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Cervical Cancer: Human Papillomavirus and Available Screening Options

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Abstract*: Cervical cancer is the second leading cause of cancer deaths in women worldwide, with most of the deaths occurring in the developing countries. Cervical cancer can be prevented with the help of early screening and effective treatment. Human Papillomaviruses are the causative agent for the development of the cervical carcinoma. HPVs are a group of small, non-enveloped viruses that infect human epithelial cells. HPVs are accountable for 95% of the cervical cancers with type 16 and 18 causing 70 % of them. HPV 16 is the most prominent sub-type to cause cervical cancer. Risk factors for cervical cancer are mostly attributed to risky sexual behavior. Several screening options are available that can reduce incidence and mortality due to cervical cancer by detecting and treating precancerous lesions.*
Keywords*: cervical cancer, human papillomavirus, screening.*

I. Introduction

Cervical cancer is a significant health care problem worldwide,. It is third most common cancer in female with the incidence as high as four fold in the countries with low ranking of HDI[1]. It is the second leading cause of cancer deaths in women globally, with an estimated 88% of deaths occurring in the developing world. Cervical cancer causes approximately 275,000 deaths annually worldwide. By 2030, cervical cancer is expected to kill over 474,000 women per year and over 95% of these deaths are expected to be in low- and middle-income countries. Although cervical cancer is accountable for large number of deaths in female every year, it is one of those few malignancies that is preventable due to its long pre-invasive state, availability of cervical cytology screening programs and highly effective treatment of pre-invasive lesions of cervix[2].

Cervical cancer usually occurs in the transformation zone of the cervix where columnar epithelium of the endocervix meets the stratified squamous epithelium of the exocervix. The constant proliferation of the cells in this region makes the viral entry into the genome of the host cell easier[3]. The infection with HPV is initiating event in cervical dysplasia and carcinogenesis and was detected in up to 99% of women with SCC of the cervix. The development of technology to test for the presence of HPV DNA in cellular specimen in early 1980s and multidisciplinary collaboration within the field and presence of HPV in most of the cases of cervical cancer has helped in the establishment of HPV as a definite etiological factor in the development of cervical cancer[4].

There are various risk factors for cervical cancer including multiple sexual partners, sexual behavior of the male partner, younger age at first sexual intercourse (less than 16 years), cigarette smoking, race, high parity and low social-economic status etc. which increases probability of HPV infection. Poor genital hygiene and intercourse without condom are highly associated with transmission of HPV. Lack of circumcision in men and frequent douching in female increases the susceptibility to acquisition and persistence of HPV infection. Frequent douching eliminates the normal vaginal micro-flora and protective cervical mucus and increase the risk of persistent HPV infection by altering vaginal milieu[5].

Chronic immune suppression is also found to be strongly associated with persistent HPV infection. Women with compromised immune status such as transplant recipient and HIV positive are at very high risk of persistent infections with STDs as well as hr-HPV and development of cervical cancer[6]. Many of these risk factors are strongly influenced by the sexual activity parameters and exposure to STD. Previously, infection with the herpes virus was thought to be the initial etiological factor for cervical cancer; however several studies has confirmed that infection with HPV was determined to be necessary cause of cervical cancer, and herpes along with Chlamydia trachomatis as co-factors[7].

The characteristically long interval between the initiation of cervical dysplasia and the onset of malignancy in pre-invasive lesion provides ample of opportunities for screening and identifying pre-malignant or pre-invasive lesions which make cervical cancer preventable with timely and regular screening program and appropriate intervention if necessary[8].

II. Human Papillomavirus

Human Papillomaviruses (HPV) are a group of more than 100 small, non-enveloped viruses containing double stranded DNA as the genetic material that infect human epithelial cells[9]. The viral nature of papilloma virus was first seen in human warts in 1907 and in 1983 Richard Shoppe isolated it from rabbit for the first time. It was not until 1970, studies related to papillomaviruses were allowed to be carried and henceforth the association of HPV with cervical cancer was established. HPVs are about 55nm in size and there genome has three functional coding regions E, L and LCR. E gene codes early viral function, L gene codes late viral function where as LCR is a long control region which lies between E and L. They consist about 72 caspomeres.

One of the recent study conducted in USA revealed that women are more prone to the HPV infection. Prevalence of HPV in women is twice than that in men. The overall prevalence rate of HPV in women was 17.9% as compared to 8% in men and among them African-American had the highest prevalence ratio of 20-29%. HPV infection was also found to be high in people with multiple sex partners to be 20.1% in compare to 7% in people with lifetime single sexual partner[10].

Till now virologist have discovered about 100 different sub-types of HPV with oncogenic potential among which HPV sub-types 16,18,31,33,35,39,45,51,52,56,58, 66,and 69 are found to specifically affect anogenital tract. These subtypes are further divided into low risk and high risk subtypes according to their role in the development of various tumors and potential of causing malignancy. HPV sub-types under low risk category are associated with genital warts and high risk category are associated with cervical intraepithelial lesion and lower genital tract cancer. One can get infected with multiple types of HPV at the same time and persistent infection with high risk sub-types of HPV can cause intraepithelial lesion with the possibility of lower genital tract malignancy if not treated. In the case of cervical cancer, cervical Intraepithelial Neoplasia (CIN) appears prior to confirmed malignancy which results from prolonged infection with certain HPV sub-types and specific symptoms[11]. Among the sub-types affecting anogenital tract, type 6 and 11 causes most of the genital warts and are considered as low risk and type 16 and 18 as high risk. Type 16 and 18 are found to have very high potential of developing genital malignancies[12]. They are leading cause of benign growth as well as malignancy in ano-genital area including vulvar, vaginal, cervical, anal and penile cancer. Eight high risk sub-types of HPV are accountable for 95% of the cervical cancers with type 16 and 18 causing 70 % of them. HPV 16 affects approximately 20% of the adult population and is found to be the most prominent sub-type to cause cervical cancer and accounts for majority of the cases[13].

HPV 16 is non-enveloped virus with double stranded DNA. Its genome contains 7 functional coding regions: E1/E2, E4, E5, E6, E7, L1/L2 and LCR. E1/E2 coding region codes for protein which controls function of E6 and E7 genes; E4 codes for the protein that controls virus release from the cell; E5 codes for protein that enhances 'immortalization' of the cell; E6 codes for negative regulators for cell cycle and p53; E7 codes for viral protein that helps cell to progress through the cell cycle even in the absence of normal mitogenic signals; L1/L2 codes for protein responsible for late viral function and formation of complete viral particle; LCR codes for normal virus replication and control of gene expression[14].

During replication process of HPV 16 which starts with the replication of viral DNA, one daughter cell moves away from basal lamina to undergo differentiation and this can cause prolonged infection because of viron production to differentiated cells only.

E5,E6 and E7 are three major onco-proteins associated with cervical cancer, in vitro and in vivo. Protein E6 and E7 inhibit tumor suppressor gene p53 and pRb. Protein E5 increases the activity of epidermal Growth Factor Receptor and hence inhibits the Major Histocompatibility Complex expression[15]. Protein E1/E2 also have important role as they control the function of E6 and E7 onco-proteins.

HPV16 E6 protein consists of 151 amino acids and is found in nuclear matrix and non nuclear membrane fractions. E6 protein also binds with p53 protein with the help of cellular protein E6-AP and promotes abnormal cell growth by rapidly targeting p53 protein. E7 protein consists of 98 amino acids and is found in nucleus. They take part in transformation by binding and disrupting functions of pRb. This will cause inappropriate release of transcription factors and deregulated expression of gene related to check points in cell division leading to malignancy[16].

III. Screening Options

Cervical cancer is preventable through comprehensive screening for precancerous lesions and subsequent early treatment. Introduction of screening programs has shown great decline in incidence and mortality of cervical cancer. It can be made more effective with improved screening guidelines and new screening technologies which are more promising with the higher sensitivity and specificity. However in developing countries initiating and sustaining conventional cytology based screening programs have been less successful due to cost and complexity of providing infrastructure required. Most of the new cases, as much as 80%, of cervical cancer are diagnosed in the developing countries and most of the cervical cancers are incurable at the time of detection due to their advance stage. Visual inspection and high risk Human Papilllomavirus

screening have emerged as alternative to cytology based screening programs for the low-resource countries.

3.1. Cervical cancer cytology

Cervical cancer cytology involves collection of exfoliated cells from the cervix with the help of speculum examination, staining the collected specimen and examining these cells under microscope.

3.1.1 Pap smear

The conventional cervical cytology test also known as Pap smear was introduced by Papanicolaou and Babes in 1920s. Pap smear is simple, safe, effective and non-invasive method for detection of non cancerous, precancerous and cancerous cells and is recognized as world's most successful cervical cytology screening test for more than 50 years[17]. Pap smear is well integrated into the health care system in many countries, especially developed countries, around the world to improve survival and reduce mortality rate in cervical cancer. Pap test posses relatively high specificity (80-85%) but has low sensitivity (50-60%) for high grade CIN (grade 2 and 3) and even less for lower grade lesions CIN1[18]. In spite of its effectiveness, sustaining high quality cytology based program like pap smear is difficult in low resources setting due to its complex process of collection, sample preparation, staining, reading, reporting and delay between reporting and provision of test results.

3.1.2 Liquid Based Cytology

Liquid based cytology (LBC) is a way of preparing cervical samples for examination in the laboratory: It was developed in mid 1990's as an alternative method to conventional cervical cytology (Pap smear). It has offered benefits over Pap smear in the reduction of unsatisfactory samples and in further testing in HPV. The procedure for LBC involves immersing the spatula used to obtain the smear into a liquid preservation solution which is then transported to laboratory for slide preparation through automated process. During this process, cells and mucus are broken by mechanical agitation and the liquid is filtered through membrane with a pore size designed to trap epithelial cells while allowing contaminating blood and inflammatory cells to pass through. The trapped epithelial cells are then collected on the membrane, transferred onto a glass slide and are stained to be examined under microscope[19].

3.2 Visual inspection techniques

Visual inspection technique involves naked eye inspection of the cervix under a bright light either after application of 3-5% dilute acetic acid or Lugol's iodine. The positive result is based on the appearance of the lesions at transformation zone close to the squamo-columnar junction or at the external os or entire cervix. The sensitivity and specificity of the visual inspection screening of the cervical cancer varies widely due to age range of the study subjects, qualification of the screeners and subjectivity in interpretations of test results. The result of visual inspection techniques are used in 'Screen and treat' approach for the screen positive subjects. Women with positive result but without evidence of invasive cancer are treated with cryotherapy, without colposcopy and biopsy to minimize cost, loss of follow-up, delay in treatment and missed disease [20]. Visual inspection techniques for cervical cancer screening has addressed the need for simple and cost effective screening approach needed for cervical cancer prevention in low-resource countries.

3.3 HPV typing

With the establishment of high-risk HPV genotypes as a required etiological factor for the development of CIN 2, CIN 3 and invasive cervical cancer, HPV typing has become important method in screening cervical cancer. There are five main groups of commercial assay for the multiplex detection of alpha HPV available which test for presence of up to 14 HPV types. The availability of commercially available sensitive molecular test kits to detect hrHPV genotypes in clinical specimens and it's high sensitivity have made it less complex and more reproducible option for screening[21]. Because of high negative predictive value of hrHPV testing, it improves diagnostic accuracy and predicts treatment failure. Women with negative test results do not need to be re-screened for next 6 years and this also minimizes over referral to colposcoy in patients with borderline or mildly abnormal cytologic test result[22]. hrHPV typing has developed as simple alternative to attending clinic for screening as it can be done on self collected vaginal swabs which is a potential advantage for women who prefer self sampling than clinical sampling due to embarrassment associated with diagnosis, wish for female doctor and discomfort associated with test[23].

3.4 Imaging techniques

3.4.1Ultrasound

Recently ultrasound is being used extensively in the assessment of Cervical Cancer as it is faster, cheaper, more widely available than other imaging techniques and requires no preparation of patient. Detailed

image of Cervical tumor can be obtained from transvaginal and transrectal ultrasound due to proximity of probe to the tumor. In one of the recent multicenter study, transvaginal and transrectal ultrasound examination has provided 96% accuracy for tumor detection with 90% sensitivity and 97% specificity.

At ultrasound examination, adenocarcinoma appears as solid lesion with isoechoic echostructure and squamous cell carcinoma as solid lesion with hypoechoic echostructure compared with surrounding cervical stroma. According to the growth pattern, the exophytic lesions appear as "mushroom-shaped" and endophytic lesions appear as 'ovoidal' and 'conic-shaped'. Cervical tumor appear richly vascularized in power doppler examination.

Ultrasound can be used to access the extension of the disease, such as depth of stromal infiltration and extension into anterior ,posterior and lateral parametria. Infiltration of the parametria is seen as irregular extension of hypoechogenic prominence into the pericervical tissue. Doppler ultrasound can be used to distinguished between parametrial lateral tumor extension and hypoechogenic vessels. When the tumor extends into the bladder or rectum, the vaginal fornix is immobile against the bladder or rectal wall and vesicovaginal or rectoveginal infiltration is diagnosed[24,25].

3.4.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses high tissue contrast resolution. It as wide field of view and lack of ionizing radiation making it particularly useful in women looking for fertility sparing surgery. MRI has high accuracy in evaluating extra uterine extension of cervical carcinoma.

High field magnet (1.5 Tesla or more) is used to evaluate cervical cancer. Anti-peristaltic agent is administered intra-muscularly before exam to reduce bowel motion artifacts and bladder is kept half full. Vagina or rectum is distended with sterile aqueous gel if vaginal or rectal infiltration is suspected clinically. Non-fat-saturated small field of view and high resolution fast spin echo T2 weighted image is acquired according to 'para axial', 'para coronal', and 'para sagittal' plane orthogonal to the long axis of cervical canal[26]. Fat-saturated fast spin echo T2 weighted image are acquired in the patient's true axial plane from the femoral lesser tronchanter to renal hila to recognize lymph involvement. Non-fat saturated T2 weighted image are acquired in the patient's true axial plane to recognize bone metastasis and hematometra.

Cervical carcinoma appears as inhomogenous hyperintense 'white' mass in compare to cervical stroma and adjacent structures on T2 weighted image. It appears as a markedly hyperintense mass with a corresponding hypointensity 'black' on the apparent diffusion co-efficient (ADC) map on diffusion weighted images. Cervical cancer can not be differentiated from adjacent structures on T1 weighted image. MRI has high accuracy in the detection and measurement of cervical carcinoma, with a less than 5mm discrepancy between the largest diameter measured on MRI and the largest diameter measured at pathology testing[27].

3.4.3 Computed Tomography

Computed Tomography (CT) is not indicated for the evaluation of cervical cancer due to its limitation in soft tissue contrast resolution and low overall staging accuracy of only 53%. At CT cervical cancer appears isodense 'gray' compared with adjacent normal structures. The sensitivity of CT for detection of parametrial infiltration is about 55%. In the case of advance cervical cancer CT can be used to recognize distant metastasis, in particular to the liver and to the lung[28].

3.4.4 Positron emission tomography and computed tomography

Positron emission tomography combined with computed tomography (PET-CT) with glucose analogue FDG detects increased glucose metabolism associated with neoplastic lesions. PET identifies tumor lesion with FDG uptake and CT provides the structural change of the neoplastic lesion. Their combination provides both anatomical and functional information in a single imaging session by fusing image. With these fused image the neoplastic lesion in abdomen and pelvis can be localized and differentiated between physiologic and pathologic FDG uptake. Images are taken 60 minutes after FDG administration. Before imaging, patient is asked to void completely to reduce radioactivity within the urinary bladder. The images are acquired in caudal and cranial planes and interpreted qualitatively and quantitatively. Qualitative evaluation is carried out by calculating standard uptake value. Both primary squamous cell carcinoma lesions and adenocarcinoma lesions of cervix, that are larger than 1cm show intense FDG uptake. Recent study showed that SUVmax was significantly higher for poorly differentiated than well differentiated tumors and higher for squamous cell tumor than for non-squamous cell tumors. The intensity of FDG uptake in primary tumor is predictive of lymph node involvement and disease outcome[29,30].

The advantage of FDG PET-CT in staging of cervical cancer is its high sensitivity for detecting distant metastases which allows stratification of women into those with locally confined disease and those with distant tumor spread[31].

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