice safe sex, limit the number of sex partners, and choose a sex partner who has no other sex partners. Use of condoms consistently and correctly during sexual activity may offer some degree of protection. Condoms do not provide complete protection from HPV infection because this virus (unlike HIV) can spread by contact with any infected area of the body. Having a healthy diet and lifestyle and consuming diet rich in beta-carotene, vitamin C, and folate (vitamin B9) from fruits and vegetables is recommended. [30]

Human papillomavirus vaccine

Vaccines against HPV infections Currently, two vaccines, Cervarix are available to protect women against HPV types 16 and 18, the oncogenic types responsible for about 70% of cervical cancers. One of these vaccines, Gardasil, also protects against HPV types 6 and 11 which causes genital warts. Both vaccines consist of virus-like particles and are recommended for women, preferably before the onset of sexual activity. The vaccines are to be administered 0.5 ml intramuscularly in three doses over a period of six months (the schedule is 0, 2, and 6 months for Gardasil and 0, 1, and 6 months for Cervarix). The HPV vaccine is safe and effective, with no serious side effects. Boys and young men may choose to get this vaccine to prevent genital warts. Also, the current vaccines cover only two high-risk types of HPV. Hence, vaccines cannot substitute screening and treatment of cervical precancers. [31]

3. Conclusions

Cervical cancer continues to be the single largest cancer among women in India and several other countries which cannot afford the logistics of cytology-based screening programs. The goal of cervical screening is to identify and remove significant precancerous lesions in addition to preventing mortality from invasive cancer. Population-based screening with cytological examination requires vast resources and highly skilled technical manpower. Such resources and skilled manpower are not available in India. Hence, we need to design cervical cancer screening programs using alternative strategies, like visual-based techniques, that are low cost but effective and compatible with the prevailing socioeconomic realities. Vaccines against HPV infections are now available, but are very expensive. The currently available vaccines do not protect against all cancer-causing types of HPV, so routine screening is still necessary.

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