ORIGINAL ARTICLE

An institution-based cervical PAP smear study, correlation with clinical findings & histopathology in the Konkan region of Maharashtra state, India

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Abstract:

Background:

Cervical carcinoma is a common cause of death in India. It is presented by spectrum of precancerous lesions, called cervical intra-epithelial neoplasia (CIN). Cervical cytological screening is designed to detect over 90% of cytological abnormalities. It has been established that cervical cancers can be diagnosed at the pre-invasive stage with adequate, repetitive cytological screening. Keeping in view of the importance of cervical PAP abnormalities & by classifying them by Bethesda terminology; correlation with clinical findings & histopathological findings was done.

Methods:

All cervical Pap smears reported in Department of Pathology from 1st August 2015 to 31st July 2016**,** were prospectively studied and classified according to revised Bethesda terminology, 2014. Also cyto-radiological and clinico-cytological, cyto-histological correlation was studied.

Results:

Due to increasing awareness among masses inculcated by social workers, most of the patients for PAP smear cytology came for routine screening to rule out cervical lesions followed by clinical finding of per-vaginal discharge. The 350 screened patients were in the third and fourth decades of life. 99/350 cases were subjected to USG study, with maximum number of cases (34 cases) showing normal study, followed by cases with ovarian cysts and fatty liver disease. Negative for intra-epithelial lesion (NILM) without any denotable organism was the pre-dominant cytological finding of PAP smear study

followed by cases of NILM with bacterial vaginosis (30 cases) with two malignancies. Intra-epithelial lesions (IELs) were noted in 16.86%. ASCUS comprised 12.29%, ASC-H comprised 1.14%, L-SIL comprised 1.71%, H-SIL comprised 1.43%, Atrophic cervical smears comprised 5.14%, Squamous cell carcinoma comprised 0.29% cases. ASC/L-SIL ratio was 7.8 and inadequacy rate for PAP smear study was 7.43%. Cytology-histopathology correlation was possible in 62 cases.

Conclusion:

Classification of cervical PAP smear cytology based on Bethesda terminology revealed it is a useful cost effective, screening tool for cervical lesions. Correlation of PAP smear cytology with 'gold standard' histological reports reveal excellent diagnostic parameters, implying the greater efficacy of cervical PAP smears.

Keywords: PAP-smear, NILM, ASC-US, ASC-H, L-SIL, H-SIL

Introduction:

The Papanicolou screen ("PAP smear") was introduced to the world by Dr. George Papanicolaou for the identification of cervical lesions/cancers. Since becoming widely known after his publication in 1941 and wide acceptance in clinical practice in the 1950s; it is currently the most commonly performed cancer screening test world-wide.[1] This has been one of the most successful cancer screening techniques in medicine.[2,3]

PAP smear screening has been widely embraced by physicians and women alike, and is considered a critical part of the routine health care of women. However in the developing world without the complex resources required to process and read Pap specimens, screening remains a challenge.[4] Among women with cervical cancer in the U.S., at least 60% did not have appropriate Pap surveillance prior to their diagnoses.[5] It is also a common women cancer in Indian population. There is still no national program on cervical pathology, detection, prevention and treatment.

In the decades since the initial development of the Pap smear, our understanding of the pathophysiology of cervical cancer has evolved considerably. The occurrence of premalignant cervical lesions, now referred to as cervical dysplasia (CIN), was recognized as early at the 1940s.[6] During the 1970s and 1980s, the human Papilloma virus (HPV) was identified within cervical lesions.[7,8] As early as 1976, Dr. Harald zur Hausen and colleagues postulated a role for the HPV in cervical oncogenesis, and his subsequent work isolating oncogenic HPV

strains and elucidating the oncogenic process earned him the Nobel Prize in Medicine in 2008.[9-11]

The discoveries of premalignant cervical lesions and the role of HPV in cervical dysplasias and cancers have also enabled physicians to gradually refine the use of Pap smear screening. As a result, the number of women who need Pap smears, and the frequency at which they are recommended, has changed significantly over the last several years.[9-11]

Computer-Assisted interpretation of cervical cytology, HPV genetic testing are the new diagnostic ways of reporting cervical pathology especially in the developed world. HPV vaccination drive has reduced worldwide morbidity and mortality due to cervical lesions.[12-14]

Cervical cytology reporting has attained uniformity worldwide due to Bathesda classification,2014 of cervical PAP smears. [12-14] Faster diagnostics yields faster therapies. So treatment is initiated faster with help of Pap smears. We study a year old analysis of cervical PAP smear study in Konkan belt of Maharashtra state, India where our tertiary care is set-up.

Material and Methods: With approval of Ethics Committee and consent of patients, all cervical Pap smears reported in department of pathology from 1st August 2015 to 31st July 2016, were prospectively studied and classified according to revised Bethesda terminology, 2014. Also cyto –histological, cyto-radiological and clinico-cytological correlation was studied.

Inclusion criteria:

1. Patients of varied age group with abnormal cervical PAP smears/ abnormal cervical biopsy with gynecological complaints.

2. Symptomatic cases with normal cervix having abnormality either in Pap smear or in cervical biopsy.

Control population:

a. Clinically asymptomatic cases with normal cervix for routine screening.

b. Suspicious cervix with normal PAP smear or cervical biopsy reported.

Results:

Maximum patients in our study were in the third decade of life followed by patients in the fourth decade of life.

Maximum patients in our study had abnormal vaginal discharge (total 82 cases). 64 cases came for routine cervical PAP screening. This was followed by cases with uterine prolapse (54 cases).

Out of 99 cases subjected to USG study, maximum number of cases (34 cases) had normal study. This was followed by cases with simple ovarian cysts and fatty liver. Maximum number of cases was of NILM in our study (245 cases).

Maximum NILM cases without any denoted infective pathology (150 cases). This was followed by cases of NILM with bacterial vaginosis (30 cases). Overall, maximum of PAP smears had NILM diagnosis (75.14 % cases) on cervical PAP smears. Intra-epithelial lesions (IELs) – 16.86%. Atrophic cervical smears comprised 5.14% cases. Inadequacy rate for PAP smear study was 7.43%.

Among IELs, ASCUS comprised 12.29% of overall cases, ASC-H comprised 1.14%, L-SIL comprised 1.71%, H-SIL comprised 1.43%, Squamous cell carcinoma comprised 0.29% cases. ASC/L-SIL ratio was 7.8.

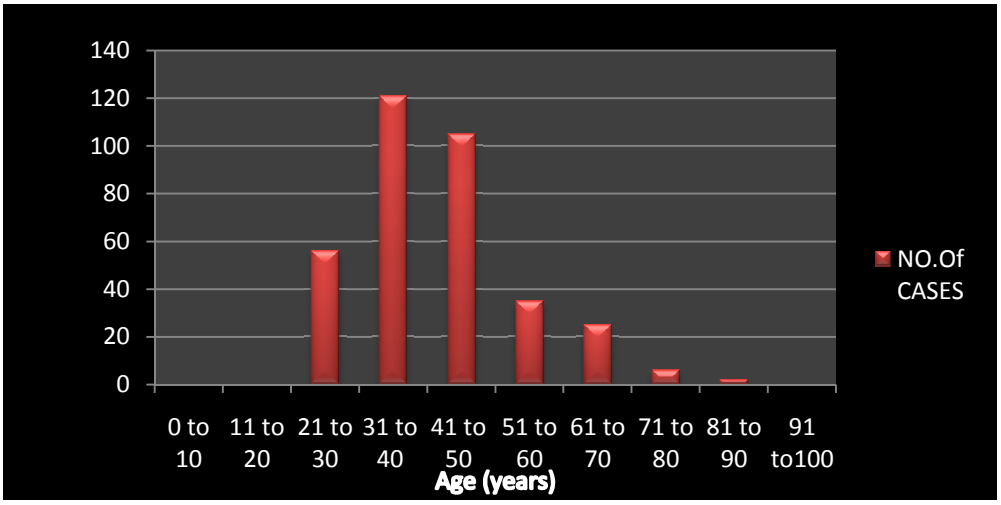
Cytology-histopathology correlation was possible in 62 cases. On correlation, sensitivity was 96.49%, specificity was 80%, positive predictive value (PPV) was 98.21%, negative predictive value (NPV) was 66.67%, and Diagnostic accuracy was 80%.

Discussion:

Age-wise distribution:

In our study, most of the patients were in parity 2 (58%). Rathod SB, et al (2015)[15] had 28.4% cases in parity 3 and 21.2% cases in parity 4. In our one year study, 350 cervical PAP smears were screened.

Graph 1: Age-wise distribution of our 350 cervical PAP smear cases



Graph 1 show that maximum patients in our study were in the third decade of life followed by patients in the fourth decade of life.

Table 1 shows the age-wise distribution of two comparative studies:

	Rathod GB,et al (2015)[15]	Our study
31-40 years	-	34.57%
41-50 years	42.4%	30%
51-60 years	21.2%	10%

Patient's complaints:

Maximum patients in our study had abnormal vaginal discharge (23.43% cases). 18.29% cases came for routine cervical PAP screening due to PAP smear screening camps at our set-up owing to increased mass awareness by social workers. This was followed by cases with uterine prolapse (15.43% cases).

USG abdomen and pelvis was done in 99 out of 350 cases. It revealed normal study in majority (37.37% cases), fatty liver associated with pregnancy (14.14% cases), simple ovarian cysts (11.11% cases), and uterine fibroids (9.9% cases).

Cervical PAP smear: Technical aspect :[10-14] Sampling must not be done during menses. Avoid vaginal contraceptives, vaginal medications for atleast 48 hours prior to taking the smears. Sexual abstinence should be about 24 hours. Post-partum smears should be taken only after 6-8 weeks of delivery.

Cusco's speculum is inserted to visualize and fix the cervix with patient in dorsal position and proper illumination. After cervical inspection, Ayre's spatula is inserted. It is inserted in a way that long end goes into cervical canal while smaller end of spatula rests on the ectocervix. Spatula is then rotated through 360 degrees maintaining contact with ectocervix. Do not use too much force to avoid hemorrhagic artifact on smeared slides. The sample should be 'evenly' spread and fixed immediately with cytofix spray fixative or 95% ethanol. Both sides of spatula should be smeared.

For endocervical sampling, use endocervical brush. Its cytobrush bristles should be visible in the endocervical canal. Rotate the brush through 180 degrees. Sample is rolled on slide, smeared and fixed as earlier quoted. If spray fixative is used, spray should be kept at 10 inches distance from the smeared slides to avoid cellular destruction by propellant in the spray. Smear should form a

monolayer for proper penetration of cell surface by fixative.

PAP smear-Sample adequacy:

An adequate cost-effective conventional cervical PAP smear should have minimum of approximately 8000-12000 well-visualized, well-preserved squamous epithelial cells. This applies to squamous cells while endocervical cells and cells obscured 'completely' with hemorrhage and inflammation are excluded from the estimate.[12-14]

Endometrial cells in exodus pattern are commonly seen after 40 years of age in cervical smears due to exfoliation. Nuclear features are important to know about the atypical features of these glandular cells.

The inadequacy in PAP smear reporting is chiefly because of sampling error, improper fixation, non co-operative patients.

Table 2 shows the comparison of inadequacy rate in PAP smear study:

Study by	Inadequacy rate
Rathore SB, et al (2013)[16]	7.4%
Kalyani R, et al (2016)[17]	17.8%
Our study	7.4%

Transformation zone (TZ) component:

Under the influence of estrogen, the original squamo-columnar junction moves onto the portio. The exposure of delicate columnar cells to vaginal environment creates squamous metaplasia. An adequate TZ component requires minimum of ten well-preserved endocervical/squmous metaplastic cells, singly or in clusters, having either honeycombing pattern of endocervical cells or spidery cytoplasm of squamous metaplastic cells. The TZ component in our study was seen in 70.3% of our cases. Exposure of cervical TZ to carcinogens, HPV begins the process of intra-epithelial neoplasia.[10]

Negative for intra-epithelial lesion or malignancy (NILM):

According to Bathesda 2001/2014 classification of cervical cytology, there is a category called NILM. [12-14] It includes non-specific inflammatory pathology and

infections due to organisms like trichomonas vaginalis (TV), Candida, bacterial vaginosis (BV), actinomycosis and HSV viral infection. Bacterial vaginosis produces Clue cells, Trichomonas vaginalis are pear-shaped organisms that prodice Cannol-ball squamous lesions, Candida produces Shish-kebab appearance while actinomyces bacteria produces Cotton-ball squamous lesions on cytology. Other non-neoplastic findings associated with NILM include post-menopausal atrophic smears, post-hysterectomy glandular cells, reactive changes associated with intra-uterine device, inflammation, radiation. In our study, out of 75.14% NILM cases, 5.14% cases were post-menopausal atrophic smears.

Table 3 shows comparative estimation of NILM cases by different studies:

Studies	Percent of NILM cases
Saha R, et al (2005)[18]	51.16%
Rathore SB, et al (2013)[16]	86%
Selhi PK, et al (2013)[19]	96.08%
Laxmi PV, et al (2016)[20]	67%
Kalyani R, et al (2016)[17]	96.92%
Our study	75.14%

After excluding the atrophic smears, the following table 4, shows the distribution of the NILM smears:

	Selhi PK, et al (2005)[19]	Our study
NILM with non-specific inflammation	90.9%	61.2%
NILM with Candida infection	2.8%	0.8%
NILM with trichomonas vaginalis (TV)	0.6%	7.35%
NILM with HSV	0.1%	-
NILM with bacterial vaginosis (BV)	-	12.24%
NILM with mixed infection: (TV+BV)	-	5.3%
Other mixed infections	-	3.67%
Increased lactobacilli	-	3.23%

NILM with specific infective etiology can vary from place to place. Most common infection was trichomonas parasitic infestation followed by bacterial vaginosis in our study. It was Candida infection by the above compared study.

Intra-epithelial lesions (IELs): It includes squamous and glandular cell abnormalities in PAP smear study.[12] Table 5 shows the comparative data on IELs by different studies:

Studies	Percent of IELs in study
Mehmetoglu HC, et al (2010)[21]	1.2%
Bal MS, et al (2012)[22]	5%
Kalyani R, et al (2016)[17]	3.08%
Selhi PK, et al (2013)[19]	2.04%
Rathore SB, et al (2013)[16]	6.6%
Our study	16.86%

Atypical squamous cells (ASC):

Among IELs comes a category called Atypical squamous cells (ASC) which refers to cytological changes suggestive of Squamous intra-epithelial lesions (SIL), which are quantitatively / qualitatively insufficient for a definitive definition. ASC have cells with squamous differentiation, high N:C ratio, minimal nuclear hyperchromasia, chromatin smudging, multi-nucleation at places.[12-14]

ASC is divided into two by Bathesda classification: Atypical squamous cells of undetermined significance **(ASC-US)** and Atypical squamous cells, cannot differentiate High-grade squamous intra-epithelial lesion **(ASC-H)**.[12-14]

According to Bathesda, 'ASC-US' term is preferred because 10-20% of these cases are proven to have CIN2/CIN3 on confirmatory cervical biopsy while the rest are proven to be cervical inflammatory pathology (cervicitis). ASC-US on cytology generally corresponds to diagnosis of Low-grade squamous intra-epithelial lesion (L-SIL) or SIL of indeterminate grade on cervical biopsy.[12-14]

Table 6 shows the comparative data on ASC-US lesions by different studies:

Studies	Percent of 'ASC-US' cases in study from overall PAP smear cases studied
Saha R, et al (2010)[18]	2.33%
Bal MS, et al (2012)[22]	0.3%
Kalyani R, et al (2016)[17]	1.46%
Selhi PK, et al (2013)[19]	1.6%
Rathore SB, et al (2013)[16]	4%
Our study	12.29%

ASC-US category was high in our study as per above table. Biopsy was possible in 18% of those cases. Biopsy revealed all these cases as chronic cervicitis without dysplasia / cervical intra-epithelial neoplasia (CIN).

ASC-H category includes small squames with high N:C ratio. These cells have the size of squmous metaplastic cells. They are also called atypical (immature) metaplastic lesions.(12)

Table 7 shows the comparative data on ASC-H lesions by different studies:

Studies	Percent of 'ASC-H' cases in study from overall PAP smear cases studied
Kalyani R, et al (2016)[17]	0.32%
Our study	1.14%

On biopsy, the two ASC-H categorized cases in our study revealed: one case as CIN3 and other as Squamous cell carcinoma (SCC).

Low grade squamous intraepithelial lesions (L-SIL): Among IELs, comes the other category L-SIL, on cytology. These squames have three times the size of normal intermediate squamous cell nuclei, irregular nuclear membranes, coarse chromatin, HPV cytopathic effect or koilocytosis. Alternatively the cytoplasm is keratinized. Peri-nuclear halos that are seen in the absence of nuclear abnormalities are not diagnosed as 'L-SIL'.

Table 8 shows the comparative data on 'L-SIL' lesions by different studies:

Studies	Percent of 'L-SIL' cases in study from overall PAP smear cases studied
Bal MS, et al (2012)[22]	2.7%
Kalyani R, et al (2016)[17]	0.24%
Laxmi PV, et al (2013)[20]	7.5%
Rathore SB, et al (2013)[16]	1.6%
Our study	1.71%

The L-SIL cases in our study were confirmed as CIN1 on cervical biopsy.

High-grade squamous intra-epithelial lesion (H-SIL): IELs with less mature cells than those found in L-SIL category of cervical cytology. They have markedly raised N:C ratio, irregular nuclear membranes, over-crowded clusters with central whirling and flattening at the cluster edges.[(12)]

Table 9 shows the comparative data on 'H-SIL' lesions by different studies:

Studies	Percent of 'H-SIL' cases in study from overall PAP smear cases studied
Bal MS, et al (2012)[22]	0.7%
Kalyani R, et al (2016)[17]	0.41%
Laxmi PV, et al (2013)[20]	6%
Rathore SB, et al (2013)[16]	0.4%
Our study	1.43%

The H-SIL cases in our study were confirmed as CIN3 and Squamous cell carcinoma on cervical biopsy.

Squamous cell carcinoma (SCC) :

SCC can be keratinizing or non-keratinizing lesions.

The former are mostly isolated singly dispersed cells on cytology with irregular chromatin pattern, hyperkeratosis, pleomorphic parakeratosis and pathognomonic tumor diathesis.

The non-keratinizing type SCC on cytology are single/syncytial aggregates of dysplastic squamous cells that are smaller in

size than H-SIL, but have irregular chromatin pattern, clinging tumor diathesis, pleomorphic cell types.[12-14]

Table 10 shows the comparative data on 'SCC' lesions by different studies:

Studies	Percent of 'SCC' cases in study from overall PAP smear cases studied
Bal MS, et al (2012)[22]	1.3%
Kalyani R, et al (2016)[17]	0.41%
Selhi PK, et al (2013)[19]	0.16%
Rathore SB, et al (2013)[16]	0.4%
Our study	0.29%

Out of two cases reported as SCC on cytology, one was confirmed as large-cell keratinizing SCC on cervical biopsy while the other was reported as CIN-3 on biopsy. Any cytology report must be confirmed on 'gold standard' biopsy report, if needed. Out of 350 cases, cervical biopsy was advised on 62 cases. The maximum cases (45.2%) were reported as chronic non-specific cervicitis.

Table 11 shows following histopathology (gold standard test) correlation with cytology

Histopathology Diagnosis	Total HPR	Cytological Diagnosis								
	No. of cases	Unsatisfactory	NILM	ASCUS	ASC-H	L-SIL	H-SIL	Atrophic	Cancer	AGC-NOS
Infections	50	1	38	7	1	-	-	2	-	-
Carcinoma	2	-	-	-	-	-	1	-	1	-
Dysplasia	5	-	1	-	-	1	1	-	1	1
Other Benign Pathology	5	2	3	-	-	-	-	-	-	-
Total	62									

*AGC-NOS: Atypical endocervical glandular cells:not otherwise specified

Table 12 shows Cytology vs Histopathology chart of 62 cases for calculating diagnostic parameters

	Histo		
Cyto	T.P. 55	F.P. 1	56
	F.N 2	T.N 4	6
	57	5	Total 62

Diagnostic parameters on correlation:

1) Sensitivity = TP/TP + FN X 100 = $\frac{55}{55+2}$ X 100 $\frac{5500}{97} = 96.49\%$

2) Specificity = TN/F.P + T.N X 100 = $\frac{400}{4+1}$ X 100 $= \frac{400}{5} = 80\%$

3) Positive predictive value: PPV=TP/T.P+FP X 100 = $\frac{5500}{56} = 98.21\ \%$

4) Negative predictive value: NPV = TN/FN.TN X 100 = $\frac{400}{6} = 66.67\%$

5) Diagnostic accuracy = TN/TN + FP X 100 = $\frac{400}{5}$ = 80 %

Correlation of PAP smear cytology with 'gold standard' histological reports reveal excellent diagnostic parameters, implying the greater efficacy of cervical PAP smears.[16,23]

Conclusion:

Premalignant and malignant lesions of cervix are common and can be diagnosed early by conventional Pap smears. Use Bathesda system, 2014 for cytological reporting of cervical PAP smears for uniformity of reporting process. Conventional Pap smears are required not only for the diagnosis and management of the malignant lesions but it is also helpful in identifying the infectious etiologies and treatment in developing countries. They need to be correlated with histopathology for further management. Most of the screened patients in our study were in the third and fourth decades of life. Classification of cervical PAP smear cytology based on Bethesda terminology revealed it is a useful cost effective, screening tool for cervical lesions. Negative for intra-epithelial lesion (NILM) was mostly the pre-dominant cytological finding of PAP smear study. Pap smear significantly correlates with cervical histology as per this study.

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