

Correlation of Cytology and Histopathology in the Diagnosis of Cervical Lesions

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Abstract: Background: Cervical cancer is the fourthmost common type of cancer among women as per WHO , accounting for about 1,90,000 deaths annually. Conventional cervical cytology by pap smear is the most widely used cervical cancer screening test in the world. Aims and objectives: To find out efficacy of pap smear cytology in screening of cervical lesions and to correlate with histopathology, and to evaluate other factors associated with premalignant and malignant cervical lesions. Materials and methods: This was a prospective clinical study, conducted on 130 women attending the gynaecology OPD of Father Muller Medical college hospital from 2016 to 2017 , who underwent pap smear and cervical biopsy for various reasons. Results: The mean age was 45.8±10.77 years, and maximum number of patients(43%) belonged to age 40-50 years. 26.9% belonged to post menopausal age group. 55.4% were multiparous with 3 or more children and were found to be at increased risk of precancerous and cancerous lesion of the cervix, though statistically not significant. Most of the patients presented with white discharge per vaginum(38.5%). The sensitivity, specificity, positive predictive value and negative predictive value of pap smear in detecting premalignant and malignant lesions of the cervix was 72.40%, 88.10%, 63.60% and 91.80% respectively. Conclusion: Pap smear was found to be an effective tool in detecting early cervical lesions and screening of carcinoma cervix .

Keywords: pap smear, cytology, cervical biopsy, histopathology

1. Introduction

Cervical cancer is the fourth most common cancer in women, and the seventh overall , with an estimated 528,000 new cases in 2012. Higher incidence is found in the less developed countries , contributing to around 85% of the reported cases annually. It accounts for almost 12% of all female cancers. Almost nine out of ten cervical cancer deaths occur in the less developed regions (WHO 2015)¹. Economically advantaged countries have significantly lower cervical cancer rates and add only 3.6% of new cancers. This incidence disparity highlights success achieved by cervical cancer screening programmes in which Pap smear is regularly obtained².

Prevention of invasive cancer by early detection and treatment of cervical intra epithelial neoplasm (CIN) currently offers the most cost effective long-term strategy for cervical cancer control^{3, 4}. The goal of screening is to diagnose and treat carcinoma cervix in early pre-invasive state, which makes the disease ideal for screening procedures.

Cervical cancer screening was first started in United States in the late 1940s after Dr George Papanicolaou developed the Pap smear. Papanicolaou and Traut, in 1941, refined the vaginal pool cellular collection technique for cytological screening of cervical cancer which would allow pre-invasive carcinoma to be recognized in an asymptomatic population. Pap's test is a cytodiagnostic tool done on superficial cells of genital tract particularly cervix. Exfoliative cytology, that is, study of cells which are shed off from various tissues of the body due to some physiological or some pathological process is the basis of the test⁵.

Aims and Objectives

- 1) To find out efficacy of pap smear cytology in screening of cervical lesions and to correlate with histopathology findings.
- 2) To evaluate various other demographical, social and economic factors associated with premalignant and malignant cervical lesions.

2. Materials and Methods

This was a prospective clinical study done, in which 130 women attending the gynaecology OPD of Father Muller Medical College Hospital from 2015 to 2017 were evaluated. Approval of the ethical committee was taken. The required data was collected by a pre set questionnaire, and informed consent was taken from each woman.

Inclusion Criteria

- Women of age between 20-65 yrs.
- Women with post coital bleeding, metrorrhagia, post menopausal bleeding, vulval itching.
- Women with foul smelling discharge per vaginum not responding to antibiotics.
- Women with unhealthy cervix or cervical erosions.

Exclusion Criteria

- Women previously treated for carcinoma cervix.
- Women with frank lesion.
- Women with previous cervical surgery.
- Women with evidence of acute pelvic infection.
- Pregnant women

As per the inclusion and exclusion criteria, 130 women attending the Gynaecology OPD, Father Muller Medical

College Hospital, from 2015-2017 were considered for the study and subjected to pap smear and cervical biopsy. A standard proforma was prepared and the clinical details and findings were entered. Pap smear was taken first, and then biopsy done. The biopsy details were entered and finally, the treatment availed. The pap smear results were categorised according to Bethesda 2001 classification system.

Squamous epithelial cell abnormality was divided into five categories including:

- Atypical Squamous Cells of Undetermined Significance (ASC-US)
- Atypical squamous cells – cannot exclude HSIL (ASC-H)
- Low grade squamous intraepithelial lesion (LSIL),
- High grade squamous intraepithelial lesion (HSIL)
- Squamous cell carcinoma (SCC).

On the other hand, glandular epithelial abnormalities were divided into three categories including:

- Atypical Glandular Cells not otherwise specified (AGC),
- Endocervical *in situ* adenocarcinoma (AIS),
- Adenocarcinoma.

Cervical biopsy was taken from abnormal areas and were categorized into:

- Normal /Chronic cervicitis
- CIN I (Cervical intra epithelial neoplasia)
- CIN II
- CIN III
- SCC(Squamous cell carcinoma)

3. Results

Results were calculated using Software used SPSS 2.0. Tests used Kappa statistics for agreement, ROC Curve Analysis, Chi Square Tests.

Table 1: Age Distribution of the Study Population

			BIOPSY					Total
			Normal	CIN I	CIN II	CIN III	SCC	
Age	<30	Count	6	2	0	0	0	8
		%	7.6%	9.1%	0.0%	0.0%	0.0%	6.2%
	31-40	Count	22	6	2	1	2	33
		%	27.8%	27.3%	50.0%	12.5%	11.8%	25.4%
	41-50	Count	38	9	1	3	6	57
		%	48.1%	40.9%	25.0%	37.5%	35.3%	43.8%
	51-60	Count	4	3	1	3	4	15
		%	5.1%	13.6%	25.0%	37.5%	23.5%	11.5%
	>60	Count	9	2	0	1	5	17
		%	11.4%	9.1%	0.0%	12.5%	29.4%	13.1%
Total		Count	79	22	4	8	17	130
		%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

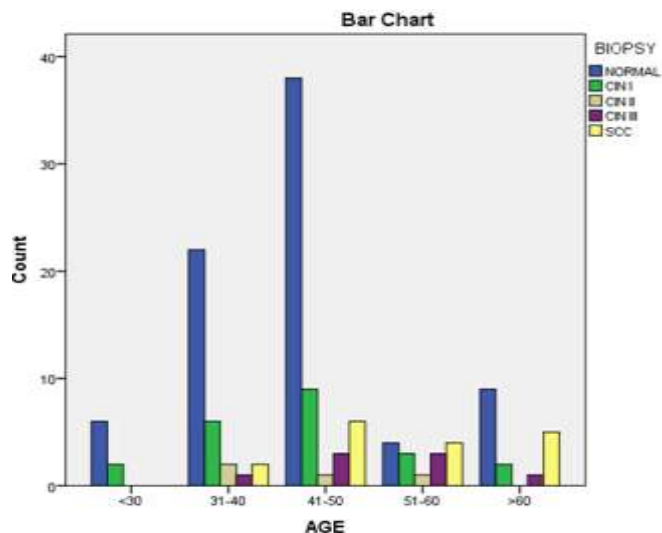


Figure 1: Correlation of Age with Histopathology

The mean age was 45.8+/- 10.77 years with a range from 24 to 65 years, and 43% of the patients belonged to age group 40-50 years. Out of 17 patients who were detected to have SCC on biopsy, 6 patients belonged to age group 41-50 years, and 5 belonged age group > 60 yrs. Only 2 patients were detected to have SCC between the age group 18-40 yrs. It was seen in the study that as the age increased, incidence of malignant and premalignant lesions also increased, though it was not statistically significant (Fisher's Exact test : 19.128; p value : 0.142).

Table 2: Parity Wise Distribution of the Study Population

		HISTOPATHOLOGY					Total
		Normal	CIN I	CIN II	CIN III	SCC	
Parity	0	1	1	0	0	0	2
	1	3	0	0	0	0	3
	2	34	10	2	3	4	53
	3	18	9	2	2	6	37
	>3	23	2	0	3	7	35
TOTAL		79	22	4	8	17	130

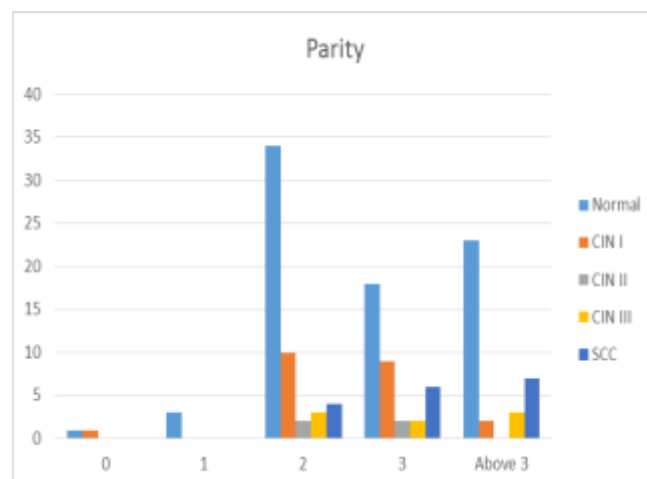


Figure 2: Correlation of Parity with Histopathology

It was seen in the study that 55.38% were multiparous with 3 or more children. Women with parity 3 and more were at increased risk of precancerous and cancerous lesion of cervix (43.05%), though not significant (Fisher's Exact test: 31.29; p value: 0.896).

Table 3: Reproductive Age Phase of the Study Population

Reproductive Age Phase	Number of Patients	% of Patients
Reproductive	57	43.9%
Peri Menopausal	38	29.2%
Post Menopausal	35	26.9%
Total	130	100%

Totally, 35 patients (26.92 %) were in post menopausal age group. Out of which 48.57 % (17) of the patients had cancerous and pre cancerous lesions.

Table 4: Socioeconomic Status Wise Distribution of the Study Population

		HISTOPATHOLOGY					
		NORMAL	CIN I	CIN II	CIN III	SCC	TOTAL
SOCIO-ECONOMICSTATUS	LOW	44 (55.7%)	12 (54.5%)	2 (50%)	7 (87.55%)	14 (82.4%)	79 (60.8%)
	MIDDLE	28 (35.4%)	10 (45.5%)	2 (50%)	0 (0%)	3 (17.6%)	43 (33.1%)
	HIGH	7 (8.9%)	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)	8 (6.2%)
TOTAL		79	22	4	8	17	130

60.8% belonged to the lower socio economic class out of which 36% had precancerous and cancerous lesion of the cervix. It was seen in the study that women belonging to low socioeconomic class had higher incidence of premalignant

and malignant lesions of the cervix, though it was not statistically significant(Fisher's Exact test:11.828; p value : 0.103).

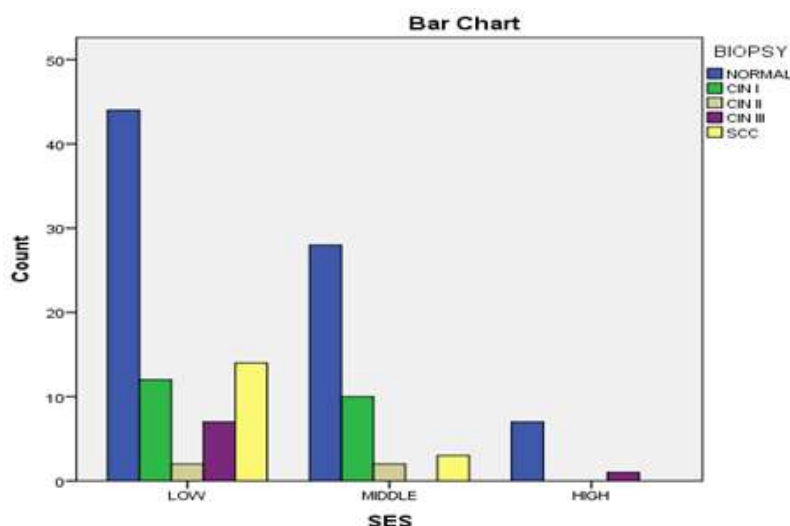


Figure 3: Corelation of Socioeconomic Status with Histopathology

Table 5: Various Clinical Presentations in the Study Population

			BIOPSY					Total
			NORMAL	CIN I	CIN II	CIN III	SCC	
Symptoms	White Discharge Per Vaginum	Count	27	12	2	4	5	50
		% within BIOPSY	34.2%	54.5%	50.0%	50.0%	29.4%	38.5%
	Abnormal Uterine Bleeding	Count	31	4	0	1	4	40
		% within BIOPSY	39.2%	18.2%	0.0%	12.5%	23.5%	30.8%
	Post Menopausal Bleeding	Count	7	2	0	2	5	16
		% within BIOPSY	8.9%	9.1%	0.0%	25.0%	29.4%	12.3%
	Post Coital Bleeding	Count	1	0	0	0	2	3
		% within BIOPSY	1.3%	0.0%	0.0%	0.0%	11.8%	2.3%
	Others/ Asymptomatic	Count	13	4	2	1	1	21
		% within BIOPSY	16.5%	18.2%	50.0%	12.5%	5.9%	16.2%
	Total	Count	79	22	4	8	17	130
		% within BIOPSY	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

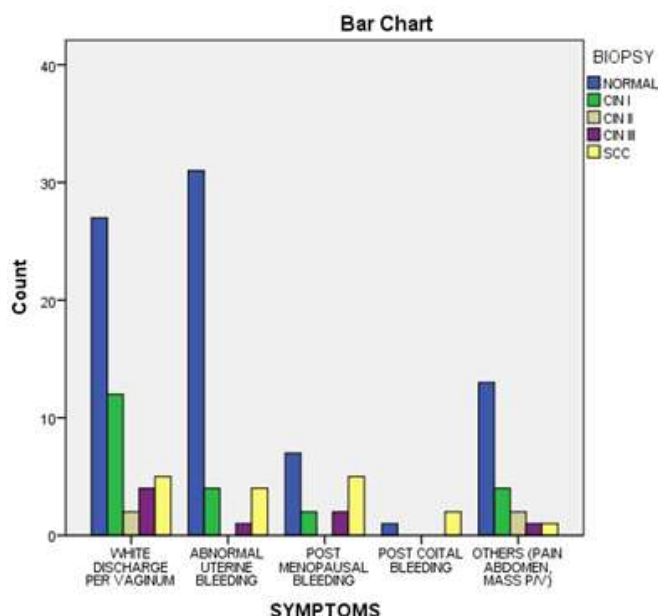


Figure 4: Correlation of Clinical Presentation With Histopathology

In the present study, the most common clinical presentation was white discharge per vaginum(38.5%), followed by abnormal uterine bleeding(30.8%).The other presentations were post menopausal bleeding and post coital bleeding. Around 16.2% of the patients were asymptomatic and were found to have abnormal pap smear on routine screening.

Table 6: Frequency of PAP Smear For Each Pathological Diagnosis

			PAP SMEAR						Total
			NORMAL	ASCUS	ASC-H	LSIL	HSIL	SCC	
BIOPSY	NORMAL	Count	59	8	10	0	2	0	79
		%	74.7%	44.4%	58.8%	0.0%	16.7%	0.0%	60.8%
	CIN I	Count	16	6	0	0	0	0	22
		%	20.3%	33.3%	0.0%	0.0%	0.0%	0.0%	16.9%
	CIN II	Count	1	2	0	1	0	0	4
		%	1.3%	11.1%	0.0%	100.0%	0.0%	0.0%	3.1%
	CIN III	Count	2	2	2	0	2	0	8
		%	2.5%	11.1%	11.8%	0.0%	16.7%	0.0%	6.2%
	SCC	Count	1	0	5	0	8	3	17
		%	1.3%	0.0%	29.4%	0.0%	66.7%	100.0%	13.1%
Total		Count	79	18	17	1	12	3	130
		%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

The study showed that out of 79 patients who had normal pap smear, 59 patients had normal biopsy report and 16 patients had CIN I report. Only 1 patient was detected to have malignancy. Out of 3 patients whose Pap smear was reported as SCC, all the 3 were reported as SCC on cervical biopsy. Pap smear showed 12 patients to be having HSIL,

out of which 8 was proven to be SCC on biopsy and 2 were reported as CIN III. Only 2 patients had normal biopsy report. This showed that in most of the patients pap smear and histopathology correlated with each other, which was statistically significant (Pearson Chi square: 118.431; p value: < 0.001).

Table 7: Statistical Comparison of PAP Smear Cytology To Histopathology

Parameter	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy	KAPPA Statistics	P Value
PAP SMEAR	72.40%	88.10%	63.60%	91.80%	84.62%	0.577	<0.001

On comparison of the test group Pap smear with the gold standard of histopathology, the test group has a sensitivity of 72.4 % and specificity of 88.1%. The test has a Positive predictive value of 63.6% and Negative predictive value of 91.8%. The test and the gold standard agree on 110 out of 130 having a diagnostic accuracy of 84.62%. The Kappa value of 0.577 indicates Good agreement with a p value of <0.001.

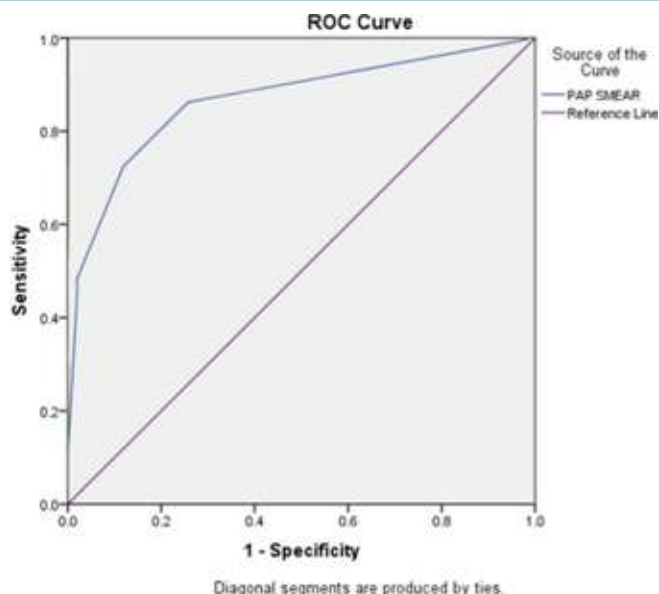


Figure 5: ROC(Receiver Operating Characteristic) Curve

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PAP SMEAR	.867	.044	<.001	.781	.952

Table 8: ROC Curve Interpretation

Test Result Variable(s)	Positive if Greater Than or Equal To	Sensitivity	specificity
PAP SMEAR	0	100.00%	0.00%
	1.5	86.20%	74.30%
	2.5	72.40%	88.10%
	3.5	48.30%	98.00%
	4.5	44.80%	98.00%
	5.5	10.30%	100.00%
	7	0.00%	100.00%

It was observed in our study that the optimal cut-off point was ASC-H, and this cut-off yielded a sensitivity of 72.40% and specificity of 88.10% to detect high grade lesions. When ASCUS was taken as cut off, sensitivity increased to 86.20%, but specificity reduced to 74.30%.

4. Discussion

Incidence of cervical cancer is very and the major burden lies on the less developed countries, because of the poor implementation of prevention programmes. An organised national screening programs using Pap's test would produce better results in reducing cervical cancer incidence as proved by various other studies.

In the present study, various patient characteristics were analysed, and pap smear cytology was compared with histopathology. The mean age in the present study was 45.8 years. In the studies done by Shojaei et al(2013) and Kohli et al (2014)⁶, the mean age was 40.9 years and 39.9 years respectively. The present study showed a trend of increasing incidence of malignant and pre malignant lesions with increasing age, which was not statistically significant.

It was seen that multiparous women with 3 or children had increased incidence of cancerous and precancerous lesion of the cervix, which correlated with the study done by Patil et al(2015)⁷. Most of the patients in the study group belonged to low socioeconomic class(60.8%), which was similar to study done by Patil et al (2015).higher incidences of cervical malignant and premalignant lesions were found in lower socioeconomic strata in the present study, though not statistically significant. Most of the patients presented with white discharge per vaginum (38%), which was comparable to the study done by Kumari et al (2015)⁸. Second most common symptom was bleeding per vagina (30.8%).

This study showed that the sensitivity, specificity, Positive predictive value and Negative predictive value of Pap smear in detecting cervical lesion was 72.40%, 88.10%, 63.60% and 91.8% respectively with diagnostic accuracy of 84.62. Analysis of various other studies showed almost similar results, with slightly higher sensitivity (table 9).

Table 9: Comparison with Other Studies

Study	Sensitivity	Specificity	Diagnostic Accuracy
Goel et al ⁹ (2001)	50.00%	97%	
Cronje et al ¹⁰ (2003)	53.30%	95%	
Kohli et al (2014)	80%	64.29%	
Patil et al (2015)	63%	95%	86%
Present study	72.4	88.10%	84.62%

The main limitation of the study was that the sample taken for the study was from the population attending the OPD, and hence did not represent general population. So, sensitivity and specificity might be higher in this study.

5. Conclusion

The regular screening of population by pap smear is a cost effective and easy method for early detection of pre malignant and malignant cervical lesions and down staging of carcinoma cervix. Hence, it should be recommended as a method of improving reproductive health, as well as a main screening tool. Since cervical cytology is also limited by both false positives and false negatives, it should be compared with other screening procedures like VIA, colposcopy and thorough gynaecological examination.

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