

Proportion and Pattern of Epithelial Cell Abnormalities in Cervical Smears- A Retrospective Study

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ABSTRACT

Introduction: Cervical cancer is a leading cause of mortality and morbidity among women worldwide. Approximately, 90% deaths due to cervical cancer occur in developing countries like India. Papanicolaou (Pap) smear test is an efficient, cost-effective screening tool to identify epithelial abnormalities in the preinvasive and early invasive stages of cervical cancer. Knowledge of the proportion and pattern of abnormal Pap smears in the local population is essential to ensure the early detection and treatment of precancerous lesions of cervix, thereby reducing the morbidity and mortality resulting from cervical cancer, which at present is preventable to a large extent.

Aim: To estimate the proportion of cervical epithelial abnormalities in the local population and describe the morphological patterns of abnormalities employing the 2014 revised Bethesda system.

Materials and Methods: This was a retrospective, hospital record-based descriptive study conducted in a tertiary care centre in Kerala, India from January 2016 to December 2018. Altogether, 9330 cervical smears stained using Pap method were retrieved from slide archive and evaluated. Data was collected from case notes, request forms and cytology registers. Morphological analysis was done using the revised 2014 Bethesda system. Proportion

of smears showing epithelial cell abnormalities and categories of epithelial abnormalities were expressed as percentages.

Results: A total of 9330 samples were studied. The proportion of epithelial abnormalities was 1.70%, of which Atypical Squamous Cells of Undetermined Significance (ASCUS) was the most frequent (1.38%), followed by Atypical Squamous Cells cannot exclude an High-grade squamous intra epithelial lesion (Atypical squamous cells-H) [HSIL (ASC-H)] (0.13%). Women with epithelial abnormalities belonged to a wide age range of 31-70 years, with majority in the 41-50 years age group. Most of the patients with abnormal Pap smears (62.3%) had normal looking or unremarkable cervix.

Conclusion: The proportion and pattern of cervical epithelial abnormalities in the local population of Kerala is comparable to that of developed nations. Patients for cervical cancer screening cannot be selected based on clinical features or appearance of cervix. Even in the absence of gynaecologic complaints, screening for cervical cancer must be done at regular intervals and Pap smear test should be employed as a routine screening procedure for all women above 30 years of age. Special measures need to be taken to ensure that postmenopausal females are screened for cervical cancer.

Keywords: Cervical cancer, Pap smear, Revised bethesda system, Screening test

INTRODUCTION

Cervical cancer is the fourth most frequent cancer among women worldwide. Every year 527,624 women are diagnosed with cervical cancer and 265,672 die from the disease [1]. India alone accounts for one quarter of the worldwide burden of cervical cancers, affecting approximately 1 in 53 Indian women during their lifetime [1,2]. Cervical cancer is the second leading cause of female cancer deaths in India, with about 60,078 deaths occurring annually. The age standardised incidence rate for cervical cancer in India (14.7%) is higher than other South Asian countries like Afghanistan (6.6%), Pakistan (7.3%) and Sri Lanka (7.8%) [2].

Cervical epithelial abnormalities ranges from patterns of undetermined significance and low to high grade premalignant lesions to frank malignancies that originates from squamous or glandular cells. As cervical cancer has a long preinvasive stage, it is regarded as a preventable disease, amenable to early detection and appropriate management, provided robust screening programmes are employed [3].

Detection of cervical epithelial abnormalities at the earliest considerably reduces morbidity and mortality. The currently available screening tests for cervical cancer includes the study of cervical cytology by Pap smear examination and Human Papilloma Virus (HPV) testing. Pap smears can identify the early cervical epithelial changes including cervical intraepithelial neoplasia and the early stage of invasive cervical cancer [4]. They can be processed using conventional method or liquid based cytology, the latter being more popular in developed nations. In the

low resource settings of developing countries, a conventional Pap test remains the mainstay of screening for cervical cancer and serves as an effective method for early detection as well as prevention/delaying of cervical cancer [5].

Over the years, screening methods have markedly reduced the incidence of cervical cancer [5]. Studies reveal a higher risk of cervical cancer in women with abnormal Pap smears or no Pap smears in the past, when compared with women who underwent regular screening [6]. However, in developing countries like India, lack of infrastructure and resources, coupled with overpopulation, often tend to render the screening programs largely ineffective.

Not many studies are available today on the prevalence of various cervical epithelial abnormalities in the Indian population. Effective community level preventive measures for cervical cancer are yet to be implemented in our country. Cervical cancer diagnosed in the advanced stages requires more expensive treatment and is associated with a poor prognosis. Knowledge of the prevalence and pattern of premalignant and malignant lesions among the local population is essential to organise an effective healthcare system that can minimise the morbidity and mortality from cervical cancer by early detection and treatment.

The introduction of 'The Bethesda System' for reporting cervical cytology has resulted in a standardised reporting pattern. The present study employed the 2014 revised Bethesda System [7] to estimate the

proportion and describe the pattern of cervical epithelial abnormalities in the local population.

MATERIALS AND METHODS

This descriptive retrospective, hospital record-based study was conducted in the Department of Pathology in a tertiary care centre in Kerala, India from January 2016 to December 2018. The study was undertaken after approval by the Institutional Ethics Committee. (IEC No.007/2018/GMCKLM).

Sample size calculation: Sample size was calculated using the formula, $N=4PQ/d^2$, where P=Prevalence taken as 2.41% from previous study in similar population [5].

All Pap smears are stored in the Department of Pathology for a period not less than five years from date of submission. A total of 9330 cervical smears were submitted to the department during the study period and were included in the study. These were collected using a wooden Ayre spatula, smeared on glass slides, immediately immersed in fixative (80% isopropyl alcohol) provided in Koplins jars and after fixation, stained using Pap method.

Data regarding clinical details were collected from request forms and registers maintained at cytology division. Cervical smears were retrieved from the slide archive and evaluated using the revised 2014 Bethesda system [Appendix]. Smears with epithelial abnormalities were categorised into ASCUS, ASC-H, Atypical Glandular Cells- Not Otherwise Specified (AGC-NOS), Low-grade Squamous Intraepithelial Lesion (LSIL), High-grade Squamous Intraepithelial Lesion (HSIL), HSIL with features suspicious for invasion and squamous cell carcinoma [Table/Fig-1].

STATISTICAL ANALYSIS

The proportion of cervical smears showing epithelial cell abnormalities was calculated and expressed in percentages. The pattern of cervical epithelial abnormalities was assessed by morphological analysis and the frequencies of different morphological categories were expressed as percentages.

RESULTS

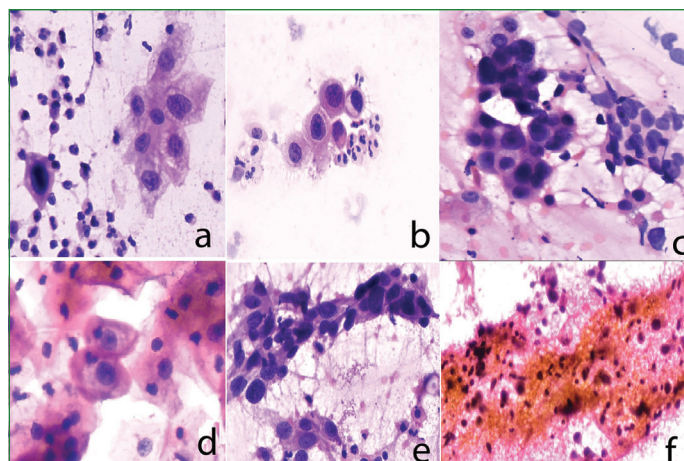
A total of 9330 cervical smears were retrospectively analysed, after excluding those unsatisfactory for evaluation due to inadequate squamous cellularity, obscuring inflammation or blood and drying artifact. Cytological findings of the smears are listed in [Table/Fig-2].

Epithelial abnormalities were observed in 159 (1.70%) cases. The most frequent epithelial abnormality was ASCUS (129 cases, 1.38%), followed by ASC-H (12 cases, 0.13%). Seven smears revealed high grade lesions and four cases of squamous cell carcinoma were observed. There were two cases of LSIL and five cases of AGC-NOS [Table/Fig-3].

Abnormal Pap smears were observed in patients belonging to the age group of 31-70 years, with majority (39.6%) belonging to the 41-50 year age group. High grade lesions were observed only in women above 40 years of age. All carcinomas occurred in the 51-70 year age group [Table/Fig-4].

Age group (years)	ASCUS	ASC-H	AGC	LSIL	HSIL	HSIL with suspicious invasion	Squamous cell carcinoma	Total n (%)
21-30	2	-	-	-	-	-	-	2 (1.3)
31-40	16	-	-	-	-	-	-	16 (10.1)
41-50	52	4	3	2	1	1	-	63 (39.6)
51-60	36	6	-	-	3	-	2	47 (29.6)
61-70	18	2	2	-	1	-	2	25 (15.7)
71-80	4	-	-	-	1	-	-	5 (3.1)
>80	1	-	-	-	-	-	-	1 (0.6)
Total	129	12	5	2	6	1	4	159 (100)

[Table/Fig-4]: Cervical epithelial abnormalities in relation to age.



[Table/Fig-1]: a) Smear showing atypical squamous cells of undetermined significance (Papanicolaou, 40X); b) Smear showing atypical squamous cells cannot exclude an HSIL (Papanicolaou, 40X); c) Smear showing atypical glandular cells- Not Otherwise Specified (NOS) (Papanicolaou, 40X); d) Smear showing Low-grade Squamous Intraepithelial Lesion (LSIL) (Papanicolaou, 40X); e) Smear showing High-grade Squamous Intraepithelial Lesion (HSIL) (Papanicolaou, 40X); f) Smear showing Squamous cell carcinoma with tumour diathesis (Papanicolaou, 40X).

Interpretation	Number of cases (n)	Percentage (%)
Epithelial abnormalities	159	1.7
Unsatisfactory	1051	11.3
NILM*	8120	87
Total	9330	100

[Table/Fig-2]: Papanicolaou (Pap) Smear result of study group.

*Negative for Intraepithelial Lesion or Malignancy

Epithelial abnormalities	No. of cases (n)	Percentage (N=9330) (%)
Atypical squamous cells of undetermined significance (ASCUS)	129	1.38%
Atypical squamous cells cannot exclude an HSIL (ASC-H)	12	0.13%
Atypical glandular cells- Not Otherwise Specified (AGC-NOS)	5	0.053%
Low-grade squamous intraepithelial lesion (LSIL)	2	0.02%
High-grade squamous intraepithelial lesion (HSIL)	6	0.06%
High-grade squamous intraepithelial lesion (HSIL) with features suspicious for invasion	1	0.01%
Squamous cell carcinoma	4	0.04%
Total	159	1.70%

[Table/Fig-3]: Epithelial abnormalities observed in the study group.

Most of the patients with abnormal Pap smears (62.3%) had normal looking or unremarkable cervix. Per speculum findings like abnormal vaginal discharge (7.5%), congested and/or hypertrophied cervix (6.9%), atrophic cervix (6.3%) and unhealthy cervix (5.7%) were less frequently encountered. Ninety nine out of 6367 patients with normal looking cervix had epithelial abnormalities in Pap smear (1.6%). Three patients in the study population presented with growths in the cervical canal and all of them had cervical epithelial abnormalities (squamous cell carcinoma, HSIL and AGC) [Table/Fig-5].

Per-speculum examination findings	No. of women with the clinical finding (n)	No. of women with cervical epithelial abnormality among those with the clinical finding	Percentage of women who had the clinical finding in the (159) cases with cervical epithelial abnormality
Cervix appears normal	6367	99 (1.6%)	62.3%
Discharge per vaginum	1109	12 (1.1%)	7.5%
Cervix congested and hypertrophied	898	11 (1.2%)	6.9%
Cervix atrophic	143	10 (7.0%)	6.3%
Unhealthy cervix	157	9 (5.7%)	5.7%
Cervix bleeds to touch	99	7 (7.1%)	4.4%
Prolapsed uterus	168	4 (2.4%)	2.5%
Growth in cervical canal	3	3 (100%)	1.9%
Cervix high up	37	2 (5.4%)	1.3%
Cervix eroded	226	1 (0.4%)	0.6%
Cervical polyp	123	1 (0.8%)	0.6%
Total	9330	159	100%

[Table/Fig-5]: Distribution of per-speculum finding and epithelial abnormalities in Pap smear.

The clinical findings that were the mostly associated with cervical epithelial abnormalities were cervix bleeding to touch 7.1% (7 out of 99), atrophic cervix 7% (10 out of 143) and unhealthy cervix 5.7% (9 out of 157 cases).

DISCUSSION

Present study used the 2014 revised Bethesda system for analysing cervical smears and found it to be immensely helpful in comparing results with various other studies from India as well as other countries. 'The Bethesda system' for reporting cervical cytology, introduced in 1988 and revised in 1991, 2001, and 2014, ensures a standardised, internationally comparable reporting pattern. It also co-ordinates the reporting terminology with HPV status and clinical management, and thereby provides clear cut thresholds and unified guidelines for management. The Bethesda system also decreases interobserver variability and facilitates research [4].

The prevalence of cervical epithelial abnormalities in this study was 1.70%. In comparison, in a one year study conducted at private medical college at Kozhikode, Kerala by Nair GG et al., they analysed 2028 samples, of which 2.41% revealed epithelial abnormalities [5]. Another study by Mulay K et al., on 6010 routine cervical smears taken in an urban hospital in India found epithelial abnormalities in 1.392% smears. The same study also analysed 10,000 cervical smears of women participating in a National Cancer Screening Program in Mauritius and found a prevalence rate of 0.47% [6]. Mufti ST et al., analysed 15805 smears in Saudi Arabia and found epithelial abnormalities in 14.52% [8]. Banik U et al., studied 1699 cervical smears of women in Bangladesh and noted a prevalence rate of 8.18% for epithelial abnormalities. They have attributed this high prevalence to the reluctance of their patients to visit tertiary health centres for cancer screening purpose [4].

Decentralisation of healthcare services in Kerala, with availability of cancer screening facilities from the primary healthcare level itself might be one of the factors contributing to the lower prevalence rate in present study, in comparison to other studies [Table/Fig-6] [3-5,9-15]. A better awareness regarding cervical cancer among the general public of Kerala as well as a high literacy rate need to be mentioned.

The ASCUS was the most frequent epithelial abnormality (1.38%) in present study. The observations by Mulay K et al., are similar, with ASCUS forming the largest group of epithelial abnormalities. (0.64% among Indian women and 0.26% among women belonging to Mauritius) [6]. Banik U et al., and Nair GG et al., observed LSIL as the most frequent finding (6.36% and 1.58%, respectively) [4,5]. As pointed out in the revised Bethesda System, differences in staining and slide preparation techniques may result in subtle differences in the criteria for ASCUS among laboratories.

Also, Banik U et al., have explained the higher LSIL rate by assuming that the women included in their study presented with a more advanced form of the lesion (LSIL) rather than ASCUS as they were never routinely screened [4]. This emphasises the role of cervical cancer screening in preventing as well as delaying cervical cancer.

On the other hand, study by Mufti ST and Altaf FJ, in a tertiary care centre at Saudi Arabia found a high ASCUS rate (7.1%), well above the acceptable range. They have attributed this to the fact that their pathologists might have preferred the diagnosis of ASCUS over LSIL, as patients diagnosed ASCUS are treated for inflammation followed by a repeat smear, while colposcopy and biopsy were carried out on patients diagnosed LSIL [8].

A 98% of epithelial abnormalities in this study occurred in 31-70 year age group. Banik U et al., also noted a wide age range (21-70 years) [4]. Nair GG et al., found the majority belonging to 33-69 age group

Authors	Study location	Sample size	Study period	Prevalence of epithelial abnormality	Most frequent epithelial abnormality
Sachan PL et al., [3]	Lucknow	1650	2018	8.48%	LSIL (5.09%)
Banik U et al., [4]	Bangladesh	1699	2010	8.18%	LSIL (6.36%)
Nair GG et al., [5]	Kozhikode, Kerala	2028	2012-13	2.41%	LSIL (1.58%)
Hemali JT et al., [9]	Surat, Gujarat	1425	2012	1.89%	ASCUS (0.77%)
Malpani G et al., [10]	Indore, Madhya Pradesh	7127	2013-15	2%	LSIL (0.57%)
Akshatha C et al., [11]	Tamil Nadu	600	2015-16	5.5%	HSIL (2.3%)
Ranabhat SK et al., [12]	Nepal	880	2009-10	1.7%	HSIL (0.68%)
Gupta K et al., [13]	Western Uttar Pradesh	4703	2013	3.23%	LSIL (1.36%)
Bal MS et al., [14]	Patiala, Punjab	300	2012	5%	LSIL (2.7%)
Bhavani K et al., [15]	Andhra Pradesh	770	2016-17	7.92%	LSIL (3.57%)
Present study	Kerala	9330	2016-18	1.7%	ASCUS (1.38%)

[Table/Fig-6]: Prevalence of epithelial abnormalities in other studies [3-5,9-15].

[5]. Thus, it is better and safer to advocate cervical cancer screening for all women above 21 years of age.

In the present study, 69.2% of patients with epithelial abnormalities belonged to the peri/postmenopausal age group of 41-60 years. These included both low and high grade lesions. This is similar to the observations in other studies like Banik U et al., (46.04% in the ≥ 45 year age group) and Nair GG et al., (44.9% cases in 51-60 year age group) [4,5]. Malpani G et al., also observed that intraepithelial lesions/dysplasia were most frequent in the 41-50 year age group. In their study on 7127 cervical smears, 30 out of total 36 malignancies occurred in women older than 50 years [10]. In the present study also, all frank malignancies and most of the high grade lesions were observed in the 51-70 year age group. As Banik U et al., and Akshatha C et al., have also pointed out, this highlights the significance of cervical cancer screening among patients above 45 years of age in developing countries [4,11].

Despite the high literacy rate and a good healthcare system in Kerala, women of older age groups often tend to under utilise cancer screening programmes. Cervical screening can be uncomfortable for older women due to oestrogen deficiency, and it is often difficult to obtain an adequate sample [12]. In postmenopausal women, hormonal changes may cause nuclear enlargement of cervical epithelial cells (without significant hyperchromasia). When atrophic changes, parakeratosis and drying artifacts are added to this, the interpretation can be quite challenging, atleast for the less experienced pathologist.

The age distribution observed in this study is comparable to the peak age of occurrence of cervical cancer in India, which is between 55 and 59 years [16]. The American Congress of Obstetricians and Gynaecologists and the American Cancer Society recommends that for women with adequate prior negative screening and no history of cervical intraepithelial neoplasia grade 2+, screening should be stopped at 65 years, as infection with HPV at this age is rare, and even if present, is unlikely to progress to invasive cancer in the woman's lifetime [17]. But, as the life expectancy is high in our female population, an increase in the age of last screening needs to be considered. Castañón A et al., found that even in women with adequate negative screening, further screening after 60-69 years may be justifiable as life expectancy increases [18]. Hence, special emphasis has to be given to educate and motivate older age group women regarding cancer screening.

In the present study, 62.3% women with abnormal Pap smears were asymptomatic, with a normal looking cervix. Banik U et al., identified that approximately one-third of the patients with abnormal Pap results had a healthy looking cervix [4]. Nair GG et al., found 51% of such cases to be asymptomatic [5]. Banik U et al., also observed that a negative history before 50 years of age does not exclude the risk of cervical cancer [4]. This signifies that patients for cervical cancer screening cannot be selected by clinical impression and per speculum examination of cervix alone and that even in the absence of gynaecologic complaints, screening for cervical cancer must be done at regular intervals. The American Cancer Society (2012) recommends routine screening for cervical cancer using Pap smear test every three years for women aged 21-29 years and, HPV and Cytology "Cotesting" every five years for women in the 30-65 year age group [17].

Studies reveal a higher risk of cervical cancer in women with abnormal Pap smears or no Pap smears in the past, when compared with women who underwent regular screening [18]. However, in developing countries like India, lack of infrastructure and resources, coupled with overpopulation, often tend to render the screening programs largely ineffective [19,20]. Despite national guidelines and health programs, the screening coverage is found to be grossly inadequate in many regions of India, ranging from 6.9% in Kerala to as low as 0.006% in Maharashtra and 0.002% in Tamil Nadu [21-23].

The burden of cervical cancer can be reduced to a considerable extent if, as in this institution, cervical cancer screening is made a routine procedure for all women above 21 years, attending the Gynaecology Out Patient Department (OPD). Still, the apparently normal female harbouring an epithelial abnormality, who is asymptomatic and therefore does not visit the hospital, may be missed. Here lies the significance of community screening programmes and awareness campaigns like the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke (NPCDCS) launched in India in 2010 that promoted cancer screening through camps in women above 30 years at different levels in rural areas and in urban slums [16].

Future studies should incorporate histopathological correlation, as well as exploration of psychosocial and cultural risk factors, in order to establish a consistent pattern of the disease in our population. Liquid based cytology may be employed to reduce the number of unsatisfactory samples. However, careful evaluation is necessary to ascertain whether this technique is cost-effective in the setting. The utility and cost-effectiveness of population based HPV testing and vaccination also needs to be studied.

Limitation(s)

The present study was limited by the non availability of histopathology reports and HPV test results for correlation. Newer sampling devices like cytobrush and processing techniques utilising cytocentrifuge, liquid based cytology and automated staining could not be employed due to financial constraints.

CONCLUSION(S)

This hospital based study on routine cervical smears revealed 1.70% cases with epithelial abnormalities, ASCUS being the most common. Patients with epithelial abnormalities belonged to a wide age range, with majority in the 41-50 year age group and were mostly asymptomatic with normal looking cervix.

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