Original Research

Cytohistopathological Correlation of 884 Cervical Pap Smears as Bethesda System 2014: A Hospital-Based Study

Anju Khairwa [1, 2, *]

1. Department of Pathology, University College of Medical Science, Delhi, India; E-Mail: anjukhairwa@gmail.com
2. Department of Pathology, ESIC Model Hospital Gurugram, India

* **Correspondence:** Anju Khairwa; E-Mail: anjukhairwa@gmail.com

Abstract

Cervical carcinoma is most common in Indian women of which Rural women are predominantly affected. The most common etiological factor is human papillomavirus (HPV). The present study aims to assess the diagnostic accuracy, sensitivity, specificity, and different patterns of cervical Pap smears by comparing histological findings. The index study is a retrospective cross-sectional analytical study. The data was collected at the pathology department from May 2017 to December 2019 according to hospital ethical protocol. Cervical Pap smears received by the pathology department underwent Pap staining. A total of 884 Pap smears were satisfactory and included in the study. The age of enrolled women was 46.4 ± 9.7 years. 800 cervical Pap smears were reported as negative for intraepithelial lesion (NILM), and 84 Pap smears were reported as abnormal. Abnormal pap smears included 64 (7.1%) atypical squamous cell-undetermined significance (ASC-US), 9 (1.01%) low-grade squamous intraepithelial (LSIL), 5 (0.56%) high-grade squamous intraepithelial lesion cannot be ruled out (ASC-H), 3 cases (0.33%) of high grade squamous intraepithelial lesion (HSIL), 2 cases (0.22%) of atypical glandular cell-not specific otherwise (AGC-NOS) and 1 case (0.11%) of squamous cell carcinoma. The cytohistological correlation was found in 56 patients, including 41.07%

with chronic cervicitis, 26.75% with chronic cervicitis with squamous metaplasia, 5.35% with cervical polyps, 3.57% with CIN-1, 14.28% with carcinoma in situ, 7.14% with squamous cell carcinoma (keratinizing), 1.78% with squamous cell carcinoma (non-keratinizing) patients. Cytohistological correlation of 56 cases revealed sensitivity (83.33%), specificity (94.73%), PPV (88.23%), NPV (92.3%) and accuracy (91.07%). The cervical Pap test is cost-effective, almost as sensitive, and accurate as histology in screening for cervical lesions.

Keywords
Cervical Pap smear; histology; correlation; carcinoma

1. Introduction

Cervical cancer is the most common tumor among women in India. Cervical cancer is a worldwide health problem and is the second most common female neoplasm in the world. Cervical cancer severely affects women's health. There are approximately 510,000 new cases of cervical cancer annually worldwide [1]. In India, rural women are more affected than urban women which might be related to poor hinge, lack of awareness and low socioeconomic status. Cervical cancer has several etiological factors, and human papillomavirus (HPV) is the most common cause of cervical cancer [2].

Cervical cancer can be detected early and is preventable because it has a prolonged pre-invasive state [3]. The availability of screening programs like cervical Pap smears is an effective option to treat the pre-invasive lesion of the cervix [3]. The cervical smear, known as the Pap test, is used as a worldwide cervical cancer screening test. Still, women continue to die from cervical cancer, because of a lack of awareness, especially in rural areas [4]. In developed countries, the incidence of cervical cancer was 58% and the mortality rate was markedly decreased up to 71% due to cervical Pap screening programs implicated in the early 1950s in the United States [5]. Thus, cervical Pap screening programs are longstanding and very successful programs. Such screening programs should be applied in developing countries, especially in rural areas strictly and regularly to overcome the burden of cervical cancer.

The Pap smear is an effortless, simple, non-invasive, rapid and effective screening procedure. The cervical biopsy is an invasive procedure, however, it is considered the gold standard for diagnosing cervical lesions [6]. The indexed study aims to assess the diagnostic accuracy, sensitivity, specificity, and different patterns of cervical Pap smears by comparing histological findings. Cytohistological correlation is an excellent way to determine the internal quality of the Pap test and efficacy of the Pap test.

2. Materials and Methods

This is a retrospective cross-sectional analytical study conducted in the pathology department of a secondary care hospital from May 2017 to December 2019 according to hospital ethical protocol. Cervical smears and biopsies were taken by the gynecologist and sent to the pathology department after obtaining informed and written consent from patients. Pap smears are processed in the cytology sections of the department, and the biopsy is performed in the histopathology sections of

the department. Usually, there was a two-week interval between cervical pap smears and biopsy samples, but it can vary.

The cervical pap smears were screened and made a final report by the pathologist.

2.1 Inclusion Criteria

- All females aged >20 years with symptoms of abnormal vaginal discharge, abdominal pain, irregular menstrual bleeding, postmenopausal bleeding, postcoital bleeding, prolapse, and burning micturition.

2.2 Exclusion Criteria

- The females <20 years,
- Unsatisfactory smear evaluation,
- Pregnant women,
- Post-total hysterectomy patients.

Data like age, socioeconomic status, and clinical history, including symptoms and signs, were collected.

The Pap smears were fixed in methanol and stained by conventional PAP staining technique, mounted with DPX and examined under a light microscope. The cytological reporting of the smears was performed according to the Bethesda system 2014 [7].

Biopsy specimens were received in 10% formalin fixative. The biopsy specimens were processed routinely and embedded in paraffin blocks and stained with hematoxylin and eosin (H&E) stain. The cytology of Pap smears was correlated with histopathology findings.

2.3 Statical Analysis

We used SPSS 16 software for statistical analysis. Continuous data were reported as mean ± SD for normally distributed variables and as median with an interquartile range for skewed variables. Categorical data were reported as percentages. A p-value <0.05 was considered statistically significant.

This study was performed according to the institute's ethical committee protocol, which follows Helsinki guidelines.

3. Results

In the indexed study, we collected a total of 900 cervical Pap smears from May 2017 to December 2019, of which 16 were identified as unsatisfactory for exclusion, resulting in a total of 884 cervical Pap smears included. Of the 884 Pap smears included, 84 smears were reported as abnormal cervical Pap smears. The age of enrolled women was 46.4 ± 9.2, and the age range was 24-80 years. Most women had a history of white discharge per vagina (50%) and pain in the lower abdomen (20%), as shown in Figure 1.
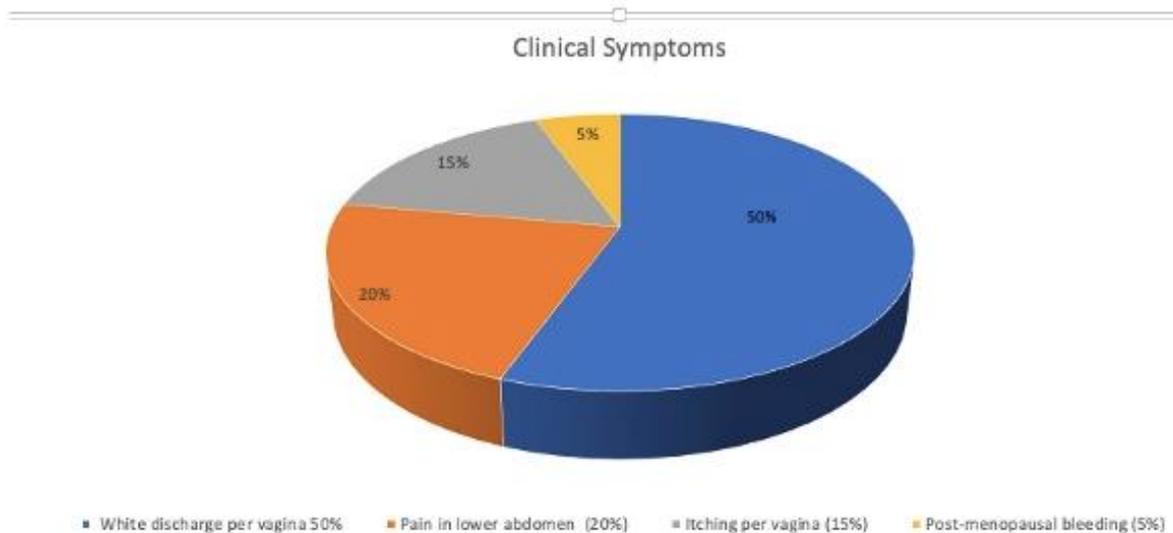
Figure 1 Clinical presentation of cervical Pap smears cases.

A total of 800 cervical Pap smears were reported as negative for intraepithelial lesion (NILM), including inflammatory smears with altered flora (30%) and bacterial vaginosis (20%), as depicted in Figure 2.
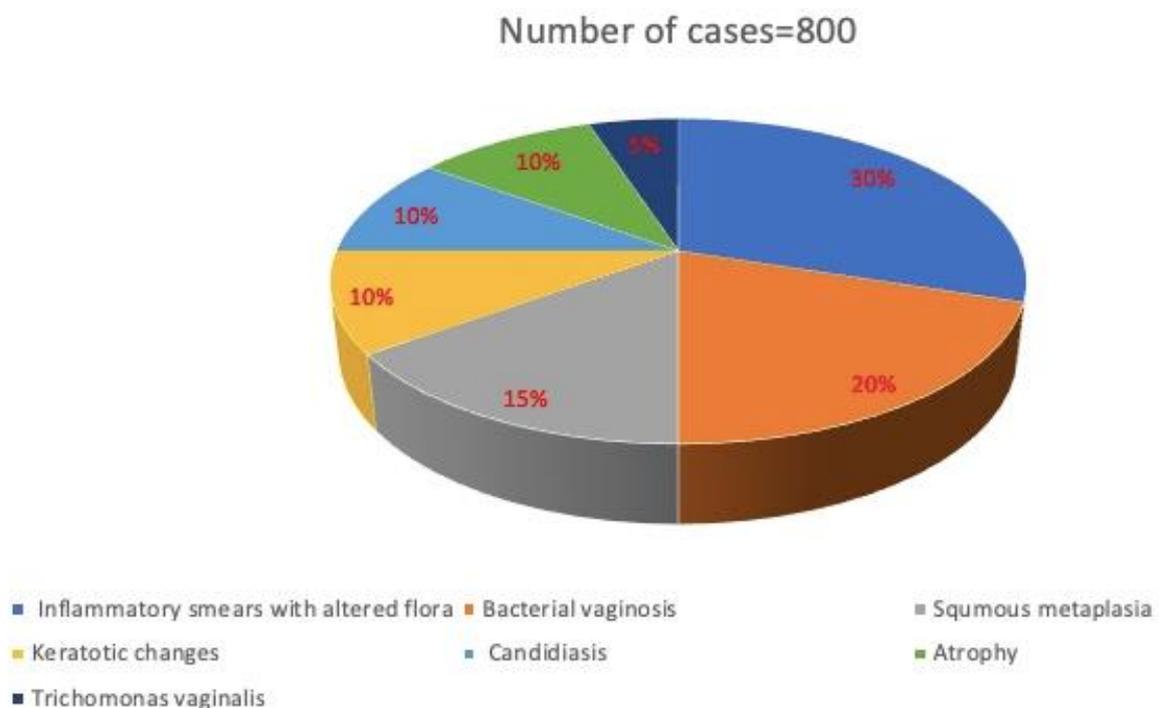
Figure 2 The pattern of negative for intraepithelial lesion (NILM) of cervical Pap smears.

Of the 84 abnormal cervical Pap smears with intra-epithelial lesions, 64 (7.1%) were atypical squamous cell-undetermined significance (ASC-US), 9 (1.01%) were low-grade squamous intraepithelial (LSIL), 5 (0.56%) were high-grade squamous intraepithelial lesion cannot be ruled out (ASC-H), 3 (0.33%) were high-grade squamous intraepithelial lesion (HSIL), 2 cases (0.22%) were

atypical glandular cell-not specific otherwise (AGC-NOS) and 1 case (0.11%) was squamous cell carcinoma. The histological findings were found in 56 patients, which are depicted in Table 1.

Table 1 Histopathological findings in 56 patients.

Histopathological findings	Number of cases	Percentage
Chronic cervicitis	23	41.07%
Chronic cervicitis with metaplasia	15	26.77%
Cervical polyps	3	5.35%
Cervical intraepithelial neoplasia (CIN 1)	2	3.59%
Carcinoma in situ	8	14.28%
Squamous cell carcinoma keratinized	4	7.16%
Squamous cell carcinoma non-Keratinized	1	1.78%
Total	56	100%

The cytohistological correlation is possible in 56 cases. The correlation of histology to cervical Pap smears is described in Table 2 and Table 3.

Table 2 Cyto-histopathological correlation of Pap smears and cervical biopsies/hysterectomies is available in 56 cases.

| Cytology diagnosis	No. of cases of Pap smear (%)	Chronic cervicitis	Cervicitis with squamous metaplasia	Cervical polyp	CIN 1	CIS	SCC-K	SCC non-K
NILM	90.4% (800)	41.07% (23)	23.21% (13)					
ASC-US	7.21% (64)			**5.35% (3)**	1.78% (1)	1.78% (1)		
LSIL	1.01% (9)				1.78% (1)	5.35% (3)		
ASC-H	0.56% (5)					7.14% (4)	1.78% (1)	
HSIL	0.33% (3)						5.35% (3)	
AGC-NOS	0.22% (2)		**Negative correlation (-ve) 3.57% (2)**				-	-
SCC	0.11% (1)							1.78% (1)

SCC - Squamous cell carcinoma, CIS - Carcinoma in situ, K - keratinizing, NILM-negative intra-epithelial lesion, ASC-US-atypical squamous cell-undetermined significance, LSIL-low grade squamous intraepithelial lesion, ASC-H - high grade squamous intraepithelial lesion cannot be ruled out, HSIL - high grade squamous intraepithelial lesion, AGC-atypical glandular cell-not otherwise specific.

Table 3 Correlation between cervical Pap smear and histopathological diagnosis.

Pap Smears	Biopsy& hysterectomy specimen		Total
	Positive	**Negative**	
Positive	(TP) 15	(FP) 02	17
Negative	(FN) 03	(TN) 36	39
Total	18	38	56

TP-True positivity, FP-False positivity, FN-False Negative, TN- True Negative

Figure 3 describes the cytohistological correlation between cervical Pap smears (LSIL) and biopsies.
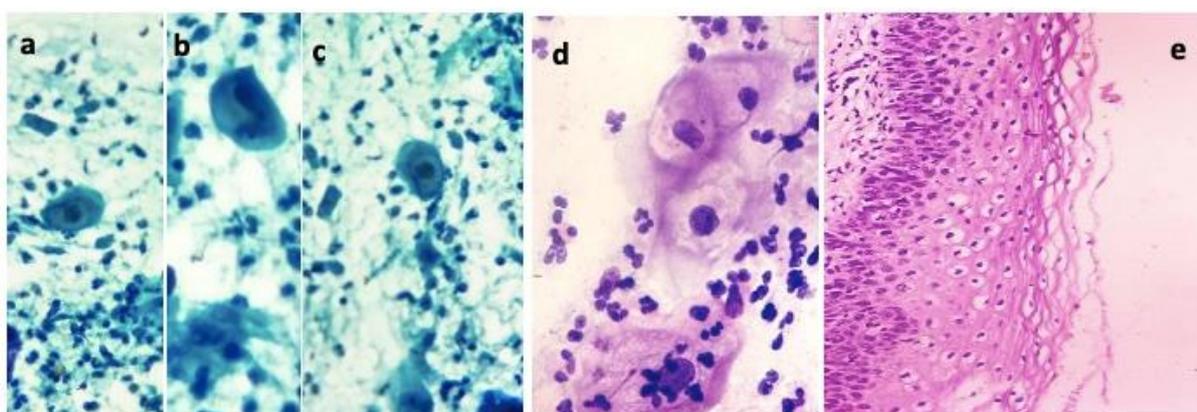
Figure 3 Cytohistological correlation. A panel of microphotographs (a), (b), (c) & (d) showing koilocytosis with nuclear atypia on Pap smears, (Pap stain, x40), (e) CIN-1 with Koilocytosis (H&E, x10), sections of the corresponding smears (a, b, c & d).

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of cervical Pap smears were described in Table 4.

Table 4 Sensitivity and specificity of cervical Pap smears.

Sensitivity	83.33%
Specificity	94.73%
Positive predictive value (PPV)	88.23%
Negative predictive value (NPV)	92.30%
Accuracy	91.07%

In our hospital, most patients were screened with Pap smears and later the diagnosis was confirmed with a biopsy when available. The patients were managed according to the ASCCP 2012/Bethesda 2014 category [7].

4. Discussion

The present study was hospital-based with a case age range of 24-80 years, as described by Patil et al. [8], the cervical Pap smears technique is the best way to screen precursor lesions of the cervix. Early detection of precancer lesions of the cervix helps to treat these cases before the progression of the lesion. The chief complaint of cases was whitish discharge per vagina (50%), which was similar to another study [9]. On Pap smears, we found the maximum cases were NILM (90.4%) according to the Bethesda 2014 report, which t was correlated with other studies [10, 11].

We found 9.5% of cervical Pap smears were abnormal (intra-epithelial lesions), which was lower than the 16.86% of intra-epithelial lesions reported in the study by Warpe et al. [12]. Bindroo et al. reported epithelial abnormality in 40.4% of cases, the most common of which was ASC-US (15.6%) [13]. In the present study, we also found ASC-UC in most of the cases, accounting for7.1%. In addition, we found a cytohistological correlation in 56% of cases, with chronic cervicitis and squamous cell metaplasia in most of the patients (64.3%), but lower than the 93% and 91% reported in other studies [9, 13]. The LSIL, HSIL and SCC were fully correlated with histopathology in the present study in available data which was comparable to another study [14].

The sensitivity, specificity, PPV, NPV and accuracy of the present study compared with other studies are shown in Table 5.

Table 5 Comparison of the present study with other studies.

Studies	Sensitivity	Specificity	PPV	NPV	Accuracy
Index Study	**83.33%**	**94.73%**	**88.23%**	**92.30%**	**91.07%**
Bindroo, et al. [13] (2019)	75.24%	97.98%	96.2%	85.38%	88.8%
Patil et al. [8] (2016)	77.7%	84.2%	70.0%	88.8%	82.1%
Dhakal et al. [15] (2016)	77.80%	100%	100%	97%	-
Bamanikar et al. [16] (2016)	89.47%	88.70%	82.92%	-	-
Joshi et al. [10] (2015)	65.38%	95.83%	94.4%	71.8%	80.0%
Atla et al. [14] (2015)	94.11%	64.28%	82.75%	85.0%	83.33%
Chaudhary et al. [17] (2014)	79.37%	81.02%	65.79%	89.52%	-

The sensitivity of cervical smears reported in the present study (83.3%) was higher than that reported in other studies [8, 10, 13, 15-17]. The specificity reported in the present study (94.73%) was much higher than that reported by Patil et al., Bamanikar et al., Atla et al. and Chaudhary et al studies [8, 14, 16, 17]. As shown in Table 5, the index study reported relatively higher PPV and NPV

than other studies, but slightly lower than a few studies. Moreover, the present study reported the highest accuracy of cervical Pap smears (91.07%) compared to other studies [8, 10, 13, 14].

In the literature review, various studies from India and around the world have shown the significance of Pap smears in cervical cancer screening, as described following.

Shaki et al. reported 1100 women aged 21-65 years as outdoor patients attending a medical camp in urban Mumbai, India, and most of the cases were benign, including about 581 (52.8%) NILM, 203 (18.4%) inflammatory, 45 (4%) ASC-US, 75 (6.8%) LSIL, and 74 women (6%) with HSIL [18]. They concluded that the Pap smear is a very easy, non-invasive, safe, and very economical tool to detect pre-invasive cervical epithelial lesions and recommended that every woman above the age of 30-35 years must undergo cervical screening and this must be continued in postmenopausal [18].

Heena et al. recruited 395 participants, most of whom were nurses (66.1%), the mean age of the participants was 34.7 years, 60.5% of participants were married, only 16 (4.0%) participants appeared to have good knowledge of cervical cancer (in terms of risk factors, vulnerability, signs and symptoms, prevention and screening modalities) and 58 (14.7%) participants had adequate knowledge. Only 86.8% of participants received a Pap smear that could be useful for detecting cervical cancer, and 26.2% of participants had a Pap smear [19]. They concluded that formal educational programs are needed for healthcare workers to improve their knowledge of the risk factors and early signs and symptoms of cervical cancer [19].

Wilailak et al. reported that in 2020, WHO endorsed a comprehensive strategy to eradicate cervical cancer at a threshold of 4 cases per 100 000 women in the 21st century, with the help of a triple worthy interference strategy including 90% of girls fully vaccinated by age of 15, 70% of women screened by age 35 and again by age 45 to achieve 90% of women with precancers should be treated, and 90% of women with invasive cancer should be managed. In countries with high incidences of cervical cancer, a huge attempt is required to control the challenges [20].

We managed or treated our patients according to ASCCP 2012/Bethesda 2014 guidelines recommendations. According to ASCCP 2012 guidelines, ASC-US and LSIL patients were managed with serial cytology for one year or three years. Colposcopy and biopsy were performed as needed in patients with ASC-H, AGC and HSIL [7, 21].

5. Conclusion

We concluded that the cervical Pap smear has good sensitivity and excellent specificity along with accuracy in detecting cervical lesions compared to biopsies/hysterectomy specimens. We also found a significant correlation between the cervical Pap smears and the histology of biopsies/hysterectomy specimens. The cytohistological correlation between cervical Pap smear and biopsy is a good technique for improving the quality of the screening program. We recommend routine or regular screening of the population by cervical Pap smears, which help early detection of precancers and cancers lesions of the cervix as the Pap smear is very cost-effective, accessible, rapid, non-invasive, and feasible everywhere. The patients should be managed according to ASCCP 2012/Bethesda 2014 guidelines.

Author Contributions

Dr Anju Khairwa is the only author and has done all work alone.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Frost JK. Gynecologic and obstetric cytopathology. In: Philadelphia: W.B. Saunders; 1979. p.634.
2. National Institutes of Health Consensus Development Conference Statement: Cervical cancer, April 1-3, 1996. National Institutes of Health Consensus Development Panel. J Natl Cancer Inst Monographs. 1996; vii-xix. PMID: 9023821.
3. Patil S, Patil A, Solanke P. Cytological screening for early diagnosis of cervical intraepithelial neoplasia (CIN) and early carcinoma of the cervix. Int J Sci Res Publ. 2015; 5.
4. World Health Organization. Comprehensive cervical cancer control: A guide to essential practice. Geneva: WHO; 2006. pp. 32-49.
5. Dickinson JA, Stankiewicz A, Popadiuk C, Pogany L, Onysko J, Miller AB. Reduced cervical cancer incidence and mortality in Canada: National data from 1932 to 2006. BMC Public Health. 2012, 12: 992.
6. Shaw PA. The history of cervical screening I: The Pap test. J SOGC. 2000; 22: 110-114.
7. Nayar R, Wilbur DC. The Bethesda system for reporting cervical cytology. 3rd ed. Swiss: Springer International Publishing Switzerland; 2015.
8. Patil PR, Jibhkate SN. Cytohistopathological correlation of Papanicolaou smears: A hospital-based study. Int J Reprod Contracept Obstet Gynecol. 2016; 5: 1695-1699.
9. Alakananda SU, Biswas I. Histopathological correlation with cervical cytology. IIOSR J Dent Med Sci. 2016; 15: 2279-2861.
10. Joshi C, Kujur P, Thakur N. Correlation of Pap smear and colposcopy in relation to histopathological findings in detection of premalignant lesions of cervix in a tertiary care centre. Int J Sci Stud. 2015; 3: 55-60.
11. Malpani G, Agrawal P, Varma AV, Khandelwal N, Tignath G. Cervical Pap smear study and detection of abnormal epithelial lesions and determination of its accuracy by cytohistological correlation in patients of tertiary care teaching hospital in central India. Int J Reprod Contracept Obstet Gynecol. 2016; 5: 2312-2316.
12. Warpe BM, Warpe SJ, Sawant SS. An institution-based cervical Pap smear study, correlation with clinical findings & histopathology in the Konkan region of Maharashtra state, India. Walawalkar Int Medical J. 2016; 3: 3751.
13. Bindroo S, Garg M, Gitika. Correlation of cervical Pap smear with histopathological diagnosis in cervical lesions: A 2 years retrospective study. Int J Contemp Med Res. 2019; 6: g17-g20.
14. Atla BL, Uma P, Shamili M, Kumar SS. Cytological patterns of cervical Pap smears with histopathological correlation. Int J Res Med Sci. 2015; 3: 1911-1916.
15. Dhakal R, Makaju R, Sharma S, Bhandari S, Shrestha S, Bastakoti R. Correlation of cervical Pap smear with biopsy in the lesions of cervix. Kathmandu Univ Med J. 2016; 14: 254-257.
16. Bamanikar SA, Chandanwale SS, Baravkar DS, Dapkekar P. Study of cervical Pap smears in a tertiary hospital. Indian Med Gaz. 2014: 148: 250-254.
17. Chaudhary RD, Inamdar SA, Haran C. Correlation of diagnostic efficacy of unhealthy cervix by cytology, colposcopy, and histopathology in women of rural areas. Int J Reprod Contracept Obstet Gynecol. 2014; 3: 213-219.

18. Shaki O, Chakrabarty BK, Nagaraja N. A study on cervical cancer screening in asymptomatic women using Papanicolaou smear in a tertiary care hospital in an urban area of Mumbai, India. J Family Med Prim Care. 2018; 7: 652-657.

19. Heena H, Durrani S, AlFayyad I, Riaz M, Tabasim R, Parvez G, et al. Knowledge, attitudes, and practices towards cervical cancer and screening amongst female healthcare professionals: A cross-sectional study. J Oncol. 2019; 2019: 5423130.

20. Wilailak S, Kengsakul M, Kehoe S. Worldwide initiatives to eliminate cervical cancer. Int J Gynecol Obstet. 2021; 155: 102-106.

21. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2013; 17: S1-S27.

Enjoy *OBM Genetics* by:

1. Submitting a manuscript
2. Joining in volunteer reviewer bank
3. Joining Editorial Board
4. Guest editing a special issue

For more details, please visit:
http://www.lidsen.com/journals/genetics