PUB: 37/2011

143 Cervical cancer: Current concepts in etiopathogenesis, screening, diagnosis and preventive measures.

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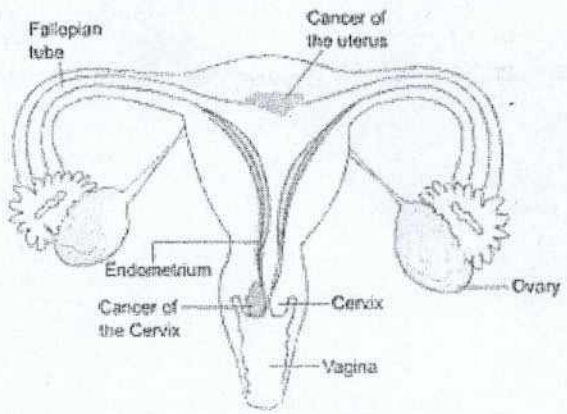
Introduction.

Cervix is a part of female reproductive system which connects at the upper part with uterus and lower part with vagina. The upper part of cervix which is close to uterus is endocervix normally lined by simple columnar cells and the lower part of cervix close to vagina is ectocervix normally lined by stratified squamous epithelium (figure 1). [1] The junction between the two is squamocolumnar junction, i.e transformation zone which is prone to develop cancer, hence sample is taken from this area for Pap test. [2]

Cancer refers to a class of diseases in which a cell or a group of cells divide and replicate uncontrollably, intrude into adjacent cells and tissues (invasion) and ultimately spread to other parts of the body than the location at which they arose (metastasis).

Figure 1: Shows parts of female genital tract and cervix.



History. [3]

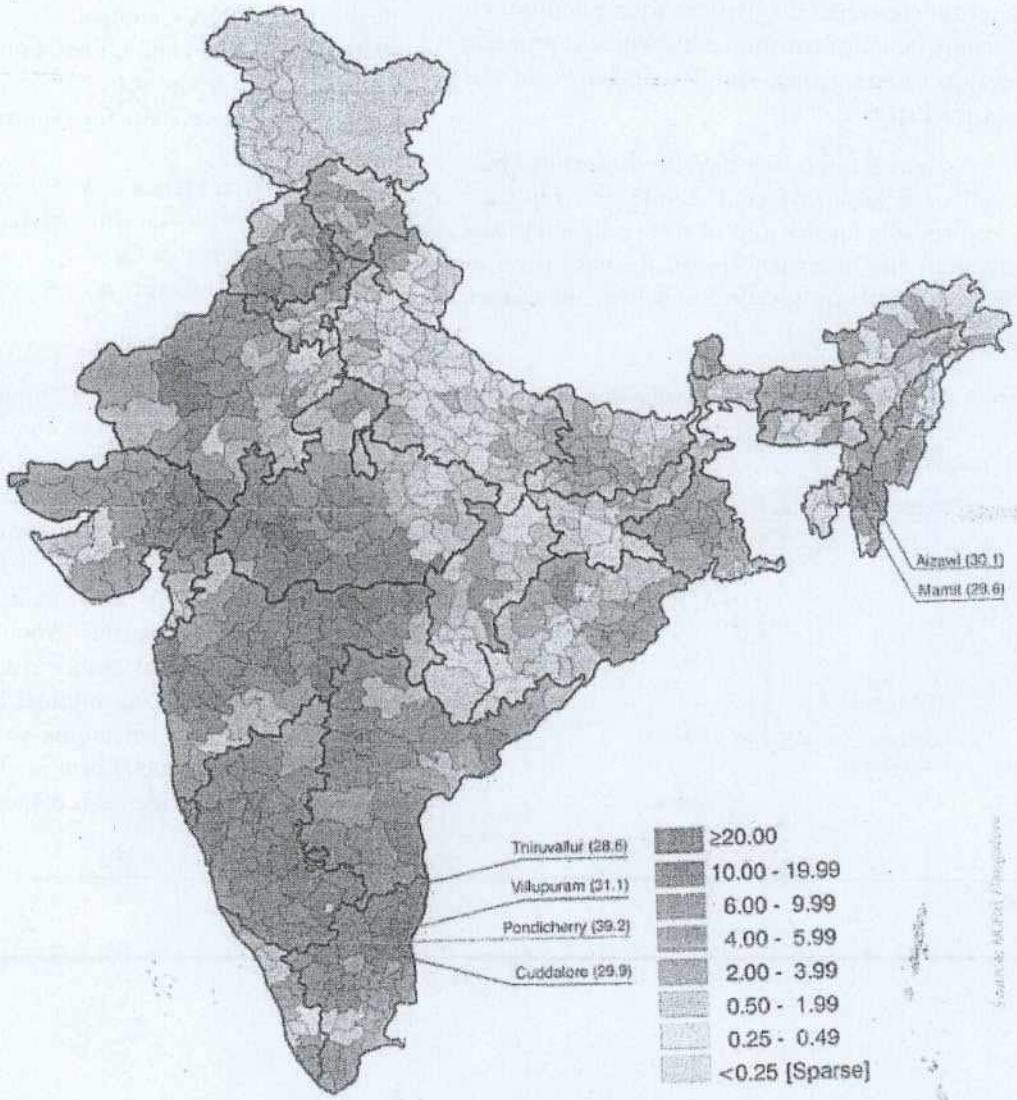
400 BC – Hippocrates: Cervical cancer incurable.
1925 – Hinselmann: Invented colposcope.
1928 – Papanicolaou: Developed Papanicolaou test.
1941 - Papanicolaou & Trout: Pap smear screening.
1946 – Ayer: Aylesbury spatula to scrape the cervix, collecting sample for Pap smear.
1949 – HPV description by electron microscope.
1963 – HPV DNA identified.
1976 – Zur Hausen and Gisam: Found HPV DNA in cervical cancer and warts.
1988 – Bethesda system for reporting Pap results developed.
1991 – Bethesda system was revised.
2000 – First HPV vaccine, FDA approved and marketed by Merck & Co.
2001 – Bethesda system was revised again.

Incidence:

Worldwide cervical cancer is 2nd most common in females. In US it is 8th most common cancer in females. 4,5 In past 50 years in US Pap test has reduced the deaths related to cervical cancer by three-quarters. In UK it is 12th most common cancer in females accounting for 2% of all female cancers and 2nd most common cancer in women less than 35 years after breast cancer. About 1000 women die per year of cervical cancer in UK. Screening programmes in developed countries has reduced the incidence of invasive carcinoma by 50% or more. [3] Internationally 500000 new cases are diagnosed each year. Annual incidence is 6.8 cases per 100000

women in South America and in Africa it is 52.8. Higher incidence is seen in low and middle income countries (LMIC) and in low socioeconomic groups. About 80% of global cervical cancers are in LMICs / developing countries and continues to rise. [1,2,3,4] 80% of new cases diagnosed in developing countries like India accounts approximately 1/4th of world cases each year. [2]

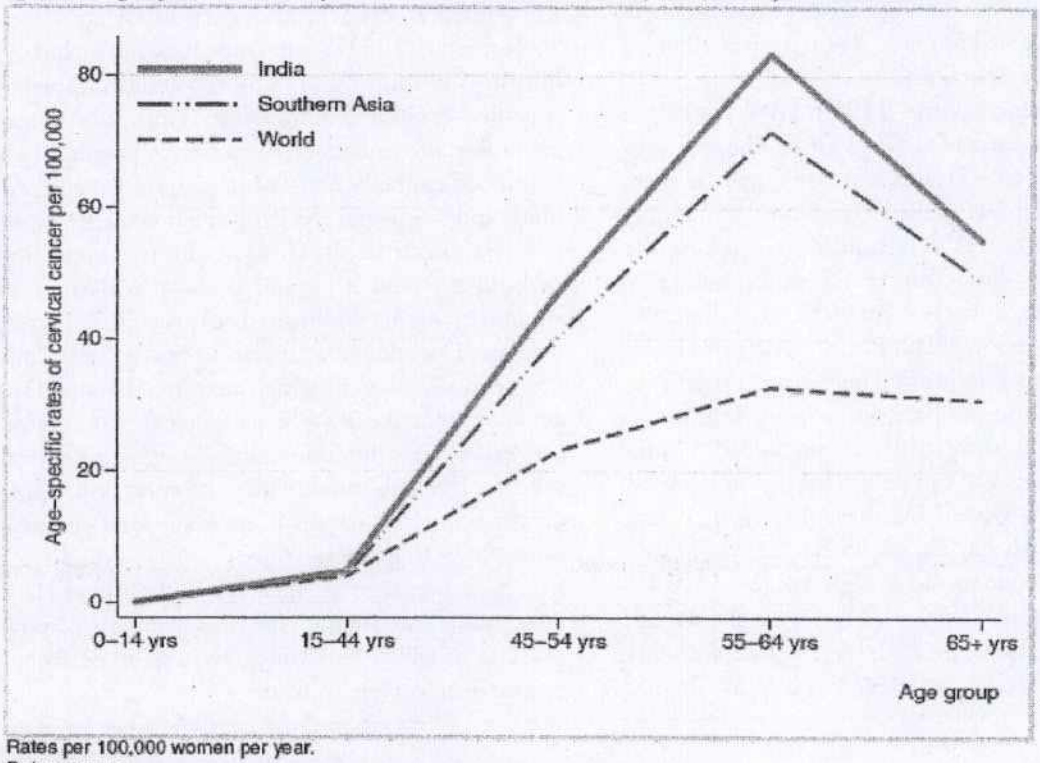
Figure 2: District wise comparison of age-adjusted incidence of cervical cancer (per 100,000 population)



Source: National Cancer Registry Programme and World Health Organisation, Atlas of Cancer in India.

Cervical cancer in India has become the most important cancer in last two decades. According to cervical cancer burden in India in 2004, cervical cancer forms 3rd largest cause of cancer mortality after cancer of mouth, oropharynx and oesophagus, had age standardised incidence rate of 30.7 per 1000000 women in 2002 and accounted for 26% of all cancer deaths in women (figure 2 &3). As of 2002, cervical cancer in India accounted for approximately 26% of global prevalence and 83% of total prevalence in South Central Asia. [1] New cervical cancer during 2007 in India was 90.70%. 70% of Indian population resides in rural areas where cervical cancer still constitutes as number one cancer. However urban population based cancer registry (PBCR) shows a statistically significant decrease in incidence rates despite the absence of any organised screening programme. Carcinoma cervix accounted for 16% of all cancer in women in urban registries in 2005. However it constitutes 37% of all cancers in women in Barshi. Barshi and Chennai have always recorded the highest incidence if cervical cancer. According to hospital based cancer registries (HBCR), Bangalore and Chennai are leading site for cervical cancer, 2nd leading is Mumbai and Thiruvanthapuram and 3rd is Dibragarh. The incidence is more in north-eastern part of Tamil Nadu and Pondicherry which also has highest prevalence of HIV. [1,5] In India, the low socioeconomic status , lack of access to screening & health services, lack of awareness of the risk factors, HPV infection, pre-cancerous lesions go un-noticed, present with full blown cancer, less affordability & follow-up, treatment is much worse for women in low socioeconomic status results in increased morbidity and mortality in disadvantaged sector of Indian society due to cervical cancer. [1]

Figure 3: Age specific mortality from cervical cancer in India, South Asia, and the World



Rates per 100,000 women per year.
Data sources:
IARC, Globocan 2002 | WHO GBD 2004 (for WHO region estimates only)

ource: WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer (a). Human apillomavirus and Related Cancers in India. Summary Report 2009. Available at http://www.who.int/hpvcentre/en/

Etiopathogeniesis (Risk factors).

In 1940s & 1950s smegma was considered as the cause, 1960s & 1970s as Herpes Simplex and in 1980s as HPV was identified in cervical cancer tissue, In Mid of 1980s HPV vaccine was developed in parallel by various researchers globally. [3]

All the causes of cervical cancer are not known. The common risk factors are:

Age: Cervical cancer may be diagnosed in any women of reproductive age. However women in middle age are at high risk. Females less than 15 years are rarely affected. [2,4]

Human Papilloma virus (HPV): HPV is a closed circular doubled stranded DNA virus. These viruses called as papilloma viruses because some of them cause a type of growth called a papilloma, commonly known as warts. HPV is a necessary factor for development of almost all cervical cancer and HPV DNA may be detected in 90% of squamous intraepithelial lesion (SIL) and in invasive cervical cancer with consistently lower percentage in controls. SIL is detected in younger women, while invasive cancer is seen in women 10-15 years older. [3,4] More than 150 types of HPV are reported (some reported more than 200 types). Of these 15 are high risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, & 82), 3 are probable high risk (26, 53 & 66) and 12 are low risk types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108) HPV 16 & 18 accounts for 70% of cervical cancer and HPV 31, 33, 45, 52 & 58 accounts for another 20% (figure 4). [3] HPV 6 & 11 are associated with low grade SIL lesions but are never found in invasive cancer. The viral genome encodes 6 early open reading frame proteins i.e E1, E2, E3, E4, E6, E7 which are functional as regulatory proteins and 2 late open reading frame proteins i.e, L1, L2, which make up the viral capsid. The major difference between the low and high risk types is that after infection, low risk HPVs are maintained as extrachromosomal DNA episomes, while the high risk HPV genome is found integrated into host cellular DNA. The recombination event often leaves E6 and E7 directly coupled to the viral promoter and enhancer sequences, allowing their continued expression after integration. Because E7 binds and inactivates the Rb protein while E6 binds p53 and directs its degradation, the functional loss of both p53 and Rb genes leads to resistance to apoptosis, causing uncensored cell growth after DNA damage. This ultimately results in malignancy. Thus P53 gene and Rb gene which are tumour suppressor genes are turned off in the pathogenesis of cervical cancer by HPV infection. In addition to cervical cancer, HPV also causes cancer of vulva and vagina in women, penile cancer in men and oral and anal cancer in both genders. [4]

In US each year more than 6.2 million new HPV infections is noted in both men and women according to CDC, of which 10% will go to develop persistent dysplasia or cervical cancer.

Hence HPV is known as the "common cold" of sexually transmitted infection worldwide affecting approximately 80% of all sexually active people with or without symptoms. [3] Global prevalence of HPV infection in general in female population is estimated to be 11.4% and it varies in different region as: 2% in South Vietnam, 43% in Zimbabwe, 7.9% in India, which is lower than world average despite number of invasive cervical cancer is highest in South Asian region. At least 50% of sexually active men and women get HPV at some point in their lives which usually resolve spontaneously within months to a few years, of which 3-10% of women develop persistent infection with high risk of going into cervical cancer. HPV DNA is much higher in individuals with invasive cancer than in those with normal cytology. HPV 16 /18 prevalence in invasive cervical cancer varies, 65% in South/Central America, 76% in North America and 82.5 % in India. 3 HPV is transmitted by skin to skin contact of infected area. [3,4] The medically accepted paradigm, officially endorsed by the American Cancer Society, other organisations and epidemiologist in 20th century is that a patient must have infected with HPV to develop cervical cancer and hence have viewed it as a sexually transmitted disease. However many disputes against this statement that HPV is only causative agent and cancer is not STD as most infected with high risk HPV will not develop cervical cancer. [1,3,5]

Human immunodeficiency virus (HIV): The role of HIV infection in pathogenesis of cervical cancer is not fully understood. However higher prevalence of HPV infection was seen in seropositive women than in seronegative women and HPV prevalence was directly proportional to the severity of immunosuppression as measured by CD4 counts. Immune system is important in destroying cancer cells and slowing their growth and spread. Impaired lymphocyte function has been postulated to enhance latent or subclinical HPV activity, resulting in a higher rate of persistent infection. Thus with HIV, cervical pre-cancer might develop into an invasive cancer faster than it would normally. Whether HIV has a synergistic effect with HPV infection either by molecular interaction or through an indirect immunologic effect remains unclear. [4]

Smoking: Risk is twice compared to non-smokers. The risk is higher when associated with HPV infection. [2] Smoking makes the immune system less effective in fighting HPV infection and researchers have found out tobacco-by-products in cervical mucus which damage the DNA of cervical cells and contribute to development of cervical cancer. [4]

Race: Certain ethnic groups like African-Americans, Hispanics and Native Americans are genetically predisposed than white women. [2,4]

Promiscuity: Women having multiple sex partners or a male partner who is promiscuous has increased risk if cervical cancer. Second wives of men whose first wives had died of cervical cancer have increased risk. However nuns and Jewish women have decreased risk. [2,3] Having more than 3 sexual partners during women's lifetime will increase the risk of cervical cancer by 94% compared to women with one lifetime parters. [1,4]

Other sexually transmitted disease (STD): Chlamydia, Herpes, Gonorrhoea and syphilis increase the risk making more susceptible for HPV infection. [2,3]

Sexual activity: Early age at first intercourse / first pregnancy, early use of oral contraceptives, multiple sex partners, multiple pregnancy, etc has increased risk of cancer. Women younger than 17 years of age with their first full term pregnancy are 2 times more likely to get cervical cancer than women who get pregnant after 25 years of age. High parity increases the risk, as more than 3 pregnancy increases the risk by 51% compared to women with no pregnancy due to unprotected intercourse, hormonal changes in pregnancy which makes women more susceptible to HPV infection and weaker immune system of pregnant female allowing HPV infection and cancer growth. Unprotected sex with uncircumcised male has increased risk due to increase chance of HPV infection. [1,3,4]

Hormones / Oral contraceptives: Exposure to hormonal drug diethylstilbestrol has high risk in daughters of mothers who has taken it and the risk is greatest when mother took the drug during their first 16 weeks of pregnancy. The average age of women when they are diagnosed with DES-related clear cell adenocarcinoma is 19 years. However use of DES during pregnancy was stopped by the FDA in 1971. DES daughters may also be at increased

risk of developing squamous cell cancer and pre-cancer of the cervix linked to HPV. [4] Long term use of oral contraceptives increases the risk. However the risk decreases as the women stops using it. [2,3] The risk of cervical cancer was doubled in women who took birth control pills longer than 5 years, but the risk returned to normal 10 years after they were stopped. [4]

Family history: Family history of cervical cancer has high risk. Genetic risk has been reported with HLA B27. [3] Women has 2 to 3 times higher risk of suffering from cervical cancer in whom her mother or sister had cervical cancer compared to one in whom no one in the family had it. There are instances of some familial tendency which causes inherited condition that makes some women less able to fight off HPV infection than others. [4]

Immunity: Reduced immunity has increase susceptibility of cervical cancer as evidenced in HIV infection and use of certain drugs like anticancer drugs or immunosuppressive drugs, autoimmune disease or in organ transplant patients in whom the susceptibity of HPV infection increases. [2,4]

Diet: Women with diets low in fruits and vegetables may be at increased risk for cervical cancer. Over weight women are more likely to develop adenocarcinoma of the cervix. [4]

Following the exposure to various risk factors, the cervical lining epithelium undergoes dysplastic changes which vary in severity. The naming of premalignant dysplastic changes has changed over 20th century. According to WHO classification, it is referred as Mild, moderate, severe/carcinoma in situ (CIS) and invasive. CIN (cervical intraepithelial neoplasia) system has classified according to spectrum of abnormality to standardised treatment as, CIN I for mild, CIN II for moderate and CIN III for severe. However Bethesda system has classified in Pap smears as, LSIL (Low grade squamous intraepithelial lesion) for CIN I, HSIL (high grade squamous intraepithelial lesion) for CIN II/III. However the cytological report of Pap smear need not match with histopathologic findings. [1,2,3] Mild dysplasia usually regress spontaneously without treatment and small percentage of it progress to more severe forms over 10 years. Moderate and severe dysplasias are at high risk of developing into invasive cancer over several years. [1]

Clinical features:

Patient may remain asymptomatic without obvious symptoms until advanced stage. Cervical cancer is seen in women of all ages, however it is more common in 35-55 years age and peak age varies with population: 30-40 years in UK, 35-39 in Sweden, 45-54 years in India as in rest of South Asia. More than 40% are seen in urban population and around 65% cases are seen in rural population according to cancer registry in Barshi. The patient usually present with abnormal vaginal bleeding as menorrhagia, metrorrhagia, bleeding after sexual intercourse, douching or pelvic examination and post-menopausal bleeding. Other presentations are, vaginal mass, vaginal discharge sometimes foul smelling, Pain during sexual intercourse (dyspareunia), pelvic pain, low back pain, dysuria, etc. In late stage with local spread the patient presents with constipation, hematuria, abnormal opening of cervix and obstruction of ureter. [1,2,3,4]

Screening:

Papanicolaou test / pap smear: Pap test is a screening test and not a diagnostic test. An abnormal Pap test has to be confirmed by other tests. [4] According to American cancer society (ACS), Pap smear screening is recommended to start at 3 years / more after first sex or can be started at the age of 21 to 25 years. The frequency varies from once a year to once in five years in absence of abnormal smear. According to ACS conventional test should be done every year and if liquid based Pap test is used, testing should be done every 2 years. At the age of 30 years, women with 3 normal Pap test results in a row may be tested every 2-3 years either by conventional or liquid based Pap test or every 3 years along with HPV DNA. However women should continue routine screening if exposed to DES before birth, history of treated for pre-cancer lesion of cervix or immunocompromised. Women 70 years or older who have had 3 or more normal Pap test in a row with no abnormal Pap tests in past 10 years may stop screening. However women with

history of cervical cancer, DES exposure before birth, HIV infection or immunocompromised may continue having routine screening as long as they are in good health. Women who had undergone total hysterectomy can stop cervical screening unless hysterectomy was done for cervical pre-cancer or cancer lesion. However in case of supra-cervical hysterectomy women has to continue according to routine cervical screening. Women who are not active sexually but were in past should continue to screen routinely. Following are the instructions to be followed before taking Pap smear; [4]

1. Do not schedule the appointment of Pap test during menstrual period.
2. Do not douche for 48 hours before the test.
3. Do not have sexual intercourse for 48 hours before the test.
4. Do not use tampons, birth control foams, jellies, other vaginal creams or vaginal medicines 48 hours before the test.

The Pap test has to be done at the start of pelvic exam after speculum is placed. The Pap smear is taken with Ayer's spatula and endocervical brush by gentle scraping or brushing. Smear is made on the glass slide in conventional cytology which is then stained with Pap stain. The advantage of this method is it works quite well and inexpensive. However the disadvantages are improper smear by which there is piling up of cells, epithelial cells may be masked by white blood cells, increased mucus, yeast cells or bacteria which cause less accurate results by which the test has to be repeated. In liquid based cytology method, the cervical cells sample are put into special preservative liquid which later is spread on the glass slide and examined. The advantage of this method is the liquid removes mucus, bacteria, yeast and pus cells, cells spread more evenly, prevents drying and distortion of cells, test need not repeated as frequently as conventional method and the supernatant can be used for HPV DNA test. The disadvantages are it is more expensive. However the results are almost same as conventional method. [1,2,3,4] The liquid based cytology has been incorporated within the UK national screening programme to reduce the number of inadequate smears from around 9% to around 1% which reduces the need to recall women for a further smear.

Automated technologies in Pap test proved less useful and more expensive. Here computerised instrument is used to detect abnormal cells in the slides which have been approved by FDA to read Pap test before cytotechnologists and cytologist see the slides. [1,4]

The results of Pap test according to The Bethesda System (2001) are 1. Negative for intraepithelial lesion or malignancy, 2. Epithelial cell abnormality and 3. Other malignant neoplasm. Smears which are negative for intraepithelial lesion or malignancy means the patient has reactive or inflammatory changes which may be due to bacteria or parasite and unrelated to cervical pre-cancer or cancer. The epithelial cell abnormalities indicate pre-cancer or cancer lesions which are divided into atypical squamous cells (ASC), squamous intraepithelial lesion (SIL) and squamous cell carcinoma. ASC are divided into atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells – HSIL cannot be ruled out (ASC-H). Squamous epithelial cell lesions are divided as Low grade squamous intraepithelial lesion (LSIL) and high grade squmous intraepithelial lesion (HSIL). In case of ASC, it is not certain whether the lesion is due to infection, irritation or pre-cancerous lesion and many are not pre-cancer lesion. Women 20 years old or younger with Pap test result of ASC-US are usually observed without treatment and women more than 20 years of age experts recommend either a colposcopy, a repeat Pap test in 6 months or HPV DNA testing. If a woman is HPV positive, colposcopy will be done. For ASC-H, LSIL and HSIL colposcopy and biopsy is recommended. Many cases of SIL are HPV positive and HPV test is usually not done. SIL cases once detected are treated and thus prevented the lesions going into invasive malignancy. In case of glandular cells if cells are atypical, then it is called atypical glandular cells (AGC) and with features of malignancy it is called as adenocarcinoma. [4]

Pap test has drastically reduced the incidence and mortality of cervical cancer in developed countries. Pap smear detects early precancerous changes and thus treatment of high grade changes prevents the development of cancer. Regular Pap screening reduces the incidence of cervical cancer by up to

80%. Abnormal Pap smear indicates cervical intraepithelial lesion (CIN) which has to be followed up / take preventive treatment. Cervical screening is saving 5000 lives each year in UK by preventing cervical cancer. In US the incidence and mortality has decreased to half than the rest of the world and cervical cancer deaths decreased approximately by 74% in last 50 years because of pap smear screening. In Australia cervical cancer has dropped on an average by 4.5% each year since organised screening began in 1991. [1,3] More than 80% of cervical cancer is seen in developing countries, but only 5% of women are screened due to lack of adequate financial and human resources at population level. In addition socioeconomic barriers to screening and stigma has decreased women undergoing screening. Only 2.6% of Indian female population had ever been screened for cervical cancer in past three years. ACCP (alliance for cervical cancer prevention) found that the optimal age for screening in low resource settings is between 30-40 years as that has a greatest public health impact. However it is not evidence based and not likely to have enough impact at population level. [1]

Cytochemistry: To overcome false positive and false negative results of pap smear and to improve the detection of dysplastic cells various adjunctive tests have been developed in which cytochemistry can be used in cervical smears to localize certain enzymes in cervical epithelial cells which indicate the degree of differentiation. Some of which are considered are acid phosphatase (ACP), non-specific esterase (NSE), glucuronidase and phosphamidate. CAP-PAP (Cervical acid phosphatase – pap) is already in use in various centres. NSE reaction is less variable and shows more uniform activity than ACP. The differentiated cells have negative or scanty reaction whereas undifferentiated cells has moderate to heavy reaction. Hence the basal cells react heavily and a progressive lighter reaction will be present in parabasal, intermediate and superficial cells. Superficial / cornified cells will be almost negative. Undifferentiated atypical cancer cells will have stronger reaction than normal basal cells. Differentiated cancer cells will have slight to moderate activity. Endocervical cells and histiocytes give strong positivity. Whereas leukocytes gives negative reaction.[6,7]

Immunocytochemistry (ICC): It is an adjuvant test for Pap test which can also be utilized in detecting dysplastic cells in cervical smears. Some of the markers used are P16INK4A, P14ARF, P53, Ki-67, MDM2, etc. The cyclin dependent kinase (CDKN2) gene encodes two structurally different proteins, a cyclic – dependent kinase inhibitor, p16 which regulates retinoblastoma protein dependent G1 arrest and a cell cycle inhibitor P14ARF which blocks MDM2 induced p53 degradation resulting in an increase in p53 levels that leads to cell cycle arrest (figure 5). Hence over expression of p16 is demonstrated in cervical neoplasia because of functional inactivation of pRb by HPV E7 protein and p14 over expression is attributable to a negative feedback result in functional inactivation of the p53 protein by E6 HPV oncoprotein. The E7 and E6 oncoproteins of HPV plays an important role in cervical carcinogenesis. The inactivation of the pRb and p53 pathways in cell cycle regulatory cascade occurs during the early immortalization step by HPV in cervical carcinogenesis and not during late malignant transformation. The lack of expression of p16 and p14 in normal cells is due to low levels of the protein against the distinct intense nuclear staining in tumour cells. Moreover intense and high immunoreactivity of p14 in basal and parabasal cells in addition to superficial cells suggest a more advanced lesion. P14 expression is also found among cervical cancer cells negative for HPV. P16 expression is mainly nuclear in CINI cases and both nuclear and cytoplasmic in CIN2, CIN3, cGIN and invasive cases. All cases positive for HPV express p16 protein although not all cases found positive for p16 were HPV positive and p16 staining intensity was lower in cases negative for HPV or those containing low risk HPV type. No non-specific staining of normal squamous cells was seen in normal smears with p16 and p14. Many studies have showed increased p16 and p14 expression which are associated with disease progression and time taken for progression were shorter among those stained positive for p16 and p14.[8,9,10,11]

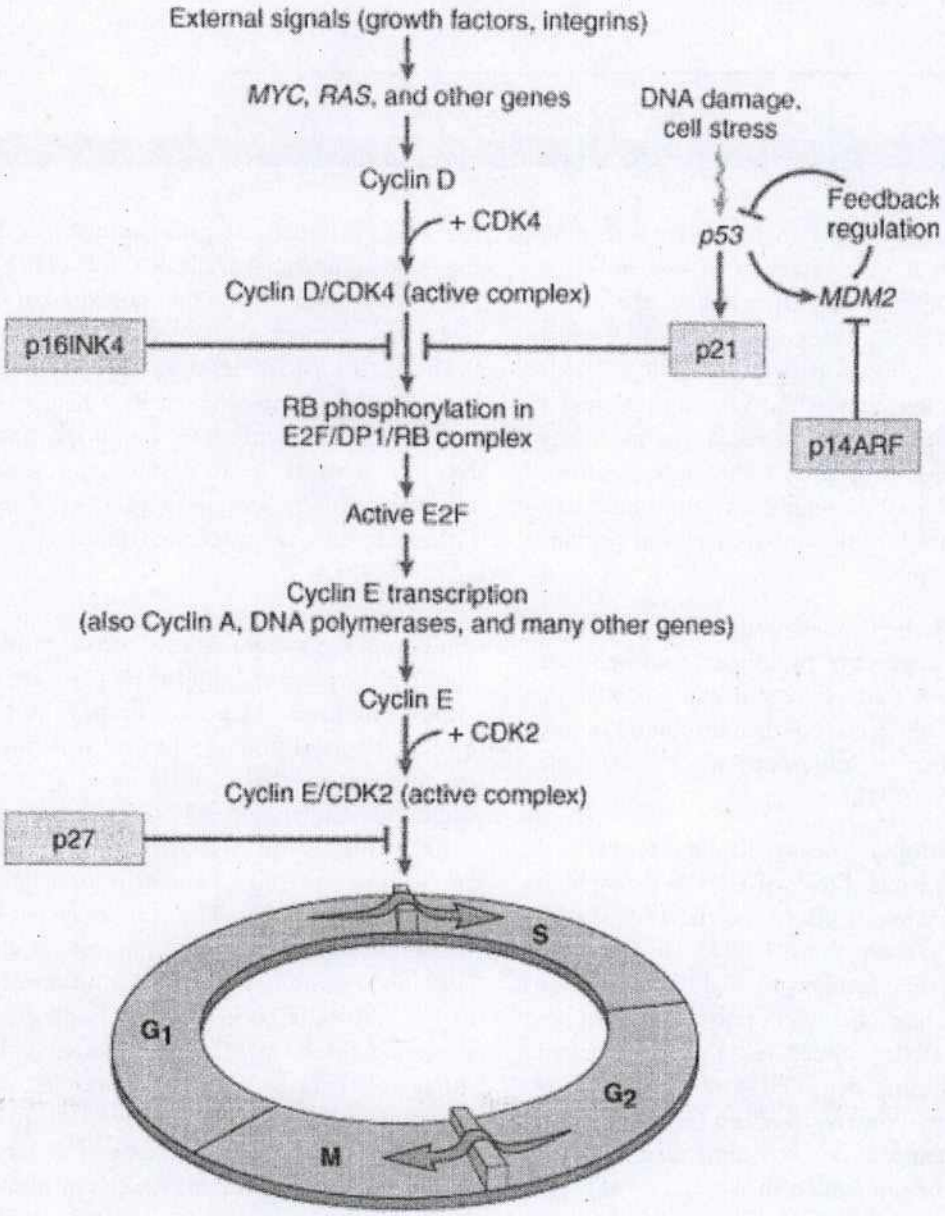


Figure 5: Shows role of p14, p16, Rb protein and p53 protein in cell cycle.

Visual inspection: This is an alternative screening methods which is cost effective in low resource settings. The test is based on naked eye visual inspection with 3-5% acetic acid (VIA) and visual inspection post-application of Lugol's iodine (VILI) used in LMICs. Sensitivity of VIA tends to be similar to that of cytological screening test and its specificity tends to be lower. Advantage is, it is less expensive than cytology based screening, easy to administer, train appropriate health care workers and provide real time results. [1]

Colposcopy: If the Pap test is abnormal or clinical symptoms are suggestive of cancer, colposcopy is done, an abnormal area is seen in the cervix and a biopsy is taken which can confirm pre-cancer, a true cancer or neither. [4] Colposcopy test can by done along with VIA or VILI. [1]

HPV DNA testing: is a newer technique for cervical cancer triage in which DNA of HPV is detected in pre-cancer or cancer cells of cervix. HPV DNA test is used in two situations, 1. FDA has approved HPV DNA test in women over 30 years of age along with Pap test (also ACS), however it does not replace Pap test. In women less than 30 years of age it is not recommended as HPV infection in young females go away spontaneously and HPV DNA test is not significant and not recommended. 2. HPV DNA test is recommended in women of any age group with abnormal Pap test (ASC-US) to find out the need for repeat Pap test or colposcopy. [4] HPV DNA is expensive, cost effective in long run, detects the HPV pressure in the cervix, higher sensitivity than cytological screening but less specific than Pap test, detect CIN lesions at an earlier stage than cytology, longer intervals between screening, decrease cervical cancer incidence and averts more deaths. [1] Its role in routine screening is still evolving. Since more than 99% of invasive cervical cancer worldwide contains HPV, some researchers recommend HPV test with routine cervical screening. However HPV testing would cause undue alarm to carriers and unnecessary increases the cost of screening. Hence efforts to develop low cost HPV test so that it can included in primary screening especially in older women in less developed countries [3] HPV DNA testing is done by various technique like PCR, RT-PCR, Hybrid capture 1 & 2. [12] In males no commercial available test for HPV though HPV grows preferably in the epithelium of the glans penis and cleaning of this area may be preventive. [3] There is insufficient information and test regarding HPV burden in men which may help to prevent further spread of infection within the population. Hence it is necessary to develop appropriate, cost effective, efficient and inexpensive HPV test. [1]
Others: Speculoscopy, cervicography. [2,3]

Diagnosis:

Following the screening tests, the diagnosis will be confirmed by cervical biopsy. Biopsies are taken by various methods as punch biopsy, colposcopic biopsy, conisation/cone biopsy (diagnostic and therapeutic, the base of the cone is formed by ectocervix and the apex is from the endocervical canal, containing transformation zone) and endocervical curettage/scraping (especially including transformation zone). The cone biopsy is done by LEEP (loop electrical excision procedure, also called large loop excision of transformation zone, LLETZ) or by cold knife cone biopsy. The biopsy will be subjected for histopathological examination. The diagnosis will be pre-cancer lesion called as CIN of different grades as I, II and III/in-situ malignancy or cancer. 5 The commonest type of cervical cancer is squmaous cell carcinoma which constitutes about 80-90% of cervical cancer, arises usually from transitional zone (squamocolunar junction) and ectocervix. The next common is adenocarcinoma which constitutes about 15% of cervical cancer arising from endocervical glandular cells. The incidence of adenocarcinoma is increasing in recent decades. Other less common histpoathological types are adenosquamous carcinoma, small cell carcinoma and neuroendocrine carcinoma. Non-epithelial cancers which can be seen in cervix are melanoma and lymphoma. [1,2,3] Once the diagnosis is confirmed, the patient is subjected to cystoscopy, proctoscopy, imaging studies like chest X-ray, CT scan, MRI, PET scan and intravenous urography to know the extent of spread of cancer locally and distant metastasis for proper staging. Following staging the patient is subjected to treatment either by surgery,

chemotherapy or radiotherapy depending on the stage and histopathological type. [2,4]

Prevention:

Avoid HPV infection: HPV infection can be avoided by altering the sexual behaviour as described under risk of sexual activity. Men who are circumscribed have a lower chance of becoming and staying infected with HPV. The reason is 1. After circumcision, the skin on the glans of penis goes through changes that make it more resistant to HPV infection. 2. The surface of the foreskin is more easily infected by HPV. However circumcision does not give complete protection and HPV infection can still occur and pass on to their partners. [4]

HPV Vaccine: HPV infection is an important factor in the pathogenesis of cervical cancer. However HPV infection is usually asymptomatic, difficult to recognise and detect. Hence HPV vaccine has emerged as one of the preventive measure. The vaccine attempt to produce an immune reaction to parts of the virus (E6 & E7 protein). It is effective against the infection of two high risk strains of HPV which responsible for about 70% of cervical cancer. Hence women should have regular Pap smear test screening even after vaccination. The two vaccines which are marketed are Gardasil and Cervarix. Gardasil is a vaccine which is marketed by Merck company, effective against HPV strains 6,11,16 &18 and is 98% effective. 6 and 11 is responsible for 90% of genital warts. Cervarix is marketed by Johnson Company and gives protection against HPV strain 16 & 18 and is 92% effective. The vaccines are licensed in US, Canada, Australia and European countries. Gardasil has been approved in 2006 and Cervarix in 2009 in US by the FDA. HPV vaccine prevent against infection and hence occurrence of intraepithelial lesions and hence malignancy not only in cervix but also in other cancers associated with HPV. Gardasil has been approved to prevent anal, vaginal and vulvar cancer and pre-cancers and prevent 90% of anal and genital warts. HPV vaccine is given to females between 9-26 years before the first infection / sex encounter as vaccine prevent HPV infection and will not protect from an infection which is already there. Gardasil is approved for use in both sexes aged 9-26 years old while Cervarix for girls between 10-25 years of age. In US vaccine is available for females between 11-12 years and in UK national vaccination programme Cervarix is given between 12-13 years. The ACS recommends that "catch up" vaccine should be given to females up to the age of 18 years. The "catch up" vaccine has not enough proof that it would be beneficial. Both vaccines are given as 3 doses over 6 months. The side effects are mild with short-term redness, swelling and soreness at sit of injection. Women with history of allergy to latex should not take Cervarix vaccine and those with allergy to yeast should not receive Gardasil. It is effective for 4-6 years and probably longer. Duration of effectiveness and booster dose is not known. HPV vaccine in India is a financial obstacle (Rs.12,000 for 3 doses), is available at personal use and not implemented at population level. Gardasil licensed for use in males in USA. However it is not introduced to boys in general population as that hasn't been established as a cost effective strategy. Vaccine in males prevents genital warts, anal cancer and prevents transmission of HPV infection in females or other males. [1,3,4]

Condoms: gives some protection (not 100%) against HPV infection transmission, genital warts, precursors of cervical cancer and other sexually transmitted diseases (STD) as HIV & Chlamydia which are associated with greater risks of cervical cancer. Exposure to semen appears to increase risk of precursor changes as prostaglandins in semen may fuel the growth of cervical and uterine tumours and use of condoms helps to regress these changes, clear HPV and prevent other STDs. [1,3] Condoms when used correctly and are used every time sex occurs can lower the HPV infection rate in women by about 70%. One reason why Condoms cannot give complete protection is that the condoms don't cover every possible HPV infected area of the body as skin of genital or anal area. [4]

Nutrition: Increased level of fresh vegetables and fruits consumption is associated with 54% increased HPV persistence. Decreased vitamin A (retinol) increases chances of cervical dysplasia independently of HPV infection. Intake of vitamin C in upper quartile had less risk of type specific persistent HPV infection. HPV clearance time has significantly

shorter among women with the higher serum levels of tocopherols. A statistically significant lower level of alfa-tocopherol was observed in blood serum of HPV positive patients with cervical intraepithelial neoplasia. The risk of dysplasia was four times higher for an alfa-tocopherol level less than 7.85 mmol/L. Women with higher folate status were significantly less likely to be repeatedly HPV test positive and more likely to be HPV test negative. Lower levels of antioxidants along with lower levels of folic acid increases the risk of CIN development. Improving folate status in HPV infected females has beneficial impact in the prevention of cervical cancer. Increasing levels of carotenoids has significantly higher likelihood of clearing an oncogenic HPV infection. [1]

Avoid smoking: which reduce the risk of cervical cancer. [4]

Staging: [4]

A staging system is a way for members of the cancer care team to summarize the extent of a cancer's spread. The 2 systems used for staging most types of cervical cancer, the *FIGO* (International Federation of Gynecology and Obstetrics) system and the AJCC (American Joint Committee on Cancer) TNM staging system, are very similar. Both systems classify cervical cancer on the basis of 3 factors: the extent of the tumor (T), whether the cancer has spread to lymph nodes (N) and whether it has spread to distant sites (M). The system described below is the most recent AJCC system, which went into effect January 2010.

Tumor extent (T)

Tis: The cancer cells are only found on the surface of the cervix (in the layer of cells lining the cervix), without growing into deeper tissues. (Tis is not included in the FIGO system)

T1: The cancer cells have grown from the surface layer of the cervix into deeper tissues of the cervix. The cancer may also be growing into the body of the uterus, but it has not grown outside of the uterus.

T1a: There is a very small amount of cancer, and it can be seen only under a microscope.

- T1a1: The area of cancer is less than 3 mm (about 1/8-inch) deep and less than 7 mm (about 1/4-inch) wide.
- T1a2: The area of cancer invasion is between 3 mm and 5 mm (about 1/5-inch) deep and less than 7 mm (about 1/4-inch) wide.

T1b: This stage includes stage I cancers that can be seen without a microscope. This stage also includes cancers that can only be seen with a microscope if they have spread deeper than 5 mm (about 1/5 inch) into connective tissue of the cervix or are wider than 7 mm.

- T1b1: The cancer can be seen but it is not larger than 4 cm (about 1 3/5 inches).
- T1b2: The cancer can be seen and is larger than 4 cm.

T2: In this stage, the cancer has grown beyond the cervix and uterus, but hasn't spread to the walls of the pelvis or the lower part of the vagina. The cancer may have grown into the upper part of the vagina.

T2a: The cancer has not spread into the tissues next to the cervix (called the parametria).

- T2a1: The cancer can be seen but it is not larger than 4 cm (about 1 3/5 inches).
- T2a2: The cancer can be seen and is larger than 4 cm.

T2b: The cancer has spread into the tissues next to the cervix (the parametria)

T3: The cancer has spread to the lower part of the vagina or the walls of the pelvis. The cancer may be blocking the ureters (tubes that carry urine from the kidneys to the bladder).

T3a: The cancer has spread to the lower third of the vagina but not to the walls of the pelvis.

T3b: The cancer has grown into the walls of the pelvis and/or is blocking one or both ureters (this is called hydronephrosis).

T4: The cancer has spread to the bladder or rectum or it is growing out of the pelvis

Lymph node spread (N)

NX: The nearby lymph nodes cannot be assessed

N0: No spread to nearby lymph nodes

N1: The cancer has spread to nearby lymph nodes

Distant spread (M)

M0: The cancer has not spread to distant lymph nodes, organs, or tissues

M1: The cancer has spread to distant organs (such as the lungs or liver), to lymph nodes in the chest or neck, and/or to the peritoneum (the tissue coating the inside of the abdomen).

Stage grouping

Information about the tumor, lymph nodes, and any cancer spread is then combined to assign the stage of disease. This process is called *stage grouping*. The stages are described using the number 0 and Roman numerals from I to IV. Some stages are divided into sub-stages indicated by letters and numbers.

Stage 0 (Tis, N0, M0): The cancer cells are only in the cells on the surface of the cervix (the layer of cells lining the cervix), without growing into (invading) deeper tissues of the cervix. This stage is also called carcinoma in situ (CIS) or cervical intraepithelial neoplasia (CIN) grade III (CIN III). This stage is not included in the FIGO system.

Stage I (T1, N0, M0): In this stage the cancer has grown into (invaded) the cervix, but it is not growing outside the uterus. The cancer has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage IA (T1a, N0, M0): This is the earliest form of stage I. There is a very small amount of cancer, and it can be seen only under a microscope. The cancer has not spread to nearby lymph nodes (N0) or distant sites (M0).

- Stage IA1 (T1a1, N0, M0): The cancer is less than 3 mm (about 1/8-inch) deep and less than 7 mm (about 1/4-inch) wide. The cancer has not spread to nearby lymph nodes (N0) or distant sites (M0).

- Stage IA2 (T1a2, N0, M0): The cancer is between 3 mm and 5 mm (about 1/5-inch) deep and less than 7 mm (about 1/4-inch) wide. The cancer has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage IB (T1b, N0, M0): This stage includes stage I cancers that can be seen without a microscope as well as cancers that can only be seen with a microscope if they have spread deeper than 5 mm (about 1/5 inch) into connective tissue of the cervix or are wider than 7 mm. These cancers have not spread to nearby lymph nodes (N0) or distant sites (M0).

- Stage IB1 (T1b1, N0, M0): The cancer can be seen but it is not larger than 4 cm (about 1 3/5 inches). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

- Stage IB2 (T1b2, N0, M0): The cancer can be seen and is larger than 4 cm. It has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage II (T2, N0, M0): In this stage, the cancer has grown beyond the cervix and uterus, but hasn't spread to the walls of the pelvis or the lower part of the vagina.

Stage IIA (T2a, N0, M0): The cancer has not spread into the tissues next to the cervix (called *the parametria*). The cancer may have grown into the upper part of the vagina. It has not spread to nearby lymph nodes (N0) or distant sites (M0).

- Stage IIA1 (T2a1, N0, M0): The cancer can be seen but it is not larger than 4 cm (about 1 3/5 inches). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

- Stage IIA2 (T2a2, N0, M0): The cancer can be seen and is larger than 4 cm. It has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage IIB (T2b, N0, M0): The cancer has spread into the tissues next to the cervix (the parametria). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage III (T3, N0, M0): The cancer has spread to the lower part of the vagina or the walls of the pelvis. The cancer may be blocking the ureters (tubes that carry urine from the kidneys to the bladder). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage IIIA (T3a, N0, M0): The cancer has spread to the lower third of the vagina but not to the walls of the pelvis. It has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage IIIB (T3b, N0, M0; OR T1-3, N1, M0): either:

- The cancer has grown into the walls of the pelvis and/or has blocked one or both ureters (a condition called *hydronephrosis*), but has not spread to lymph nodes or distant sites. OR

- The cancer has spread to lymph nodes in the pelvis (N1) but not to distant sites (M0). The tumor can be any size and may have spread to the lower part of the vagina or walls of the pelvis (T1-T3).

Stage IV: This is the most advanced stage of cervical cancer. The cancer has spread to nearby organs or other parts of the body.

Stage IVA (T4, N0, M0): The cancer has spread to the bladder or rectum, which are organs close to the cervix (T4). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

Stage IVB (any T, any N, M1): The cancer has spread to distant organs beyond the pelvic area, such as the lungs or liver.

Treatment:

Treatment is surgery in early stages and chemotherapy / radiotherapy in advanced stages. [3,4]

Prognosis: [4]

The 5-year survival rate refers to the percentage of patients who live at least 5 years after their cancer is diagnosed. The numbers below come from the National Cancer Data Base, and are based on people diagnosed between 2000 and 2002.

Stage	5-Year Survival Rate
0	93%
IA	93%
IB	80%
IIA	63%
IIB	58%
IIIA	35%
IIIB	32%
IVA	16%
IVB	15%

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