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Screening for Cervical Cancer

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ABSTRACT

Screening is a public health intervention administered to a target population without symptoms. Screening is not performed to diagnose a disease, but to identify individuals with a higher likelihood of developing the disease itself or a precursor to the disease. Not all diseases are suitable for screening programs. The following criteria help determine whether a disease is suitable for a screening program: (1) The disease is bound to have serious consequences. (2) The disease must have a detectable preclinical and asymptomatic stage. (3) Treatment at the preclinical stage should influence the long-term course and prognosis of the disease being screened. (4) Care must be available and accessible to those who have a positive screening test. History, screening tests and treatment options for cervical pre-cancer meet these criteria.

1. Introduction

Screening is a public health intervention administered to a target population without symptoms. Screening is not performed to diagnose a disease, but to identify individuals with a higher likelihood of developing the disease itself or a precursor to the disease. Not all diseases are suitable for screening programs. The following criteria help determine whether a disease is suitable for a screening program: (1) The disease is bound to have serious consequences. (2) The disease must have a detectable preclinical and asymptomatic stage. (3) Treatment at the preclinical stage should influence the long-term course and prognosis of the disease being screened. (4) Care must be available and accessible to those who have a positive screening test. History, screening tests and treatment options for cervical pre-cancer meet these criteria.[1-5]

Screening is a test of all women at risk for cervical cancer, most of whom are asymptomatic. Screening aims to detect precancerous changes, which, if left untreated, can lead to cancer. Screening is only effective if there is a regular system for follow-up and treatment. Women who are found to have abnormalities on screening need follow-up, diagnosis and possibly treatment, to prevent cancer progression or to treat cancer in its early stages.[6,7]

Several tests can be used to screen for cervical cancer. The Pap smear (cytology) is the only test that has been used in a large population and has been shown to reduce the incidence and mortality of cervical cancer. Other tests (VIA, VILI, HPV) are also promising and are recommended by several major world organizations such as the American College of Obstetricians and Gynecologists (ACOG), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the US Preventive Services Task Force (USPSTF). All three cervical cancer screening methods provide highly effective cancer prevention, so it is important for service providers to choose the strategy that best fits their practice. The most critical aspect of screening is to screen all women, regardless of the method used. This test can be used as a single or sequential test. When using one test, a positive result indicates the need for treatment. When using a series of tests, women who test positive on the first test receive another test and only those who test positive on the second test are treated. Women with a positive first screening test followed by a negative second screening test were followed up. Available treatments include cryotherapy, large loop excision of the transformation zone (LEEP / LLETZ), and cold knife conization (CKC).[8,9] Regardless of the test used, the key to an effective program is to reach the majority of women at risk with appropriate screening and treatment. quality. An organized screening program designed and managed at the central level to reach the majority of women at risk is better than opportunistic screening.[10]

Pap tests should not be done annually as sometimes precancerous lesions are mentioned without actually being present. This false positive result can lead to unnecessary treatment. Recent guidelines for screening mass populations retain the benefits of diagnostic tests but they reduce the risk of unnecessary treatment. Women who have had a total hysterectomy (including cervix) for benign disease and have no history of cervical cancer or a history of severe precancerous lesions should not be screened. Finally, women who have been vaccinated against the HPV virus should continue screening according to the guidelines for their age group.[11]

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion that may be present in one of three stages: CIN1, CIN2, or CIN3. If left untreated, CIN2 or CIN3 (collectively referred to as CIN2 +) can develop into cervical cancer. Instead of screening and diagnosis with standard sequences of cytology, colposcopy, biopsy, and histological confirmation of CIN, an alternative method is to use a 'screening and treat' approach in which treatment decisions are based on screening tests and treatment. given immediately or, ideally, immediately after a positive screening test. Available screening tests include the human papillomavirus (HPV) test, visual inspection with acetic acid (IVA), and cytology (Pap test). Available treatments include cryotherapy, large loop excision of the transformation zone (LEEP / LLETZ), and cold knife conization (CKC).[12]

Diagnostic or confirmatory tests are medical tests that are performed to aid in the diagnosis or detection of disease. Because not all women who test positive on cervical screening tests actually have pre-cancer, subsequent diagnostic tests are sometimes used for definitive diagnosis or confirmation of pre-cancer or cancer. Diagnostic testing has major resource implications. They can create significant barriers for women to accessing services, potentially delay treatment, and / or increase the number of women who are lost to follow-up and who may therefore never receive treatment for their precancer. Colposcopy, biopsy and endocervical curettage (ECC) are the most commonly used diagnostic tests for cervical precancer. This method requires a high level of resources and training. If a colposcope, biopsy forceps and endocervical curettage are available, these procedures can be administered at the primary care level by physicians and intermediate-level providers who have undergone competency-based training and appropriate supportive supervision. More often, it is performed as an outpatient procedure at the secondary care level (district hospital).

Early diagnosis of cancer generally increases the chances of successful treatment by focusing on detecting the patient's symptoms as early as possible. Delays in accessing cancer care are common in the end-stage presentation, especially in lower-resource

settings and vulnerable populations. The consequences of delayed or inaccessible cancer care are lower chances of survival, greater morbidity of treatment and higher costs of treatment, resulting in avoidable cancer death and disability. Early diagnosis improves cancer outcome by providing the earliest possible treatment and is therefore an important public health strategy in all settings.[9]

Early detection of cancer can effectively reduce cancer-related deaths. In resource-limited countries, cancer is often diagnosed at an end-stage disease resulting in lower survival and the likelihood of greater morbidity and higher costs of treatment. Even in countries with strong health systems and services, many cases of cancer are diagnosed at an advanced stage. Therefore, addressing delays in cancer diagnosis and inaccessible treatment is essential in all settings for cancer control.[13]

Early diagnosis aims to reduce the proportion of patients diagnosed at an advanced stage. There are three steps to early diagnosis of cancer. Decision making depends on a number of factors, including the cancer being targeted, the risk of a particular cancer in a particular population and the capacity and resources of the health system in a particular country. In areas where most patients are diagnosed at an advanced stage, early diagnosis can have a major impact and build the capacity of the health system.

Diagnosis is based on histopathological assessment of cervical biopsy. Women with symptoms of cervical cancer require a pelvic examination, visualization of the cervix and vaginal mucosa, and cervical cytology. The cervix and vaginal mucosa should be visualized by speculum examination. The cervix may appear normal when the disease is microinvasive or in the endocervical tract. Cervical cancer can metastasize via lymphatic vessels to the pelvic, para-aortic, mediastinal, supraclavicular, and inguinal lymph nodes. Inguinal and supraclavicular lymph nodes. Enlarged and hardened inguinal and supraclavicular lymph nodes may be palpable in advanced disease. Colposcopy and biopsy should be performed in symptomatic patients or women with cytology suggestive of invasion without visible lesions. A cone biopsy is mandatory if malignancy is suspected either clinically or in cervical cytology but is not confirmed on the histopathological review of cervical biopsy. The cone should be excised type III (depth > 1 - 5 cm) in one piece.[14]

If abnormal cervical screening test results are found, or any symptoms of cervical cancer, the patient will usually be referred for a colposcopy. This is a test to look for abnormalities in the cervix. Colposcopy is usually done by a nurse. If the patient has abnormal bleeding, the doctor may recommend a chlamydia test first before being referred for colposcopy. A small microscope with a light at the end (colposcope) will be used to view the cervix. This microscope is outside the body. Apart from examining the cervix, it is also possible to take a small tissue sample (biopsy) so that cancer cells can be examined. After a biopsy, it is possible to experience vaginal bleeding for up to 6 weeks. If it is proven that you have cervical cancer based on the results of histopathology, the patient will be referred to a gynecologist for further examination. Treatment to remove abnormal cells can sometimes be done in conjunction with colposcopy.[15]

Cervical cancer screening techniques

A good screening test should:

a. Accurate: the test results are correct
b. Reproducible: repeating the same test will give the same results
c. Inexpensive: affordable for the health system in terms of financial and human resources, and for all patients and their families in terms of access to the necessary services
d. Relatively easy: uncomplicated to perform and provides follow-up care for women with abnormal results
e. Acceptable: well tolerated by both the patient and the provider
f. Safe: the testing procedure and management of screening positive subjects had no or minimal side effects
g. Available: accessible to the entire target population.

In theory, the best screening test is the one that has the lowest rate of false-negative results (i.e. if the result

is negative / normal but the woman does have the disease), and simultaneously has the lowest rate of false positives (i.e. if the result is positive but the woman is not in fact. have abnormalities). False negatives can lead to an increased risk of cancer if routine checks are not available. A false positive result can lead to over-treatment and increase patient anxiety.

In practice, it is important to select the most appropriate screening test taking into account both the particular setting in which the program will be implemented and the human, financial and infrastructure resources available to use the selected test. The test must be suitable for a population-based screening program to ensure that it reaches the entire target population and not only those with greater access to health services. For long-term sustainability, the health system must have the capacity to maintain the necessary equipment and replace the necessary supplies. Choosing the best test is a balance of all of these factors.

HPV molecular test

The molecular HPV testing method is based on DNA detection of high-risk HPV strains in vaginal and / or cervical samples. Testing women under 30 for this virus is not recommended because many young women are infected with this virus, but most HPV infections will spontaneously clear from their bodies before they reach 30 years of age. So, testing for HPV in women younger than this will detect many women with temporary HPV infection and may subject them to unnecessary procedures and medications that can cause harm, anxiety, discomfort, and cost problems. For this reason, HPV testing should be performed for women over the age of 30, or the age specified in the updated national guidelines. The high-risk HPV DNA test has a high negative predictive value of 98% for precancerous lesions. The HPV DNA test has a high sensitivity rate of 90.2 - 96.1% and a lower specificity rate of 84.2 -94.5%. Due to its good performance, HPV testing is the first line in screening for precancerous lesions, although according to the Centers for Disease Control and Prevention (CDC) nearly 90% of HPV infections can be eliminated within the first 2 years, so a confirmatory diagnosis is necessary to avoid overtreatment. The risk of overtreatment decreases in older patients due to the tendency for persistent infection and faster disease progression.

The HPV test is very sensitive to detect HPV infection in women. However, although HPV infection is a necessary precursor for cervical cancer, a positive HPV test does not confirm that the woman has precancer; it just makes sure that there is an HPV infection.

The molecular detection of HPV DNA or RNA is currently the gold standard for HPV identification. Three categories of molecular tests are available to detect HPV infection in tissue and chipped cell samples, all based on HPV DNA detection and include non-amplified hybridization tests, southern transfer hybridization (STH), dot blot hybridization (DB) and in situ hybridization (ISH), signal amplified hybridization testing such as hybrid capture assay, target amplification testing such as polymerase chain reaction (PCR) and in situ PCR. PCR based on HPV detection is very sensitive and specific. Furthermore, detection of HPV E6 / E7 mRNA and the presence of oncogenic activity in cervical specimens can be done by reverse transcriptase (RT) PCR or by nucleic acid sequence-based amplification (NASBA). In the NASBA test, single-stranded nucleic acids or RNA equivalents (e.g. viral genomic RNA, mRNA, or rRNA) are amplified against the background of double-stranded DNA.[16] To detect HPV infection, whether it is for the purposes of diagnosis or screening of a disease can be done cytologically, colposcopic, immunocytochemical, and DNA-based testing. In cervical cancer screening, there are two methods used, namely cytological examination through a pap smear test, and DNA-based examination using the DNA-RNA hybridization technique, namely the Hybrid Capture (HC) method. Pap smear is the most popular method because it has a fairly good specificity besides that the cost is relatively affordable, but it turns out that this method has many disadvantages including: a high degree of subjectivity and false positive results, many results classified as ASCUS

(Atypical Cell of Undetermined Significance) or the meaning of atypical squamous cell conditions (65% - 75%). While the HC method is a cervical cancer screening method that has a high level of sensitivity and specificity as well as a low false positive result. The HC method is based on detecting the presence of papilloma virus DNA in cells using a viral DNA hybridization technique with a specific RNA probe. Thus the HC method is a cervical cancer screening method that utilizes papilloma virus DNA as a marker. This examination is quite effective in preventing cervical cancer.

There are several molecular techniques used for the detection of HPV DNA. The molecular techniques that will be discussed are:

a. Southern blot hybridization method directly

Southern Blot is a method for testing the presence of a DNA sequence in a DNA sample. This method was invented by a British biologist named Edward M. Southern who developed this procedure in 1975 at the University of Edinburgh. This method combines the agarose gel electrophoresis process to separate DNA based on size with the electrophoretic DNA fragments transferred to the filter membrane. The membrane is then hybridized with a specific probe. At the start of HPV research, the Southern Blot was the gold standard method for the analysis of the HPV genome. The process of transferring separate DNA fragments by gel electrophoresis techniques to membranes such as nitrocellulose membranes is carried out based on the capillary principle, where the buffer which is the mobile phase is assumed to carry DNA fragments from the gel to the membrane. DNA is negatively charged while the membrane is positively charged so that the DNA fragments will stick to the nitrocellulose membrane. Southern Blot has a low sensitivity for detecting HPV in clinical specimens and identifying HPV types. The Southern Blot method is time consuming, requires large amounts of DNA, and requires trained technicians. The Southern Blot method cannot be performed on tissues that are fixed with formaldehyde because DNA will be degraded. [17]

b. Hybrid capture II assay (HC II)

Hybrid Capture System (HC-II) is a hybridization inspection method with the latest technology in the field of molecular biology. The HC-II technique is used in an earlier condition, that is, the possibility of a person being infected with HPV before the virus makes changes to the cervix which can eventually lead to cervical cancer. HC-II has been recognized worldwide and approved by the FDA (Food and Drug Administration) United States. HC-II has high accuracy in detecting HPV infection because it is able to detect the presence of HPV DNA in very small amounts. The HC-II technique is an antibody capture / solution hybridization / signal amplication assay that uses qualitative chemiluminescence detection of HPV DNA. In general, HC-II is a DNA-RNA-based technique that can detect accurately and quickly with a sensitivity of 98% and a specificity of 98% .[63] The HC II method has an accuracy of 92 ± 94% for cytology / histological examination techniques, requiring a long examination shorter, no or little contamination and can quantitatively estimate the number of viruses without knowing the HPV genotype. The HC II method uses 2 types of probes to detect HPV, namely the high risk HPV probe (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and the low risk HPV probe. (HPV types 6, 11, 42, 43, 44) [18]

c. Amplification Method of Target Polymerase Chain Reaction (PCR)

Target amplification is the most flexible and sensitive DNA analysis technique compared to Southern Blot and HC II techniques. This technique can be used to detect, quantify viral load, sequence DNA bases, and analyze mutations. PCR or polymerase chain reaction is an enzymatic method to multiply exponentially a certain nucleotide sequence in vitro. PCR was first developed by Kary Mullis in 1985. This PCR method can be done multiplex where the DNA targets are multiple and can be analyzed simultaneously. The sensitivity of the target amplification method can be increased by the synthesis of a specific target DNA base sequence. The way PCR

works is to amplify the isolated DNA in 3 stages, namely denaturation (DNA linearization occurs at 95 ^{o}C), annealing (primary attachment to the target DNA to be reproduced), and elongation (polymerization). The result of amplification can then be detected by electrophoresis technique using agarose gel electrophoresis apparatus. Electrophoresis technique is a technique that separates molecules based on their molecular weight in an electric field in a solid or semi-solid medium.[66] The PCR method can be applied with a small number of samples and components, PCR is a sensitive method and can detect the types of HPV, especially the subtypes of HPV. high risk. The PCR genotyping method is time consuming, expensive, and requires a sophisticated laboratory.[19]

d. PCR-Reverse Line Hybridization (Linear array HPV genotyping test)

PCR - Reverse Line Blot (RLB) is a modified PCR method, where PCR amplification results are detected using hybridization with specific oligonucleotides immobilized on the nitrocellulose membrane. This technique is very sensitive and can detect DNA around 100 ag. This technique can be used to detect the HPV genotype in mixed infections. The way PCR - RLB works is as follows: The oligonucleotide probe with a specific HPV type is immobilized on the membrane then hybridized with a PCR product labeled with biotin which was previously denatured under alkaline conditions. After the hybridization process, the membrane is then washed. Hybrid yields can be detected by adding streptavidin - peroxidase and a substrate which will produce color on the probe lines and interpret it visually.[20]

Additional markers associated with cellular changes are being studied for use in screening tests. In women with abnormal smears, histological analysis of the biopsy sample is used to establish a definite diagnosis of the underlying lesion. However, for cytology, histology was also influenced by the substantial degree of mismatch among observers even among a panel of pathologists, suggesting that biomarkers would also enhance standardization and robust quality control of histological diagnoses. p16INK4a (p16) is a biomarker associated with progression to cervical precancer. In particular, p16INK4a is an inhibitor of the cyiclin-dependent enzyme kinase associated with the production of oncoprotein E7. p16 is inactivated in many cancers by mutation, deletion or hypermetylation in the gene, so there is no expression of p16 by the gene. This increases the activity of CDK4 and CDK6 and leads to premature phosphorylation and inactivation of pRB. If pRB is directly inactivated at the nucleic acid level or at the protein level, the cell will be free of growth inhibition mediated by cyclin-dependent kinase inhibitor p16INK4a. In sl that proliferate, there was an increase in p16 levels. Expression of p16 as negative feedback control via pRB. The absence of control of pRB leads to an increase in p16. The inactivation of pRB by high-risk HPV virus through E7 causes the expression of p16 levels to increase which shows p16 as a sensitive and specific biomarker which is activated by the oncogenes of the HPV virus. p16 is reported to be highly expressed in CIN2+ lesions and is rarely detected in benign tissue. Recent studies pairing detection of p16INK4a with Ki-67 demonstrated improved performance compared to traditional cytology or p16INK4a alone. Currently, dual p16INK4a / Ki-67 staining is used as triage after primary DNA testing. Host methylation and viral DNA methylation also reflect cancer progression and are being investigated for triage after primary HPV testing. Methylation analysis of two specific host genes, MAL and miR-124-2, has been shown to be comparable to cytology for triage in a study of more than 12.000 women.[75] In a small clinical study (n = 201), the GynTect host methylation test, which targets six DNA regions, yielded positive results for all women with cervical cancer, 61.2% CIN3, 44.4% CIN2, and 20.0% cases of CIN1.[76] Furthermore, DNA methylation of virus end regions (eg L1) has been shown to correlate with disease progression and has been evaluated in screening and triage settings. One triage classifier, S5, detects DNA methylation of the viral end regions of the HPV genotypes 16, 18, 31, and 33 as well as the promoter regions for the human gene EPB41L3. Relative sensitivity and specificity were assessed in a study of 15.744 women compared with

established triage methods, including fluid-based cytology (LBC) and HPV tests. For CIN2 / 3, the sensitivity and relative specificity of the S5 classifier were 76% and 44%, respectively, and LBC was 51% and 67%, respectively. For CIN3, the sensitivity and relative specificity of the S5 classifier were 93% and 42%, respectively, and for LBC were 61% and 64%, respectively. While the S5 classifier did not show increased specificity over LBC, it did demonstrate a high baseline sensitivity for CIN3, leading the authors to conclude that this could be useful in simplifying the existing triage algorithm. Other promising biological markers undergoing validation or clinical evaluation include proteins involved in cell cycle aberration and miRNA. Although these biomarkers do not yet have clinically validated tests, they have the potential to be used in the development of new screening tests.

Compared to the HPV DNA test, the oncoprotein test generally has lower sensitivity and higher specificity. Arbor Vita (Fremont, CA) has commercialized the lateral-flow oncoprotein E6 test, OncoE6, for HPV types 16, 18, and 45.[7] The lateral-flow readings are fairly simple and have separate lines of detection for each HPV type, allowing for partial genotyping.[7] The clinical sensitivity and specificity of the OncoE6 test ranged from 31.3% to 53.5% and 98.9% to 99.4%, respectively.[7] When limiting the analysis to patients who were positive for the three genotypes covered by the test, sensitivity increased to 64.5%; [7] Therefore, the limitation of sensitivity is due not only to the genotype being missed. The equipment for the OncoE6 test is reasonably priced at an estimated cost of US $ 2.000. However, these tests require more than 45 minutes of sample preparation with multiple pipetting and centrifugation steps, and are therefore not yet the optimal solution for low-resource countries. Automating sample preparation and limiting live test times, as well as increasing the number of genotypes detected, can improve the performance and usability of the OncoE test.[7]

Visual screening methods

Visual inspection with acetic acid (IVA) is a method for detecting early cell changes seen when using a speculum to examine the cervix with the naked eye after applying dilute acetic acid (3–5%) to the cervix. This requires training and supervision of primary care providers, as well as ongoing quality control and quality assurance.

IVA is suitable for use in women with a visible squamocolumnar junction (SCJ), usually in those younger than 50 years of age. This is because the SCJ gradually shrinks into the endocervical canal as menopause occurs, so that lesions can be missed when relying on visual inspection.

IVA requires the use of a speculum and a light source, and trained health personnel. The examiner performs a speculum exam, identifies the CNS and carefully examines the cervix for suspicious visual signs of cancer or precancer. A 3–5% acetic acid solution is applied liberally to the cervix with a large cotton swab.

After removing the cotton swab, the examiner waits at least a minute, during which time any areas that have turned slightly white simply due to inflammation or physiological cell changes (metaplasia) will shrink. Acetowhite changes in the cervix that do not shrink after one minute are more likely to be associated with cervical precancer or cancer. If this change is seen in the transformation zone and has clear boundaries, it is considered a positive result. If no persistent acetowhite change is recorded, a negative result is reported.

The IVA test can detect early changes and changes that indicate more advanced precancer. Immediate outcomes allow patients to be offered care at the same visit (ie, single visit approach). Alternatively, if the patient chooses not to do so immediately or if treatment is not available, then treatment can be started at the next visit immediately thereafter. Diagnostic steps, such as colposcopy and / or biopsy, are usually not performed at this time (at the same screening facility), but if the cervix shows unusual signs or the examiner suspects cancer, the patient may be referred for further diagnosis.

The IVA is a subjective test and therefore depends on the skills and experience of the examiner conducting

the test. Skills should be used regularly, and refresher courses are recommended. Because this test is subjective in nature, quality control and quality assurance for IVA are very important. This can be achieved through regular supervision and monitoring.[21]

Cytology-based screening method

Cytology-based screening involves taking a sample of cells from the entire transformation zone. The cells are fixed on a slide in the facility (Pap smear) or placed in a transport medium (liquid-based cytology) and then sent to a laboratory where a cytotechnologist examines the cells under a microscope. If abnormal cells are seen on microscopic examination, the degree of abnormality is classified using the Bethesda System.

Cytology-based screening programs can use one of two available methods: conventional Pap smear (or Pap test) or fluid-based cytology (LBC). With conventional cytology, a cell sample is smeared on a slide, and preserved with a fixative. LBC was introduced in the mid-1990s; it is a refinement of conventional cytology and is increasingly being used in high and medium resource settings. For LBC, instead of smearing the sample onto a slide, the sample is placed in a preservative solution container and sent to the laboratory for microscopic examination.

Collection of a cytological sample requires a sufficient speculum and lighting to visualize the entire surface of the cervix. The examiner takes the specimen from the surface of the cervix and endocervix using a spatula or brush and transfers the specimen to a slide (Pap smear) or preservative solution (LBC). Samples should be appropriately labeled and sent to the laboratory, where skilled personnel are required to process and interpret them.

A well-implemented cytology program can successfully prevent cervical cancer. However, cytology programs are multi-stepped and face significant challenges, especially in low-resource settings. Specimens must be properly collected, repaired / preserved, shipped safely to the laboratory, accurately processed and interpreted, and the results reliably sent back to the examiner. The patient needs to accept the results and get the necessary follow-up or treatment. Hence, there are many opportunities for logistical challenges to interfere with a successful screening program.

Liquid-based cytology has several advantages over conventional methods. The specimens obtained are more representative of the sample area, and generally there is a lower level of unsatisfactory specimens and a reduced likelihood of inflammatory or blood cell clouding cells that need to be examined on the slide. In addition, each specimen takes less time to interpret, and the material collected can also be tested for HPV DNA and other STIs. However, it is an expensive technique that requires advanced technology, including state-of-the-art laboratories and highly trained technicians. Current evidence does not suggest that LBC is more effective at reducing cancer morbidity and mortality than conventional cytology.

Classification of cervical precancerous lesions

For CIN treatment, hysterectomy is only recommended for women with no hope of bearing a child. From 1980 to 2000, developments in molecular biology led to an understanding of HPV and cervical carcinogenesis. CIN1 / mild dysplasia / koilocytic atypia were defined as the histological and cytological equivalents of HPV infection. These lesions have a low risk of development, mostly regressing during clinical observation and treatment. Meanwhile, CIN2 or CIN3 and CIS are the morphological equivalents of cell transformations associated with HPV oncogenes. These lesions are of a persistent character and have a greater likelihood of developing an invasive tumor. [22]

This concept greatly influences the cytological classification of cervical PAP and supports the Bethesda system. LSIL and HSIL are the recommended terminology for all intraepithelial neoplasia associated with HPV in the lower anogenital area, and not only for CIN.

There are many systems used in different parts of the world to classify and name cervical precancerous conditions, based on cytology and histology. More

useful classification systems incorporate information about the natural history of disease, which has been acquired over the last few decades.

Cervical cancer screening recommendation ACOG, ASCCP, USPSTF

	ACOG	ASCCP	USPSTF
Pap only	Every 3 years	Every 3 years	Every 3 years
Pap-HPV cotest	Every 5 years, age 30 - 65	Every 5 years, age 30 - 65	Every 5 years, age 30 - 65
High-risk HPV only	Every 3 years, age > 25	Every 3 years, age > 25	Every 5 years, age 30 - 65

ACOG = American College of Obstetricians and Gynecologist; ASCCP = American Sociaety for Colposcopy and cervical Pathology; HPV = human papillomavirus; USPSTF = US Preventive Service Task Force

Figure 1. Cervical cancer screening recommendations.

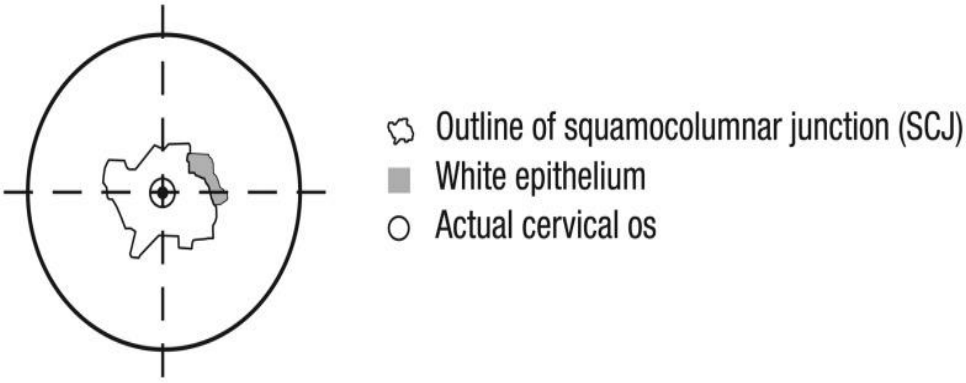

Figure 2. IVA results recorded on labeled images

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