

Study of cervical cytology and its correlation with clinical and histopathological findings

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ABSTRACT

Background: Cancer of the cervix is the second most common cancer among women in the world. It accounts for 12% of all cancers in females. This study aims to evaluate the pattern of cervical cytology and its correlation with clinical and histopathological findings. **Materials and Methods:** This is 10 years retrospective and prospective study, in which all the Papanicolaou (Pap) smears were reported as per the 2001 Bethesda system. Clinical and histopathological correlation was done in cases where cervical biopsy or total hysterectomy specimens were available. **Results:** A total of 3791 Pap smears were studied with respect to age group, clinical signs and symptoms, and cytology findings. Cervical biopsy correlation was done in 200 cases. Most of the patients were in age group of 31–40 (35.61%) years. The Pap smear findings revealed 88.02% as negative for intraepithelial lesion or malignancy (NILM), 5.99% epithelial cell abnormality (ECA), and 5.99% were unsatisfactory. ECA comprised atypical squamous cells of undetermined significance (ASCUS) with 2.98%, low-grade squamous intraepithelial lesion with 1.19%, and high-grade squamous intraepithelial lesion with 0.66%. There were 36 cases (0.95%) of malignancy. Sensitivity, specificity, and positive predictive value of Pap smear in diagnosing ECA and malignancy were 89.47%, 88.70%, and 82.92%, respectively. **Conclusion:** Pap smear test is ideal screening method for cervical carcinoma. Nonspecific inflammation and ASCUS were most common finding among NILM and ECA group, respectively. Biopsy is considered to be the gold standard for carcinoma cervix provided that it is taken from representative areas.

Key words: Carcinoma cervix, epithelial cell abnormality, Papanicolaou smear

INTRODUCTION

Cancer of the cervix is the second most common cancer among women in the world. It accounts for 12% of all cancers in females. In developing countries, including India carcinoma of the cervix is the major cause of morbidity and mortality. Incidence and mortality of cervical cancer in India is 134,420 and 72,825, respectively per year.^[1,2] Cervical cancer tends to occur in middle age. It is rare in women under 20 years of age and most common in women over 40 years. Most number of deaths usually occurs in women in their fifth and sixth decade

of life.^[3] Poor living conditions, lack of hygiene, early age of first intercourse, multiple sexual partners, and human papillomavirus (HPV) infections are major etiological factors for the development of cervical carcinoma.^[4] Epidemiological studies suggest that HPV is associated with a 10-fold or greater risk of cervical neoplasia than controls.^[5] It is now known that certain strains (16 and 18) of HPV are present in most cervical cancers, several newer strains as etiological factor are under investigation.^[6] Papanicolaou (Pap)-stained cervical cytology smears also detect the presence of various genital infections such as *Trichomonas vaginalis*, *Candida* species, actinomycetes such as organisms, bacterial vaginosis, *Neisseria gonorrhoeae*, herpes simplex virus (HSV), and HPV. The Pap smear is the screening test if any abnormalities are detected in

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Access this article online

Quick Response Code:



Website:

www.ccij-online.org

DOI:

10.4103/2278-0513.197869

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Cite this article as: Bamanikar SA, Baravkar D, Chandanwale S, Dharwadkar A, Paranjape S. Study of cervical cytology and its correlation with clinical and histopathological findings. Clin Cancer Investig J 2016;5:403-8.

Pap smear; a biopsy diagnosis is advised for correlation and confirmation. The present study is carried out to evaluate the pattern of cervical Pap smear cytology at a tertiary care hospital and to correlate it with clinical and histopathological findings.

MATERIALS AND METHODS

This was a retrospective and prospective study carried out from August 2006 to 2015. All the Pap smears received from the Department of Gynecology within this period were included in the study. Patients with history of previous hysterectomy and pregnant women were excluded from the study. Patient data in the form of name, age, clinical complaints, and per vaginal findings were collected from requisition form and noted on structured pro forma. Approval for the study was obtained from the Institute Ethics Committee. Pap smear was reported using the 2001 Bethesda system. Correlation with histopathological findings was done in cases where cervical biopsy or total hysterectomy specimens were available.

Statistical analysis

Statistical analysis was carried out using the SPSS, version 20.0 and OpenEpi (version 3) software (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp., Armonk, NY, USA).

Sensitivity, specificity, and positive predictive value of the Pap smear test were calculated using histopathology diagnosis of cervical biopsy as the gold standard.

RESULTS

In this study, 3791 Pap smears were studied with respect to age group, clinical signs and symptoms, and cytology findings. Cervical biopsy correlation with Pap smears was done in 200 cases.

Most of the patients were in age group of 31–50 years (64.07%). Out of 3791 cases studied, 2046 cases were symptomatic, and 1745 cases were asymptomatic. Asymptomatic group comprised patients who came for routine checkup and Pap screening camps conducted during rural health checkup.

Whitish discharge per vaginum was the most common symptom with 908 cases (23.95%). The second most common symptom was pain in the lower abdomen (19.55%). Intermenstrual bleeding and dyspareunia were present in 9.44% and 1.03% of cases, respectively.

Gross appearance of cervix on per speculum examination was analyzed in 725 cases. Cervical erosion was the most

common finding with 45.52% followed by hypertrophy and bleeding on touch in 255 (35.17%) and 136 (18.76%) cases, respectively.

Out of total 3791 cases, 227 (5.99%) were reported as unsatisfactory smears either due to inadequate material or hemorrhagic smears. Negative for intraepithelial lesion or malignancy (NILM) was most common finding (88.02%). There were 227 cases of epithelial cell abnormality (ECA) accounting for 5.99% of the total [Table 1].

63% of smears were reported as NILM in the age group of 31–50 years; 37.17% of smears were reported as atypical squamous cells of undetermined significance (ASCUS) in the age group 41–50 years. Low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) were reported to be present in 33.33% and 36% smears respectively; in age group of 31–40 years. 19 cases (52.78%) of malignancy were detected in age group of 41–60 years. Out of 3337 smears reported as NILM, 2111 (63.26%) were normal. Nonspecific inflammation was reported in 735 cases comprising 22.03% of all NILM cases [Figure 1]. Among specific inflammation category, bacterial vaginosis (5.87%) was most common finding. *Trichomonas* [Figure 2] and *Candida* infections were reported in 66 (1.98%) and 30 (0.90%) cases, respectively. HSV was least common finding among NILM category with 21 (0.63%) cases [Table 2].

Out of 227 cases of ECA, ASCUS was most common finding with 113 cases [Figure 3]. Atypical glandular cells of undetermined significance (AGUS) was reported in eight cases. There were 45 cases of LSIL which accounted for 1.19% of total ($n = 3791$) and 19.82% of ECA. HSIL was reported in 25 cases, 0.66% of total cases. There were 36 cases of malignancy, out of which 32 were squamous cell carcinoma [Figure 4], and 4 were diagnosed as adenocarcinoma [Table 3].

Out of total 3791 cases of Pap smear, histopathological processing of cervical biopsy or hysterectomy specimen was available in 200 cases. Six cases were reported normal. There were 118 cases of chronic cervicitis. LSIL and HSIL were reported in 33 and 23 cases,

Table 1: Cytological diagnosis in Papanicolaou smears examined

Findings	Number of cases (%)
Unsatisfactory	227 (5.99)
NILM	3337 (88.02)
ECA	227 (5.99)
Total	3791 (100)

NILM: Negative for intraepithelial lesion or malignancy, ECA: Epithelial cell abnormality

Table 2: Pattern of cases reported as negative for intraepithelial lesion or malignancy on Papanicolaou smear

Cytology-diagnosis	Number of cases	Percentage of NILM (n=3337)	Percentage of total (n=3791)
Normal	2111	63.26	55.68
Nonspecific inflammation	877	26.28	23.14
Bacterial vaginosis	196	5.87	5.17
<i>Trichomonas</i>	66	1.98	1.74
<i>Candida</i>	30	0.90	0.79
HSV	21	0.63	0.55
Atrophic	36	1.08	0.95
Total	3337	100.00	88.02

HSV: Herpes simplex virus, NILM: Negative for intraepithelial lesion or malignancy

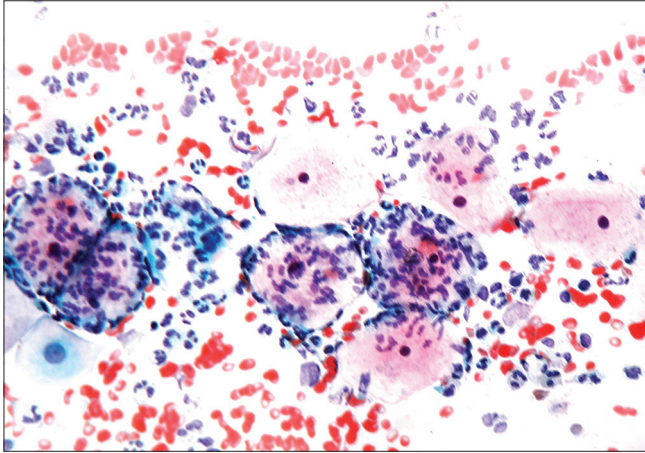


Figure 1: Inflammatory Papanicolaou smear (x100)

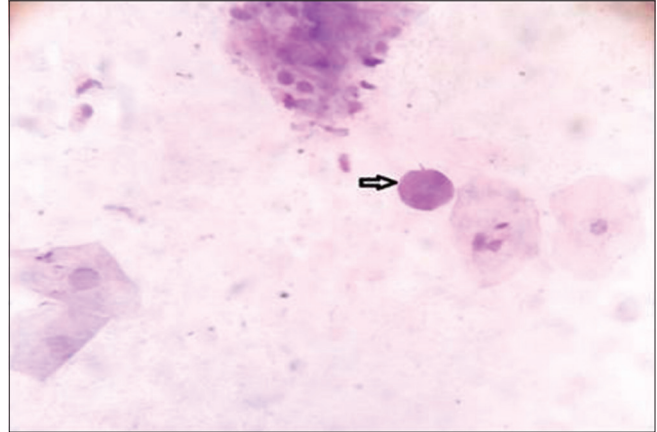


Figure 2: *Trichomonas vaginalis* (arrow) on Papanicolaou smear (x400)

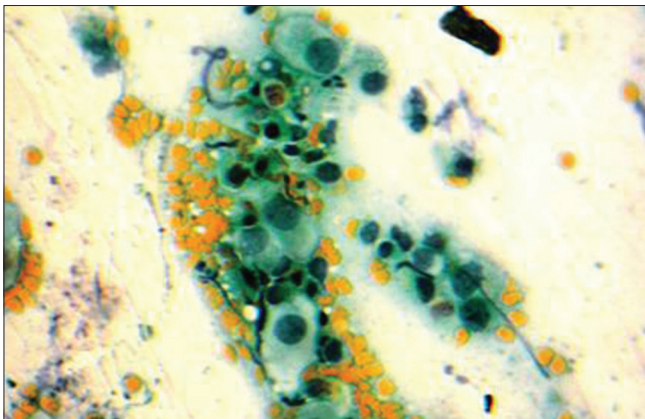


Figure 3: Atypical squamous cells of undetermined significance on Papanicolaou smear (x400)

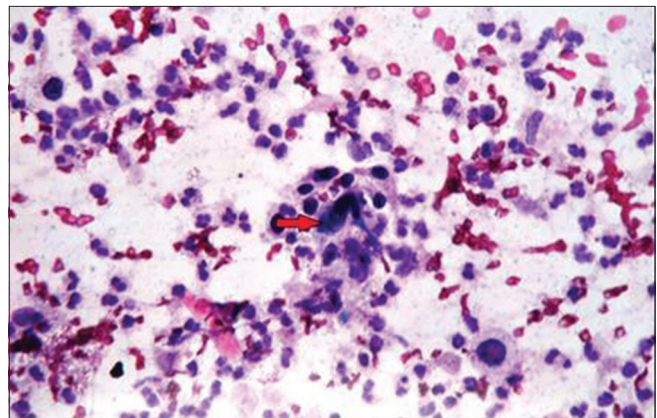


Figure 4: Squamous cell carcinoma with tadpole cell on smear (H and E, x400)

respectively. Out of 200, 20 cases were reported malignant. Out of 20 cases of malignancy, 18 were diagnosed squamous cell carcinoma [Figure 5], and two were adenocarcinoma [Table 4].

Out of 3371 Pap smear cases of NILM, 118 were processed for histopathological examination. One hundred and seven cases were reported as inflammatory, three cases as normal, six cases as LSIL, and two as HSIL on histopathology. Out of 121 cases of ASCUS and AGUS, 13 cases were processed for histopathological examination, 6 were reported as

inflammatory, 1 as normal, 4 as LSIL, and 1 was reported as malignancy.

In case of LSIL, 27 cases were processed for histopathological examination, 3 were reported as inflammatory, 16 as LSIL, and 1 turned out to be malignant on histopathology. All 25 cases of HSIL were processed for histopathological of which 2 were reported as NILM, 6 as LSIL, 13 as HSIL, and 4 were reported malignant on histopathological examination. Total of 17 cases reported malignant on cytology, 2 were reported as HSIL, and 14 as malignant on histopathological examination [Table 5].

Sensitivity, specificity, and positive predictive value of Pap smear was 89.47%, 88.70%, and 82.92%, respectively in our study. Overall, diagnostic accuracy of the Pap smear was 89%. Concordance rate in our study was 89.5%.

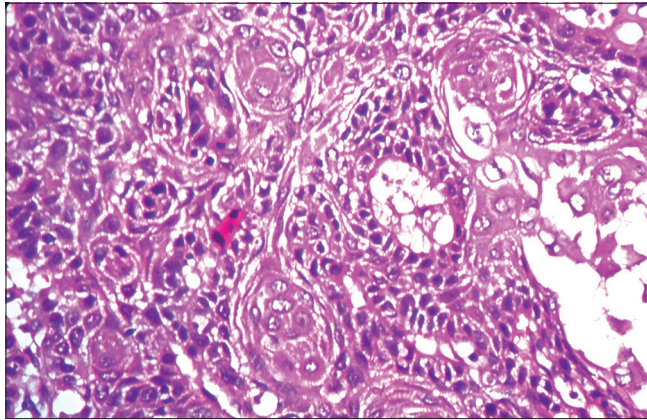


Figure 5: Squamous cell carcinoma on histology section (H and E, ×100)

Table 3: Pattern of epithelial cell abnormality in Papanicolaou smears examined			
ECA finding	Number of cases	Percentage of ECA (n=227)	Percentage of total (n=3791)
ASCUS	113	49.78	2.98
AGUS	8	3.52	0.21
LSIL	45	19.82	1.19
HSIL	25	11.01	0.66
Malignancy	36	15.86	0.95
Total	227	100.00	5.99

ECA: Epithelial cell abnormality, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, AGUS: Atypical glandular cells of undetermined significance

Table 4: Distribution of histopathological diagnosis of 200 cases	
Histopathological findings	Number of cases (%)
Normal	6 (3)
Chronic cervicitis	118 (59)
LSIL	33 (16.5)
HSIL	23 (11.5)
Malignant	20 (10)
Total	200 (100)

LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion

Cytology	Histopathology					Total
	Normal	Chronic cervicitis	LSIL	HSIL	Malignancy	
NILM	3	107	6	2	0	118
ASCUS and AGUS	1	6	4	1	1	13
LSIL	2	3	16	5	1	27
HSIL	0	2	6	13	4	25
Malignancy	0	0	1	2	14	17
Total	6	118	33	23	20	200

ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, NILM: Negative for intraepithelial lesion or malignancy, AGUS: Atypical glandular cells of undetermined significance

DISCUSSION

The study was conducted to evaluate the pattern of cervical cytology and its correlation with clinical and histopathological findings. Among various screening tests used for cervical cancer, Pap smear is considered to be an ideal screening test. This study emphasized the importance of Pap smears screening for early detection of premalignant and malignant lesions of cervix.

Cytological findings were classified as per the 2001 Bethesda system. Results and observations of our study were compared to various other national and international studies done by other workers.

In our study, maximum number of the patients 35.61% were in the age group of 31–40 years and 1.35% were in the age group of >71 years. Similar observations were made by other studies where maximum numbers of cases were in age group of 31–40 years.^[7,8]

Our study showed 53.97% symptomatic and 46.03% asymptomatic cases. Whitish discharge per vaginum (23.95%) was the most common symptom as was also reported in other similar studies.^[8-10] Other symptoms were lower abdominal pain, intermenstrual bleeding, and dyspareunia in descending order. In our study, clinical signs of the patients were analyzed using per speculum gross appearance of the cervix. Various parameters included were erosion, bleeding on touch, congestion, and hypertrophy of the cervix. Cervical erosion (45.52%) was the most common presentation in our study. Hypertrophied cervix was present in 35.17% of the cases. A study done by Kaveri and Khandelwal.^[8] revealed similar observations with cervical erosion (38.3%) being the most common finding.

Pap smear cytology findings were broadly categorized into unsatisfactory, NILM, and ECA.

In our study, 5.99% of smears were reported unsatisfactory. This category included smears with inadequate material and hemorrhagic smears. Percentage of unsatisfactory smears reported by other workers Bukhari *et al.*^[11] (1.8%),

Bal *et al.*^[12] (4%), and Kapila *et al.*^[13] (3.9%) were lower as compared to our study. Possible explanation for this higher rate may be large sample size in our study or due to less satisfactory sample collection facilities at some of the rural cervical screening camps. Shrivastava *et al.*^[10] reported 8.08% cases as unsatisfactory for interpretation which was higher as compared to our study.

In our study, Pap smears reported as NILM was most common finding with 88.02% of all smears examined. This was in accordance with other studies in literature.^[9,14,15]

In our study, among 3337 cases reported as NILM, 2111 cases were reported normal. Among infectious category, nonspecific inflammation was most common finding (877 cases, 26.28% of all NILM cases). Atrophic vaginitis was noted in 1.08% cases of all NILM categories. Out of specific inflammation category, bacterial vaginosis was reported in 195 (5.87% of NILM) cases, and HSV (0.63%) was least common finding. Similar observations were obtained in other studies reported.^[8,10] In our study, ECA rate was found to be 5.99%. ECA rate reported by various studies in literature are comparable to our study. ECA group comprised ASCUS, AGUS, LSIL, HSIL, and malignancy. Abdullah,^[15] Altaf,^[16] Balaha *et al.*,^[17] and Filipi and Xhani^[14] reported ECA rate as 5%, 4.7%, 4.95%, and 4.8%, respectively.

In our study, ASCUS the most commonly reported ECA with 113 (2.98%) cases while AGUS as ECA was reported in 0.21% cases. These findings are in line with other study reported by Kapila *et al.*^[13] with ASCUS and AGUS in 2.2% and 0.8% of cases, respectively.

In our study, there were 45 cases reported as LSIL on cytology with 1.19% and HSIL was reported in 25 cases (0.66%) of all cases.

Abdullah^[15] reported LSIL and HSIL in 1% and 0.55% of cases, respectively. Similarly, Filipi and Xhani^[14] reported LSIL and HSIL in 1.6% and 0.18% of cases, respectively.

Frank malignancy was reported in 36 cases (0.95%) in our study, and this was comparable to other study which reported malignancy in 0.7% of cases.^[18]

In our study, out of total 3791 cases of Pap smear, 200 cases (5.27%) underwent further diagnosis of biopsy either in form of cervical biopsy or hysterectomy. Cervical biopsy is the gold standard for detection of carcinoma cervix. Biopsy must be obtained from representative area.

In our study, sensitivity, specificity, and positive predictive value of Pap smear in diagnosing ECA and malignancy were 89.47%, 88.70%, and 82.92%, respectively. Tamboli and Khatod^[19] reported sensitivity, specificity, and positive predictive value of Pap smear as 90.65%, 90.27%, and 89.81%, respectively, and the values reported by Jones and Novis^[20] were 89.4%, 64.8%, and 88.9%, respectively. These findings were comparable with our study [Table 6].^[21-23]

Pap smear was able to differentiate most of the benign, inflammatory, and malignant lesions but not in case of ECA, importantly LSIL and HSIL, where biopsy is advised. Biopsy is considered to be the gold standard for carcinoma cervix provided that it is taken from representative areas.

Sensitivity and specificity of Pap smear can be increased by adopting proper technique and adequate sampling from transformation zone. Various methods of Pap smear sampling such as conventional and liquid based are used. In our study, Pap smears were sampled by conventional method. Use of liquid-based cytology is advised to improve sensitivity and specificity of Pap smear. Pap smear screening coupled with HPV testing will improve overall detection rate of carcinoma cervix.

CONCLUSION

A pap smear test is ideal screening method for cervical carcinoma. Nonspecific inflammation and ASCUS was the most common finding among NILM and ECA group, respectively. Biopsy is considered to be the gold standard for diagnosis of carcinoma cervix provided that it is taken from representative areas.

Acknowledgment

We are grateful to the technical staff from the Department of Pathology for their help in processing the samples and retrieving patient records during the study project.

Table 6: Comparison of sensitivity, specificity and positive predictive value of Papanicolaou smear with other studies

Studies	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Jones and Novis ^[20]	89.4	64.8	88.9
Chhabra <i>et al.</i> ^[21]	81	95	92.8
Sosic <i>et al.</i> ^[22]	87.3	96.86	63.95
Hegde <i>et al.</i> ^[23]	83	98	97.9
Tamboli and Khatod ^[19]	90.65	90.27	89.81
Kaveri and Khandelwal ^[8]	86.5	92.18	89.4
Present study	89.47	88.7	82.92

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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