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e-Newsletter

ISCCP

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From the Editor's Pen

Dear ISCCP Members,

This is the first issue of news letter released by the new team of ISCCP. Myself alongwith my editorial board will try our best to continue with the great work performed by the previous team of ISCCP. On behalf of editorial board, I will like to invite all ISCCP members to contribute for the newsletter in the form of review articles, original articles(studies including surveys with simple analysis), view points, case reports, images with description.

In the what's app group I had observed that many consultants are actively participating in the discussions and are highlighting very important points. It is my utmost request to all the members to pen down those cases and send to me at prakasharuna@hotmail.com

We all know that everybody is not a great writer or born writer but we all as health professional are good prescription writers. It is the first few lines or few words which are the most difficult to write down. I want all of you to come forward with small write ups. We have more than 400 members in our society from all over India. If even 50% of the members contribute with one page of their views or any important case, we will have good number of articles to read. We will come to know regarding each other's practices and importantly we will come to know the discussion on the management which in routine we are not able to do so.

In this issue we have included two review articles related to biomarkers and newer modalities in diagnosis of cervical intraepithelial neoplasia by esteemed gynaecologist and pathologist. We have also included the view point by Dr Dinesh Gupta and case report by Dr Bharti. I am really thankful to them for contributing towards the newsletter. We have received few other cases which we will be publishing in the subsequent issues.

As an editor of the Newsletter, I assure all of you that we will publish all the articles contributed by the members in one or the other way. I request all the contributor's to click high quality images and take the images of the colposcopy from the "C" drive of their computer where they are saved so that better understanding of the images will be there.

I request all of you to communicate to us regarding the events held by you so that it can be included in the newsletter in the "Events Corner". Looking forward for more and more submissions from the members.

Chief Editor
Prof Aruna Nigam

Forthcoming Conference

14th Annual Conference of ISCCP

19th-21st April, 2019
at Vishakhapatnam

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Biomarkers in Cervical Cancer Screening

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Introduction

Incidence of invasive cervical cancer in industrialized nations is 1:10000 while in low resource nations it is 1:1000, the cause being the failure of these nations to participate in screening programs. Thus it is important to offer feasible and affordable screening tests and improve the efficiency of current screening programs.

Current Cervical Cancer Screening Approaches

1. Cytology based Pap test – This approach has lot of pitfalls. The results of Pap test cannot be reproduced. It has a sensitivity of 34-94% for CIN 2 and needs to be repeated frequently. It has large proportion of inconclusive or mildly abnormal test results that may mask a low number of high grade precancerous cases. Triaging is also important.
2. HPV Screening - British hart study found that primary HPV screening is a promising alternative to primary screening using cytology. HPV infected women without disease or cervical lesions would still require further work up.
3. Visual Screening approaches – It is difficult to detect small ectocervical and endocervical lesions by visual screening. VIA is unspecific and might lead to over-treatment and it has low sensitivity.

Biomarkers

Biomarker is a characteristic that can be objectively measured. It is an indicator of normal or pathologic process or a pharmacological response to treatment. They are found in blood, body fluids and tissues and are measured by genetics, proteomes, cellular or molecular substances.

Potential Improvement of Cervical Cancer Screening Programs By Use of Biomarkers

These allow to identify persons at risk of developing cancer at a time point that still allows for a successful curative intervention before ICC develops. It is desirable to have assays with both high sensitivity and specificity. Currently HPV testing is one option to triage ASC-US cytology. Biomarkers used in triage should be specifically associated with disease progression.

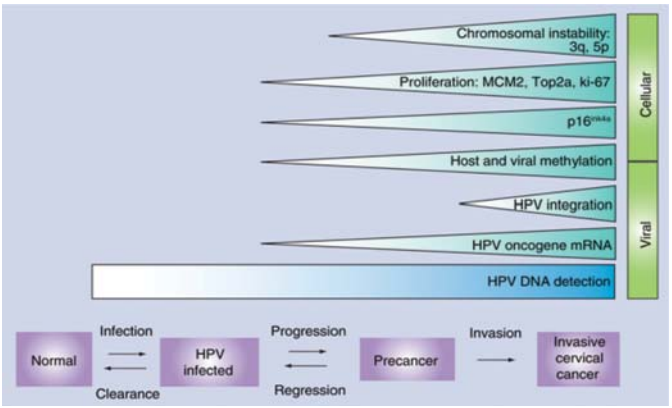


Fig 1. Human papillomavirus natural history and cellular and viral biomarkers used in cervical cancer screening

Biomarkers Derived from the Analysis of Molecular Key Events of Cervical Carcinogenesis – E6 & E7

The initial events in cervical transformation are an infection with high risk HPV. The majority of these infection regress spontaneously; a small proportion persists and induces CIN. The risk of progression to invasive cancer rises with the grade of the lesion. Two early genes E6 and E7 were found to be the most important factors in cellular transformation induced by high risk HPV. E6 and E7 control cellular functions i.e. inactivation of pRB (E7) and degradation of p53 (E6). Loss of pRB leads to E2F mediated cell cycle activation that would normally be counteracted by apoptotic programs in host cells. E6 and E7 are selectively expressed in the upper epithelial layers to activate the viral replication machinery. By the restriction of viral replication to terminally differentiated cells, the virus avoids harmful consequences for its host. Altered expression pattern of HPV oncogenes due to E6/E7, leads to progression from HPV infected tissue to dysplastic lesions. 567 copies/ml is the cut off.

In high grade CIN lesions, E6 and E7 are strongly expressed in basal epithelial cells and viral oncogenes interfere substantially with cell cycle control of these replication competent host cells. In the cells uncontrolled proliferation, deregulated cell cycle control and hence chromosomal instability occurs that results in multiple numeric and structural chromosomal aberrations. In the course of repair processes in chromosomally unstable cells, HPV genomes may become integrated into host cell chromosome.

Other Types of Biomarkers

1) Surrogate biomarkers of deregulated HPV oncogene expression
   - p16INK4a
2) Markers of chromosomal instability
   - DNA aneuploidy
   - HPV integration (PCR based quantification of E2 and E6/E7 gene ratio)
3) Markers of proliferation and host genome replication
   - Ki-67
   - MYC (cellular oncogene amplified and over expressed)
   - Cyclins (regulatory proteins of cell cycle)
   - Telomerase (TERC and TERT gene amplification)
   - Replication complex proteins (MCM5 & CDC6)
4) Markers of cellular stress and invasion
   - HSP (over expression of HSP40, HSP60 and HSP70)
   - CA9/MN antigen (for cytological diagnosis of AGUS)
5) Epigenetic markers, factors enhancing viral oncogene activity
   - Methylation of CpG islands
   - RASSF 1 methylation, LOH and CGH losses detected at 3p21 region
   - Brn-3a transcription factor (potent activator of HR-HPV gene expression)

Surrogate biomarkers of deregulated HPV oncogene expression

$p16^{INK4a}$ (Cyclin-Dependant kinase inhibitor)

It is a marker of deregulated HPV oncogene expression. Under physiological conditions $p16^{INK4a}$ is expressed when cells undergo a genomic stress situation such as substantial shortening of telomeres in ageing tissues. Independent from HPV, expression of $p16^{INK4a}$ is sometimes observed in single cells that undergo modifications of their normal differentiation program due to genomic stress.

The pathological expression in HPV transformed cells is indicated by a very strong diffuse staining pattern in the replicating cells of the basal and parabasal cell layer. $p16^{INK4a}$ positive low grade lesions have a higher risk of progression than $p16^{INK4a}$ negative lesions. $p16^{INK4a}$ immunostaining has been used to triage ASC-US and L-SIL cases for high grade CIN. Since $p16^{INK4a}$ can be performed from the initial cytology specimen, this application could be a new option for the regular follow up of unclear cytology results.

Markers of chromosomal instability

DNA aneuploidy

Disturbances of the mitotic spindle apparatus are induced early by deregulated expression of HPV oncogenes resulting in non-diploid nuclei (aneuploidy). Aneuploidy precedes HPV integration in advanced dysplastic lesions further supporting the notion that integration of viral genomes is the consequence but not the cause of chromosomal instability and transformation.

HPV integration

HPV DNA is integrated by chance during the cellular repair processes of double strand breaks. HPV integration is an indicator of severe ongoing chromosomal instability and an advanced stage of the transformation process. PCR based quantification of the E2 and E6/E7 gene ration. E2 is frequently lost upon HPV integration and the theoretical ratio of 1:1 between the two genes is expected to be shifted towards E6/E7.

Markers of proliferation and host cell genome replication

Ki67

This protein is strongly expressed in CIN lesions. Ki67 cell clusters are a good criterion to discriminate low grade CIN lesions from normal and reactive epithelia.

MYC

The cellular oncogene MYC is found amplified and overexpressed in cervical cancer._There is a tight correlation between MYC expression and HPV16 infection at pre-invasive stages, indicating different oncogenic properties of different HR-HPV types.

Cyclins

Large family of regulatory proteins with central functions in the coordination of the cell cycle. Cyclin D1 was found to be overexpressed in low-grade lesions induced by LR-HP, while it was absent in HR-HPV induced lesions. Cyclin E in liquid based cytology specimens was analysed and a strong association was found

Telomerase

It is found overexpressed in many human cancers. Several groups have used a functional telomerase assay to evaluate telomerase activity on cervical smears. Increased telomerase activity was mainly found in advanced dysplasias with varying sensitivity for the detection of HGCIN

Replication complex proteins

MCM5 and CDC6 belong to the DNA pre-replication complex that is usually expressed in replicating, but not in quiescent cells. In dysplastic cervical cells, a continuous activation of the replication complex is found. In frame of the HPV-PathogenISS study, Branca and colleagues found that topoisomerase II alpha (TOP2A) expression was correlated with the progression from CIN2 to CIN3.

Markers of cellular stress and invasion

HSPs are chaperones protecting cellular functions in response to various cellular stresses that were found to be overexpressed in a number of cancers. In cervical precancer, overexpression of HSP40, HSP60 and HSP70 were associated with increasing lesion grade.

CA9/MN antigen has been identified as a marker for all grades of CIN. For the cytological diagnosis of atypical glandular cells of unknown significance (AGUS), CA9/MN expression pointed to relevant lesions. Laminin 5 is part of cell adhesion complexes and was found to be an invasion marker in various epithelial tumors, including cervical cancer.

Epigenetic markers, factors enhancing viral oncogene activity

Methylation of CpG islands is an epigenetic modifier of gene expression. The brn-3a transcription factor is a potent activator of HR-HPV gene expression. A massive overexpression was found in women with CIN3 as compared to women without cervical lesion.

Identification of Biomarkers for Cervical Cancer Screening by Profiling Approaches

Chromosomal abnormalities

Comparative genomic hybridization (CGH) assays can measure altered distributions of genomic DNA on a genome wide basis. The typical chromosomal losses are 2q, 3p, 4p, 4q, 5q, 6q, 11q, 13q, and 18q, frequently gained regions are 1q, 3q, 5p, and 8q. The most consistently observed alteration seems to be the gain of chromosome 3q with TERC gene, an event that has been associated with the progression from severe dysplasia.

a. Alteration of gene expression - HPV-induced transformation, including CDKN2A/p16^{INK4a}, topoisomerase 2A, and minichromosome maintenance proteins 2, 4, and 5.

b. Alteration of protein expression, serum based markers - A number of protein biomarkers have been analyzed in serum to detect cervical cancer, among them the SCC antigen, IGF2 and VEGF-C and CYFRA 21.1. None of these markers has shown a clinical utility superior to the analysis of directly sampled exfoliated cells so far.

Markers Analyzed in the HPV-Pathogen Iss Study

13 markers were selected from different sources, mainly including genes known to be involved in the carcinogenesis of other tumor entities. Several markers have been analyzed in retrospective, cross-sectional and prospective analyses, including ERK1, Survivin, VEGF-C, 67kd-laminin receptor, nucleoside diphosphate kinase nm23-h1, MMP2 and TIMP-2, E-cadherin and NF-kappa-B. Two very promising marker candidates in this series are Survivin and VEGF-C. Survivin is involved in both cell cycle and apoptosis regulation. It was also found to be an early marker of cervical carcinogenesis. VEGF overexpression was found to be an early marker of CIN and correlated linearly with lesion grade.

HPV E6/E7 mRNA

High-risk HPV E6 and E7 proteins immortalize and malignantly transform infected cells. It acts by inhibiting two host anti-cancer proteins p53 and pRB. HPV E6/E7 mRNA expression is found in virtually all HPV positive cancer cases. Positivity rate increases with the severity of disease on cytology and histology. Optimal cutoff value of more than or equal to 567 copies/ml was determined using ROC.

ProEx C, PreTect HPV-Proofer and APTIMA E6/E7 mRNA. When done as trial in HPV positive cases resulted in reduced colposcopy referrals. It has no role in primary screening. I t has lower sensitivity than HPV but higher specificity, so not useful as a stand-alone test (can miss CIN 2+). It has stronger correlation with cervical disease than detection of HPV DNA alone

Serum antibodies to HPV16 proteins

Slot Blot Assay is done to detect serum Ab against E4, E7 and VLP-L1 antigens. Seropositivity to 1, 2 or 3 antigens showed associations of increasing magnitude with cervical cancer-OR 2.6, 19.9 and 58.5 respectively. Best clinical performance to discriminate cervical cancer from CIN 2, 3 was the combination of anti-E4 and/or Anti E7 antibodies, which displayed high sensitivity (93.3%) and moderate specificity (64.1%).

p16INK4a	Ki-67
Surrogate marker of HPV E7 mediated pRB catabolism, s/o transformation of the cervical mucosa	Proliferation marker confined to the parabasal cell layer of normal stratified squamous mucosa
On IHC, diffuse staining for p16INK4a is present in CIN 2, CIN 3, SCC and endocervical glandular neoplasia	On IHC, Ki-67 expression in the stratified squamous epithelium in CIN lesions correlates with the extent of disordered maturation
Rarely directed in benign lesions or CIN 1 lesions caused by Low risk HPV types	Cannot discriminate HPV mediated dysplasia from proliferating cells in benign reactive processes.

Dual staining – p16/Ki-67

Positivity increases with histologic severity: 26.8% in normal histology, 46.5% in CIN1, 82.8% in CIN2, 92.8% in CIN3 (77.8% for women <30 years without HPV 16, 100% for women ≥ 30 years with HPV 16). It is ideal for detecting pre-cancers with the highest risk of progression to cancer. It has the potential to reduce referral to colposcopy and biopsy. It can be an important component of new HPV-based screening as HPV has high sensitivity and NPV while dual-stain can help to decide which screen-positives need treatment.

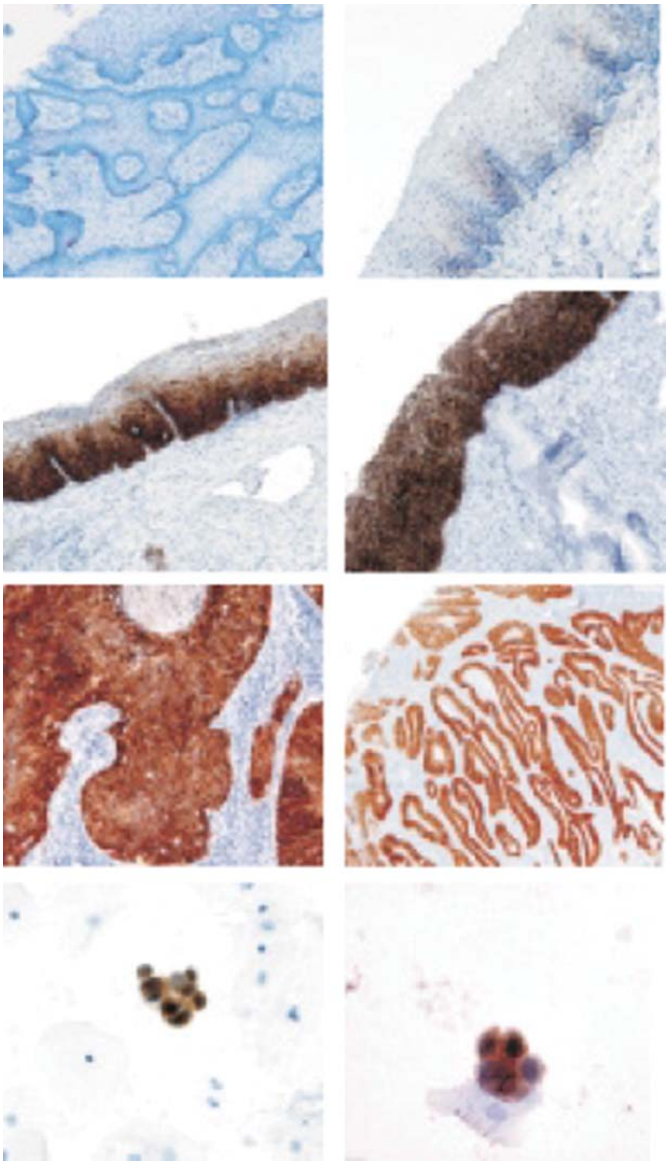


Fig 2. p16^{INK4a} staining of HPV positive specimens

Dual staining vs Pap & HPV

In a multicentric study with more than 27000 women, it was found that dual-stained cytology was more sensitive than Pap at all ages, (86% vs 68%) with comparable specificity (95% in both cases). It was found that HPV was more sensitive than dual- stained cytology in women over 30 (93% vs 84%), less specific (93% vs 96%). Thus potential role of dual-staining cytology in screening younger women where HPV testing has its limitation.

MCM2 & TOP2A

Both expressed in cells with aberrant S phases and HPV transformed cells along with HPV E6/E7 proteins. ProEx assay (Becton-Dickinson) is based on an antibody cocktail recognising both MCM2 & TOP2A proteins. On comparison with P16^{INK4a} testing, the BD ProExC panel had higher sensitivity for detecting LSIL but less specificity for HSIL. It has potential use for triage of HR-HPV positive women to increase specificity (98.3% vs 85.0%) and PPV (41.7% VS 9.3%) compared to HR-HPV test alone.

TERT & TERC Gene

E6 proteins promote the transcription of Telomerase Reverse Transcriptase (TERT) which stabilizes and repairs repeated DNA sequences at the telomere end of chromosomes. Chromosome 5p contains the TERT gene and Chromosome 3q contains the TERC gene. Gain of these chromosomes detected by FISH is associated with CIN2+ in cervical tissue biopsies, with 97% specificity. Number of copies of TERT and TERC gene also serve as a useful marker for identification of progressing lesions.

Genetic Susceptibility

Aberrations of chromosomes 3,8,5,7,X and 18 may be early events in cervical carcinogenesis. TNF α (-238/-308) and TNFRII-VNTR (-322) polymorphisms are potential genetic biomarkers of susceptibility. Incidence of TNF α mutation is proportional to clinical progression. Loss of heterozygosity inactivates tumor-suppressor genes hence leading to high grade tumour. High frequency of loss of heterozygosity on chromosomes 2p, 3p21.2, 6p21.2, 17p13.1 and 18q21.2 is seen in women with cervical carcinoma

Micro-RNA

Altered expression of miRNAs occurs in many cancer types**.** Cellular and viral miRNAs act as markers for diagnosis. Onco HPV induce aberrant expression of 13 cellular miRNA. The elevated expression of miR-16, miR-25, miR-92a and miR-378 and the decreased expression of miR-22, miR-27a, miR-29a and miR-100 were attributed to oncoprotein E6/E7.

Epidermal Growth Factor Receptor

EGFR is a product of proto-oncogene c-erbB-1 (HER-1) which is located on human chromosome 7. Ligand binding with EGFR can increase proliferation of cells and accelerate malignant transformation. EGFR protein expression is minimum in chronic cervicitis and low grade CIN and it is maximum in Squamous Cell Carcinima. This suggests that high levels of EGFR protein expression may be involved in the progression of cervical cancer. The underlying mechanisms for overexpression are likely both gene amplification and increase in the number of gene copies.

EGFR

EGFR has dual significance. EGFR can be used in differential diagnosis of high grade and low grade CIN and early diagnosis of cervical cancer. It is biological indicator of the preliminary prognosis of cervical cancer. Anti-EGFR agents and chemotherapy with radiation is being considered as therapeutic strategy. GEFITINIB, an EGFR inhibitor has some effect on recurrent cervical cancers which are resistant to standard therapy.

DNA Methylation

DNA methylation is crucial in activating and silencing genes during normal development, its disruption contributes to carcinogenesis. A 10% decrease in methylation at IGF2 gene region was associated with a 2 fold risk of Squamous cell carcinoma and CIN. Methylation levels at the H19 DMR and PEG1/MEST were also associated with increased risk of Squamous cell carcinoma and CIN. The association is stronger for women over 30.

EPB41L3 methylation was the single best classifier of CIN 2/3 in HPV+ and HPV- patients with highest levels in Squamous cell carcinoma. Methylated biomarkers may be used in combination for triage of women with HR-HPV infection. In cervical cancer, aberrant methylation can be detected in cervical smears upto 7 years prior to diagnosis indicating promise as a biomarker.

Biomarkers in Cervicovaginal Fluid

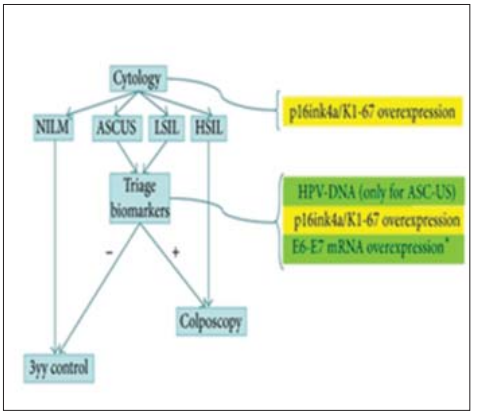
Several proteomes were detected in cervicovaginal fluid with at least 16 biomarkers which were unique to precancerous state. Alpha actinin-4 and pyruvate kinase isozyme M1/M2 in CVF shows promising results in detecting precancerous lesions. AA-4 discriminated samples from healthy and both high-risk and low-risk HPV infected women were collected and the levels correlated with virus persistance and clearing, with a discriminatory value of 18 pg/ml.

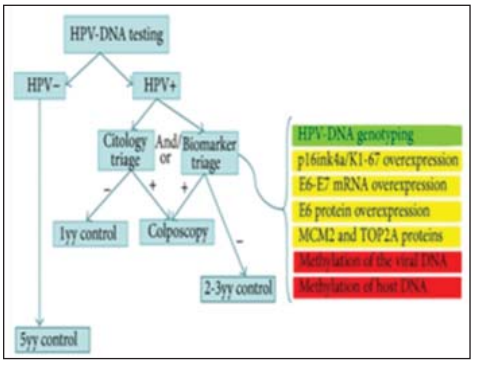
Panel Approach

Alpha-1-acid glycoprotein 1, Alpha-1-antitrypsin, serotransferrin, haptoglobin, alpha-2-HS glycoprotein and vitamin D binding protein**.** This panel of six proteins showed 67% sensitivity and 88% specificity in discriminating patients of CIN from healthy controls.

Type of biomarker	Test format	Application	Quality of evidence/ regulatory approval	Manufacturers and test names
Viral markers				
Detection of carcinogenic HPV DNA (and HPV genotyping)	Signal amplification (e.g., Digene Hybrid Capture-2) Target genome amplification by PCR (e.g., Amplicor®, Linear Array®)	Primary screening Triage of equivocal cytology	Large population-based studies and randomized trials Many tests licensed for use in the USA and Europe, many in final regulatory stages	Qiagen: Digene hc2, caseHPV™, QIAensemble™† Roche: Amplicor®, Cobas® 4800†, Linear Array®‡ Cervista® HPV HR† CLART® HPV2† Autogenomics: Infinit® HR-HPV QUAD† BioRad: HR-HPV Dx PCR Innogenetics: InnoLiPA™‡ Multimetrix: Multiplex HPV Genotyping Kit† Greiner: Papillocheck® HPV-Screening† Abbott: RealTime HR HPV®† Not commercialized: GP 5+/6+ EIA†
Detection of E6/E7 mRNA	Nucleic acid sequence-based amplification Transcription-mediated amplification *In situ* hybridization	Adjunct to primary HPV-based screening Triage of equivocal or mildly abnormal cytology	Multiple clinical studies published Large population-based studies underway	GenProbe: Aptima® Norchip: PreTect® Proofer† BioMerieux: NucliSENS EasyQ® HPV† IncellDx: HPV OncoTect®‡
Detection of HPV protein	Immunostaining of histology and cytology slides (L1) ELISA (E6)	Adjunct to primary HPV-based screening Triage of equivocal or mildly abnormal cytology	Some clinical studies published	Cytoimmun: Cytoactiv® ArboreVita: AVantage™ HPV E6
Cellular markers				
$p16^{ink4a}$ (also with addition of Ki-67)	Immunostaining of histology and cytology slides ELISA	Primary screening Triage of equivocal or mildly abnormal cytology	Multiple clinical studies published Large population-based studies underway	mtm Laboratories: CINtec® and CINtec® PLUS
MCM2 and TOP2A	Immunostaining of histology and cytology slides	Primary screening Triage of equivocal or mildly abnormal cytology	Some clinical studies published	Becton Dickinson: ProEx™ C

Fig 3. Major classes of biomarkers being developed and validated for use in cervical cancer prevention research





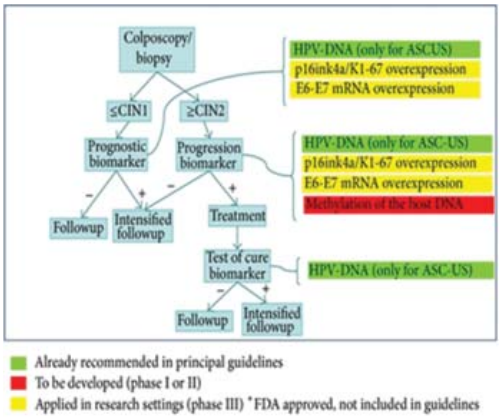


Fig 4. The future : Biomarker Triage

Summary

- The advantage of cellular markers like p16INK4a is the association with the transformation process independent of the underlying HPV type. This allows to analyse only a single marker.
- HPV based assays will always need to target several oncogenic types
- p16INK4a has shown excellent results in improving the reproducibility of cervical precancer histology diagnoses.
- Combined protocol using p16INK4a staining as a biomarker and nuclear assessment of p16INK4a positive cells might substantially improve the triage of unclear cytology results.
- p16INK4a ELISA format may offer a quick and simple assay that can determine the risk of underlying high grade disease independent of the observer's education and a skilful lab environment.
- SUCCEED study aims at collecting biological material from more than 1500 women with transient HPV infection, different grades of cervical dysplasia and cervical cancer and will allow for a thorough comparison of different candidate biomarkers at different steps in the progression to cervical cancer.
- Introduction of regular vaccination programs against the oncogenic high risk types HPV16 and HPV18 is expected to have an influence on the incidence in the long term
- It is assumed that these changes in disease prevalence and a possible shift towards more frequent infections by HPV types not targeted by vaccine might make cytology based screening more ineffective than it is now and will therefore increase the demand for new biomarkers

Diagnosing Cervical Intraepithelial Neoplasia: What is New? Pathologist Perspective

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Cervical carcinoma is a significant contributor to cancer-related morbidity and mortality worldwide. In India and many other developing countries, it is one of the most common causes of cancer in females. Lack of education and empowerment of women along with inadequate screening programmes for cervical cancer are partially responsible for the high burden. Carcinoma of the cervix is a preventable condition, efforts must be put into detecting and treating the pre-invasive lesion. Slow progression of the disease from a precancerous to invasive malignant lesion coupled with easy accessibility due to colposcopic evaluation and biopsy makes monitoring disease progression relatively easy and gives ample opportunity for early detection and considerably improved prognosis. It is one of the best examples of cancer that documents the remarkable effects of prevention, early diagnosis and curative therapy on the mortality rate.[1]

The ultimate aim of various modalities of diagnosis and treatment is to prevent the development of invasive cervical cancer. Significant advances have been made in elucidating the potential mechanisms of cellular transformation especially with reference to Human Papilloma Virus in both cytological and surgical specimens, however morphological assessment of surgical material remains the "gold standard" in the diagnosis of cervical intraepithelial neoplasia (CIN).[2] The best way for morphological evaluation is histopathology, which serves as a reference standard for diagnosing cervical intraepithelial neoplasia (CIN) and informs clinical management by identifying which women will be treated, followed, or returned to routine screening.

Cervical cancer arises from the metaplastic epithelium of the Transformation Zone (TZ) (squamo-columnar junction) and develops slowly through progressive

dysplastic changes to Carcinoma In Situ (CIS) and invasive cancer. A diagnosis of CIN is primarily based on the presence of atypical nuclear changes along with loss of normal squamous maturation (polarity). CIN is divided into three stages according to the degree of epithelial dysplasia and differentiation. The main interpretive categories include distinguishing normal from dysplasia (CIN) of any grade and low-grade (CIN1) lesions from high-grade (CIN2/3) lesions. The majority of low grade precursor lesions regress spontaneously without treatment. Only a small part of them progress to high grade lesions and eventually invasive cancer. Management of CIN is often based on punch biopsy which is used primarily to confirm the diagnosis of a high grade abnormality, thereby reducing the number of unnecessary treatments and the associated morbidity. Biopsy also plays a role in the management of women undergoing ablative treatment for CIN because pre-treatment biopsies are required to exclude invasive disease.[1] Significant variability in cervical diagnoses, has been noted, especially for CIN2, the threshold for excisional treatment. Errors in histologic diagnosis lead to either overtreatment of patients who will not benefit from intervention or, conversely, under- treatment of patients with clinically significant high-grade lesions that received false negative diagnoses.[3]

Although morphological assessment of surgical material remains the "gold standard" in the diagnosis of CIN, inter-observor variability in diagnosis is worrisome. This has fueled attempts at more objective, reproducible diagnostic parameters to accurately diagnose CIN. Diagnosis of CIN, can be tricky leading to discrepancy between pathologists in distinguishing them from its mimics. The use of alternative, more objective methods as an adjunct to histology often allows resolving uncertain cases.

Carcinogenesis is associated with molecular genetic damage to the cervix. Some of the products of this process can be used as prognostic and diagnostic markers of tumor progression. New biomarkers are needed to more accurately stratify precursor lesions according to their malignant potential, so appropriate treatment can be instilled. Research has been conducted to develop new biomarkers for cervical cancer screening as an adjunct to histopathology. Majority of the work has been related to human papilloma virus (HPV) detection because HPV is a recognized etiologic agent responsible for the initiation of cervical neoplasia.[4] Persistent HPV infection with high risk subtypes is known to be a risk factor for persistent and/or progressive cervical dysplasia.[5] It has also been proposed that HPV DNA integration into host DNA is critical in cervical carcinogenesis through disruption of the E1/ E2 open reading frames of HPV genome and subsequent loss of the E2-controlled regulation of E6 and E7, the viral oncogenes of HPV, resulting in loss of the normal maturation sequence, representing persistent, proliferative HPV infection. This cellular immortalization presumably results in the transformation into high-grade dysplasia (CIN 2 and 3), with a potential to progress to invasive carcinoma. more advanced techniques, including HPV genotyping, will be used to identify and triage those women most likely to harbor a clinically significant cervical lesion. However, mere identification of the presence of HPV infection may not be sufficient, assays for HPV viral load and mRNA detection may be useful in both the triage of abnormal cervical cytology, and detecting persistent infection, which is associated with an increased risk for disease progression.[3]

Diagnostic interpretation of dysplasia in the cervix typically includes analysis of hypercellularity, significant atypia, mitotic figures and disorientation from the parabasal to upper layers . However, unusual histological features, including mildly increased cellularity, the absence of mitotic figures and questionable atypia, may be observed in the lesion which becomes a source of diagnostic ambiguity and inter-observer variation. This lack of reproducibility and the fact that there are many benign changes that can mimic dysplasia of the cervical epithelium have led to significant efforts to identify a surrogate marker for high-grade CIN.

Immunohistochemistry(IHC) serves as a useful adjunct to histopathology where immunostaining by antibodies against cell cycle–related antigens has also been used to support the interpretation of cervical biopsy specimens. Immunostaining improves diagnostic reproducibility as well as diagnostic accuracy of the CIN lesions. Cellular markers with promising potential are varied and can be categorized into different classes such as, cell cycle check points, tumor suppressor gene expression, apoptotic markers, angiogenetic parameters.etc. The usefulness of the markers and their clinical implications in cervical screening are being studied. Amongst those analyzed are IHC markers of cell proliferation for CIN. Ki67 and MIB-1 are markers of proliferation and they are strongly expressed in CIN lesions, they can be used as an ancillary method for the diagnosis of squamous intraepithelial lesion (SIL) versus atrophic change and atypical squamous metaplasia. Ki-67, a proliferation marker, is elevated in HPV-infected mature squamous epithelia and is useful for confirmation of the diagnosis in equivocal low-grade SIL.[6] Expressed normally in the parabasal cells of mature squamous epithelium,

qualitative evaluation of Ki-67 cells involving the upper two-third of the epithelium has been reported to have improved specificity in detecting CIN. It is extremely helpful in distinguishing between cervical atrophy and high-grade dysplasia. Although being a sensitive marker of cervical neoplasia, the increased proliferation seen on Ki-67 must be interpreted with caution while examining reactive, inflammatory lesions.[2]

The inhibition of cell cycle regulatory proteins by E6 and E7 is known to initiate the carcinogenesis process. The p16 is a cell cycle regulatory protein which is the main target of HPV. The value of p16IN^{INK4a} as a marker of High Risk-HPVs and CIN has been well established in recent years, with studies showing increased immunoexpression of p16^{INK4a} in neoplastic cervical epithelial cells and a positive correlation with HR HPV infection and the degree of cervical neoplasia. In biopsies of suspicious cervical lesions p16 is used to discriminate the low grade lesions with potential to progress to high-grade lesions, p16 could help to recognize underestimated CIN. More recently the ProExC immunostain, has been a useful adjunct to confirm a diagnosis of high-grade squamous intraepithelial lesion (HSIL) and to distinguish it from its mimics. ProExC is a valuable marker for distinguishing dysplastic squamous and endocervical lesions of the cervix from squamous metaplasia. ProExC may eventually be used in conjunction with morphology and human papillomavirus evaluation for better classification of indeterminate cervical lesions in Papanicolaou smears.[7,8] Other markers of relevance are p53 and CD34. P53 plays an important role in the progression of the severity of intraepithelial cervical lesions. Thus, testing this marker in dysplastic cervical lesions might improve the accuracy, precision and sensitivity of cervical lesions diagnosis. CD 34 is used to assess Mean Vascular Density (MVD) in the lesions, it is sequentially increased from LSIL through HSIL, and then into invasive carcinoma and is considered an ancillary marker for the risk of malignant transformation of cervical intraepithelial lesion. Immunohistochemistry plays a useful adjunct to histopathological evaluation in reducing inter-observer variation.

Besides this, assessing various oncogenes may also be useful, like MYC oncogene which is frequently amplified and over expressed in cervical neoplasia, demonstrated by PCR. More so, the utility of other genes like p53 and pRb are also being explored. DNA methylation changes are an early event in carcinogenesis and are often present in the precursor lesions of various cancers. Such changes might therefore be used as markers of cervical neoplasia, either alone or in conjunction with cytology and/or HPV testing. Possibilities of their clinical significance are still to be realized and their clinical utility is still under investigation. [9] HPV infection may lead to DNA hypermethylation, disruption of the normal cell cycle and chromosomal aberrations, all of which may lead to changes in DNA content. Studies using DNA-cytometry of Feulgen- stained cytology material to assess ploidy have demonstrated significant differences in aneuploidy between HSILs and LSILs.[3] DNA image cytometry has become increasingly standardized and represents an objective and highly reproducible diagnostic procedure.[3]

Fluorescent in situ hybridization (FISH) technology has increasingly been recognized as a valuable tool to evaluate cervical dysplasia.[10] Studies have demonstrated that one of the most consistent chromosomal abnormalities identified in cervical carcinoma is gain of chromosome arm 3q, which is detected in approximately 70% of cervical carcinoma Patients with HSIL or squamous cell carcinoma cytologic diagnoses had significantly higher percentages of cells with 3q26 gain. FISH scoring system can detect gain of 3q and FISH analysis for 3q appears to hold more promise as a useful biomarker and may have the potential to provide valuable information in the identification of disease, risk of disease progression, and clinical management of patients.New technologies are actively being pursued in addition to histopathology for rapid, specific, sensitive, and cost-effective methods, especially to enable HPV detection and genotype identification in a proper clinical setting, also to determine any molecular marker that could predict its persistence or clearance. It will be useful if a clinical test could identify which women are at increased risk for developing cervical cancer in the future, prior to the development of SIL/CIN.

Take Home Message

1. Morphological assessment of surgical material is the "gold standard" in the diagnosis of CIN.
2. Significant inter-observer variation in the diagnosis of CIN still exists.
3. Potential benign mimics of high- grade cervical dysplasia (CIN 2 and 3) include basal-cell hyperplasia, immature squamous metaplasia, reactive/ inflammatory lesions and squamous atrophy are often a source of diagnostic dilemmas.
4. Immunohistochemistry(IHC) serves as a useful adjunct to histopathology where immunostaining by antibodies against cell cycle–related antigens improves diagnostic reproducibility as well as diagnostic accuracy of the CIN lesions.

5. New technologies are actively being pursued in addition to histopathology for rapid, specific, sensitive, and cost-effective methods, in a proper clinical setting to determine molecular markers and identify at risk population.

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View Point: Molecular HPV Detection Methodologies

Dr Dinesh Gupta

"HPV Knowledge Centre", Cure Health Diagnostics Reference Laboratory, New Delhi

One, the persistent infection with high risk HPV (hr-HPV) as a necessary, yet insufficient cause for cervical cancer development and two, that this cancer by and large, develops over a prolonged period of time, are perhaps the two key factors that deter its commensurate clinical use in India, given the propensity of this disease and less than a quarter of a government sector healthcare GDP contribution. The scenario is further complexed by the cervical precursor lesions, pathologically identified as the high grade CIN (or HSIL), which are more often not clearly and frequently detected at the traditional cytomorphological correlation [1].

Hence molecular HPV detection methodologies have expectedly been seen as playing a significant role in the largely lifetime unscreened or minimally once-in-a-while 'spot screened' handful of population. Ideally, a high specificity HPV test, rather than a high sensitivity HPV test should have made its first mark in India as a reliable stand-alone diagnostic approach to determine the risk of HG CIN. But it so happens that we have had a more sensitive HPV test in the clinical domain developed first rather than the more specific one! Due to the higher prevalence of HPV infection among younger women, a higher sensitivity on HPV test does lead to a higher false positive disease rate among a screening population.

To a common practicing clinician who is not generally familiar with the principles and technologies of different HPV methodologies, how does a particular test result correlate on a sensitivity parameter with a disease prevalence and how it impacts clinical interpretations for a given patient, adds another grey area to the extended benefits of HPV testing in the routine clinical setting. One would have expected a country-specific clinical practice guideline to have dwelled upon some of these technological areas to have concisely guided the large number of clinical practitioners in scientifically resolving such diagnostic dilemma around cervical cancer screening and clinical disease detection strategies. After all, India boasts of having reaped the benefits of nearly a decade of epidemiological research data base to evolving in to a country-specific objective clinical practice.

Since majority of CIN lesions regress naturally, the challenge of cervical cancer screening and diagnostics is the accuracy with which we are able to detect them using a test that has a high specificity for HG CIN that is disposed for aggressive progression than the one that may naturally regress[2,3]. But the low specificity of many HPV tests sets in significant sensitivity variability in the clinical diagnosis of high grade cervical lesions[4]. The clinical practice guidelines thus aim at improving the specificity for detecting the high-grade precursor disease by resolving diagnostic disparities through the cascading pathways and utilising the knowledge of HPV biomarkers. This is too intricate to follow in

the absence of an organized screening program and non-existent recall system, and also expensive for the disease management program in largely the private sector dominated healthcare pattern in India particularly. Most spot-screening camps on the handful of population in the Indian context also result into a very poor follow-up compliance thereby decimating the comprehensive gains of such programs towards reducing the effective disease burden.

Current Methodologies

The HPV molecular methodologies broadly fall under three categories.

- Cell or tissue in situ probe hybridization tests
- Signal amplification tests
- Target amplification test which largely co-exist in the research to clinical domains.
- Nucleic acid sequencing technology: Lately it has emerged as a powerful methodology but data and results interpretations are restricted to the academic interest or for research use only (RUO).

The objective however, of any of the molecular methodologies has been to guide most appropriate clinical diagnoses and management of precancer disease by a colposcopy and/or directed histopathology confirmation prior to arriving at a decision-to-treat high grade CIN.

The target (single-strand) ssDNA: probe RNA hybridisation and signal amplification test such as the digene hc2 has been considered as a robust one; and validated over the largest cross-sectional population in most countries including India since 1999. It stands out as very dependable test for routine clinical use due to its high sensitivity and high negative predictive value (NPV). But it also suffers from poor specificity and low positive predictive value (PPV). High sensitivity results in to far too many false positives of non-clinical cases in the screening set up. The high sensitivity with hc2 is actually a boon in the screening paradigm as it detects more latent infection than many other tests but it also leads to far too many referrals for colposcopy at the same time[5]. Though colposcopy was once imagined for applying in the primary screen set up due to low cost (and not the patient charges, per se), it is impractical to deploy it owing to its subjectivity. Also, the resultant psychological agony that may be quite serious for a particular patient should the colposcopy and/or directed histopathology findings not conform to subclinical disease detection. The colposcopic grading system alone cannot accurately assess severity of lesions, making it an insufficient and unreliable option for precision diagnosis. A few workers also suggested taking two or more cervical biopsies from the TZ area of the cervix in order to improvise the specificity of the colposcopy[6,7]. However, lesions with other oncogenic types than 16 and/or 18 may still be missed out because they do not always cause as distinct acetowhite areas on VIA test as well as miss at colposcopy.

The Other HPV realtime PCR systems

It is largely believed that the home-brewed realtime PCR tests as well as the bulk of non- or poorly validated, commercially available realtime PCR tests should exclude the clinical use owing to the fact that they tend to produce inconsistent and hence totally unreliable patient reports, even though they appear to be less expensive. These tests suffer from variability of reagent quality from batch to batch, poor adherence to quality control (despite the use of procedural internal control any realtime PCR test include) and obligatory tissue destruction step to release target nucleic acids for amplification that grossly limit the assay specificity which is especially important when dealing with an omnipresent oncogenic and sexually transmitted virus like HPV. More critically, these tests are also not validated by significant numbers of population under a referenced study. They thus lack the ability to differentiate cases associated with high risk of CIN development from those that are reversible due to their benign conditions. The routine clinical practice must therefore clearly discourage such molecular HPV tests for patient care and management protocols.

Take-Home Message

In this molecular era of disease detection, it is strongly suggested that the *gynecological oncologists must consciously understand through their pathologists the HPV Test being deployed by them for primary screening in order to correctly predict potential long-term benefits of HPV testing especially those who need closer monitoring and follow-up*. There is of course a need for a more specific HPV Test in the routine use to predict disease prognosis than the currently available HPV DNA tests.

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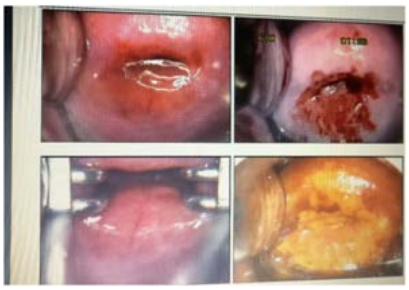
Case Report

Dr Bharati Abhyankar
Purva Hospital, Kolhapur, Maharashtra

35 year old, P2 L2 female presented to gynae OPD with profuse vaginal bleeding during the present menstrual cycle. There was no past history of menorrhagia, pain lower abdomen or postcoital bleeding or vaginal discharge. She was given progesterone to control this episode of bleeding. Patient came for second opinion and wanted all possible test so investigations done are as follows

Investigations:

- Pelvic ultrasound: Normal.
- PAP Smear: Negative for intraepithelial malignancy
- Colposcopy:
  - Squamocolumnar junction visible
  - Transformation zone Type 1
  - Mature squamous epithelium
  - Ectopy present
  - No Aceto-White lesion present.
  - Only one prominent vessel seen at 6 o'clock.
- ECC Was normal.
- HPV DNA test: High risk type positive.

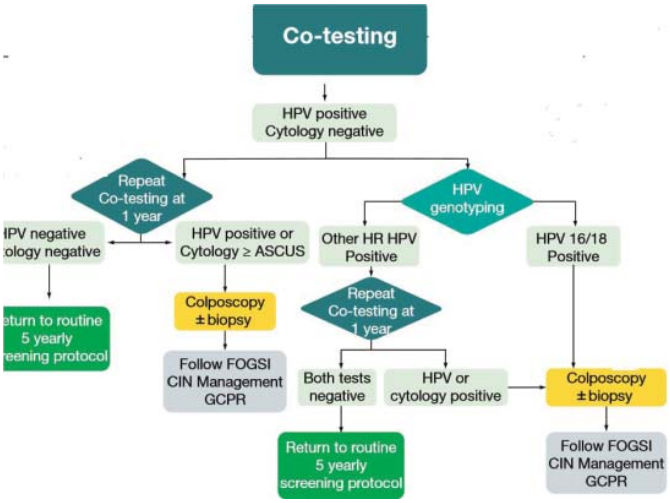


Treatment: Follow up after one year.

Editor's Comment

It is very tricky to handle anxious patients in today's era with patients coming with enormous information available from internet especially in a private practice.

One should do the counselling and individualize the treatment as per guidelines as far as possible according to circumstances. I am just putting the flow chart (taken from FOGSI guidelines) for the females (more than 30 years) with normal pap smear and positive HPV DNA testing on screening only with reference to above patient's findings (without discussing the management guidelines for her single episode of heavy bleeding).



Information

ISCCP Colposcopy Training Centres

Training period : 1 month

Currently 4 centres for ISCCP training- Safdarjung Hospital, New Delhi, Maulana Azad Medical College, New Delhi, PSG Coimbatore & Jaipur

Journal Scan

Dr Deepti Goswami
Director Professor, Department of Obstetrics & Gynaecology, Maulana Azad Medical College, New Delhi

J Low Genit Tract Dis. 2017 Apr; 21(2):112-119. doi: 10.1097/LGT.0000000000000306. PubMed PMID: 28263237; PubMed Central PMCID: PMC5365351.

International Image Concordance Study to Compare a Point-of-Care Tampon Colposcope With a Standard-of-Care Colposcope.

Mueller JL, Asma E, Lam CT, Krieger MS, Gallagher JE, Erkanli A, Hariprasad R, Malliga JS, Muasher LC, Mchome B, Oneko O, Taylor P, Venegas G, Wanyoro A, Mehrotra R, Schmitt JW, Ramanujam N.

The authors have developed a low-cost, intravaginal, optical cervical imaging device, the point-of-care tampon (POCkeT) colposcope. They have presented their findings regarding its performance vis a vis standard-of-care colposcope in this article.

There were 2 protocols of this study. The first protocol included 44 women. White-light cervical images were collected from them blinded by device. These images were evaluated by 8 physicians from high, middle, and low-income countries.

For the second protocol, green-light images were also collected and evaluated by the highest performing physician from the first protocol who has experience in both a high- and low-income country. For each image, physicians assessed cervix characteristics and severity of precancerous lesions. Corresponding pathology was obtained for all image pairs.

Results

- For the first protocol, average percent agreement between devices was 70% across all physicians.
- The POCkeT and standard-of-care colposcope images had 37% and 51% agreement with pathology for high-grade squamous intraepithelial lesions (HSILs), respectively.
- HSIL POCkeT images had decreased visibility of vascularization and lack of contrast in lesion margins. After changes were made for the second protocol, the 2 devices achieved similar agreement to pathology for HSIL lesions (55%).

The authors concluded that, physician interpretation of cervix images acquired with POCkeT colposcope was comparable to a standard-of-care colposcope.

BJOG. 2018 Jun 12. doi: 10.1111/1471-0528.15326. PubMed PMID: 29893472.

Portable Pocket colposcopy performs comparably to standard-of-care clinical colposcopy using acetic acid and Lugol's iodine as contrast mediators - An investigational study in Perú

Mueller JL, Lam CT, Dahl D, Asiedu MN, Krieger MS, Bellido-Fuentes Y, Kellish M, Peters J, Erkanli A, Ortiz EJ, Muasher LC, Taylor PT, Schmitt JW, Venegas G, Ramanujam N.

This was another study by the same team to evaluate the performance of the low-cost, portable Pocket colposcope that they have developed. The overall objective being to develop a tele- colposcopy platform for primary care clinics.

The study involved 200 Peruvian women who had abnormal cytology and/or showed HPV positivity.

Cervical images were captured with the standard of care colposcope and this Pocket colposcope using acetic acid and Lugol's iodine. Biopsies were taken as per the existing protocols.

Images from 129 patients were sent to four physicians for evaluation and diagnosis.

Results

- Physician interpretation of images from the two colposcopes agreed 83.1% of the time.
- The average sensitivity and specificity of physician interpretation compared to pathology was similar for the Pocket (sensitivity = 71.2%, specificity = 57.5%) and standard-of-care colposcopes (sensitivity = 79.8%, specificity = 56.6%).
- Use of Lugol's iodine as a secondary contrast agent improved the percent agreement between colposcopes (8.9%) and the sensitivity and specificity of physician interpretation (6.0% and 9.0%, respectively).

The authors concluded that the Pocket colposcope performed similarly to a standard-of-care colposcope to identify pre-cancerous and cancerous lesions of the cervix in the population studied.

Further reading

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Cervical Cancer News From Around The World

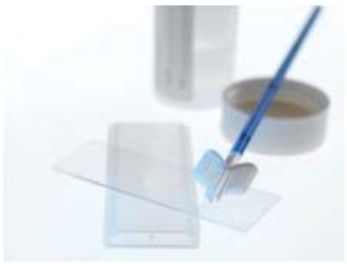
Dr Roopa Hariprasad
Scientist D, IEMR-NICPR

Everything you need to know about new cervical screening

The New Daily: 4:30pm, May 25, 2018

HPV test was officially introduced for primary screening of cervical cancer in Australia in December 2017, and revolutionizes testing for cervical cancer. Royal Australian and New Zealand College of Obstetricians and Gynaecologists' spokesperson Dr Charlotte Elder said the new test screened for the human papillomavirus (HPV).

By contrast, Pap smears had looked only for changes to cervix cells. HPV is a common sexually-transmitted infection that affects up to 80 per cent of people at some time in their lives.



The new test is considered a bit improvement on Pap smears. *Photo: Getty*

To read more: click on the link: https://thenewdaily.com.au/life/wellbeing/2018/05/25/new-cervical-screening-test/

Australia could become first country to eradicate cervical cancer

The Guardian 3rd March 2018

Free vaccine program in schools leads to big drop in rates, although they remain high in the developing world. Australia could become the first country to eradicate cervical cancer, according to an announcement from the International Papillomavirus Society. New research, published on Sunday, reveals that Australia's free HPV vaccine program in schools has led to a dramatic decline in future cervical cancer rates.

Within 40 years, the number of new cases is projected to drop to "just a few", professor Suzanne Garland from the Royal Women's Hospital, who led the research, said.

To read more: click on the link: https://www.theguardian.com/society/2018/mar/04/australia-could-become-first-country-to-eradicate-cervical-cancer

Expert: vaccination can end cervical cancer within 20 years

The Irish Times Thu, May 24, 2018, 01:00

Prof Ian Frazer, a co-creator of the HPV vaccine, says it protects against nine strains of virus which are together responsible for more than 95 per cent of cervical cancers.

In Australia, where the vaccine Gardasil was developed and where a HPV vaccination programme has been in place since 2007, scientists predict there will be no new cervical cancers by 2028 in women who have been immunised.

He will also be the keynote speaker when the college marks eight years of the vaccine's use in Ireland at a conference on the practical aspects of Gardasil and the implications of the cervical cancer screening controversy.

To read more: click on the link: https://www.irishtimes.com/news/health/expert-vaccination-can-end-cervical-cancer-within-20-years-1.3505911

Vaginal bacteria may have a role in cervical cancer

Newsletter Medical News Today, Wednesday 6 June 2018

The composition of bacteria in the vagina could be an important factor in the development of cervical cancer, according to a recent study.

How are vaginal bacteria and cervical cancer linked?

Infection with some particular strains of human papillomavirus (HPV) is a well-known risk for cervical cancer. However, researchers at the University of Arizona in Phoenix suggest that other factors may also be relevant because of their influence on the condition of the cervix. An article (https://www.nature.com/articles/s41598-018-25879-7) now published in the journal *Scientific Reports* describes how they found that women with cancer or precancer of the cervix had different vaginal bacteria to women who did not have cervical tissue abnormalities.

To read more: click on the link: https://www.nature.com/articles/s41598-018-25879-7

ISCCP Activities

Professor Nisha Singh
Department of Obstetrics and Gynaecology, King George's Medical University, Lucknow

Prof Aruna Nigam organized CME on **'OVERVIEW OF CERVICAL LESIONS AND MANAGEMENT GUIDELINES'** on 10th APRIL, 2018 at Hamdard Convention Centre, Jamia Hamdard, attended by approximately 250 delegates apart from the invited faculty and organizing committee (50 in number).

Dr Mala Srivastava orgnized a CME on Screening and Prevention of Cervical Cancer was organised at Sir Ganga Ram Hospital on 27/3/18, under the aegis of Cervical Cancer Awareness and Prevention Sub-committee of AOGD, ISOPARB, ISCCP, IMS-Delhi Chapter. About 64 delegates participated in the CME.

Dr Bharati Abhyankar conducted one awareness programme. The eminent, popular personalities SindhutaiSakpal and Dr. Nishigandha wad were present for the programme. About four hundred ladies, from all levels of society attended the programme.

Dr Leela Digumarti

- Cervical and breast cancer screening camp was conducted in Malkapuram, a suburb of Visakhapatnam, on 21st April 2018.
- An awareness talk on breast and cervical cancer was given on 30th April 2018 at the Visakhapatnam Steel Plant under "*Ayushmaan Bharath*".
- Cervical and breast screening camp was conducted on 19th May 2018 at Vijayanagaram, 60 kms from Visakhapatnam.

Guidelines for Authors

All members of ISCCP are requested to send manuscripts pertaining to (but not exclusively limited to) to cervical cancer prevention/ treatment for publication in the newsletter. The matter should be original and not published/under consideration for publication elsewhere.

This could be in one of following forms:

1. **Original Article:** Articles from original research (including aim, methods, results and discussion), should not exceed 5-6 typed pages, word limit of 1500 words and not more than 10 references. Tables and Figures could be included as per requirement.
2. **Review Article:** The article should not exceed 3-4 typed pages, word limit 2500 words with not more than 8 references.
3. **Case Report:** An interesting case report which has "take home message", word limit 800 words with not more than 3-5 references. Image should be sent separately in JPEG format
4. **Report of conferences/ CME? awareness/training camps:** up to 300 words with 2-3 images

References: References should be recent, relevant, indexed and in Vancouver style. References to literature cited should be numbered consecutively and placed at the end of the manuscript. In the text they should be indicated as superscript. All papers submitted are subject to review process. All accepted papers will be suitably edited before publication.

Submit to: Dr Aruna Nigam, praksharuna@hotmail.com