

# TRENDS IN CERVICAL PAP SMEAR CYTOLOGY IN A TERTIARY HOSPITAL: IMPLICATIONS FOR CERVICAL CANCER SCREENING IN LOW-INCOME COUNTRIES

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## Abstract

**Background:** Screening rate for cervical cancer in Nigeria is low and not much is known about the changing trend in the premalignant stages of the disease.

**Objective:** To evaluate the trend of epithelial cell abnormality in the Pap smear in the past 10 years.

**Methods:** A 10-year review of cervical smear cytology (2008 -2017) at a tertiary institution in Nigeria using clinical and histopathological records. There were 5850 cervical smear cytology during the period.

**Results:** A total of 5212 (89.1%) were analyzed. The modal age ranged from 35 to 44years. Majority 4481 (85.9%) of the smears were negative (Negative intraepithelial lesion or malignancy). Smear unsatisfactory for interpretation accounted for 398(7.6%). The prevalence of abnormal Pap smear

was 6.5% (CI 5.8% - 7.1%). ASCUS -3.5%, LSIL – 2.2%, HSIL – 0.4%, malignancy – 0.3% and ASC-H – 0.1%.

The mean age of women with malignant smear was 51.2 ± 10.0years; compared to 42.4± 10.7 and 46.4± 13.4years for LSIL and HSIL respectively. There was moderate increase in LSIL in 2012 and 2013 with a decline in 2014. However, the rate of LSIL, in the last 4 years, increased from 3.5% to 17.9% (p<0.0001). HSIL increased from 15.8% in 2013 to 21.1% in 2015 but had a sharp decline afterwards. Malignant cytology rate fluctuated over the years without a specific pattern.

**Conclusion:** Given the increasing rate of LSIL in this setting and late commencement of cervical screening among our women, there is an urgent need to increase the awareness of the benefits of early detection of cervical cancer using Pap smear.

**Key Words:** Pap smear, abnormal epithelial cells, LSIL, HSIL

## Introduction

Cervical cancer is the fourth most common malignancy among women worldwide<sup>1, 2</sup>. It is the second most common cause of cancer-related deaths in women in developing countries<sup>1, 3</sup>. According to GLOBOCAN, 569,847 new cases and 311,365 deaths were recorded in 2018<sup>1, 4</sup> and about 14,943 new cervical cancer cases are diagnosed annually and about 10,403 cervical cancer deaths occur annually in Nigeria (GLOBOCAN 2018)<sup>4</sup>. Cervical cancer (CC) screening by Pap smears has led to a decrease in the incidence of CC worldwide. However, the screening rate for cervical cancer in Nigeria is low and not much is known about the changing trends in the premalignant stages of the disease.

Cervical cancer is considered preventable, as the premalignant stages can be detected by exfoliative cytology like a Papanicolaou (Pap) smear examination<sup>5</sup>. The Papanicolaou (Pap) test is a screening test performed using the cells from the uterine cervix.

This test was introduced by George Papanicolaou as a cervical pathology screening test in 1941<sup>6</sup>. It involves exfoliating cells from the transformation zone of the cervix to enable examination of these cells microscopically for detection of cancerous or precancerous lesions.

Screening with Pap smear has been seen to be accompanied by a dramatic reduction in the incidence of invasive cervical cancer in different countries of the world. To date two types of Pap tests are in use: conventional and liquid-based cytology. Even as the liquid-based test is popular in the developed countries, in low resource settings, a conventional Pap test is the mainstay screening system<sup>7</sup>.

Various studies reveal that a majority of the cervical cancer mortality of the world comes from developing countries<sup>2,8,9</sup>. According to the World Health Organization (WHO), the highest burden of cervical cancer occurs in developing nations where there is a lack of effective screening programs and low uptake of Pap smear or pelvic examination<sup>5</sup>. This may be attributed to the absence of an efficient cervical cancer screening system. Well-organized cervical cancer screening programmes have reduced the mortality from cervical cancer by up to 50% in the developed world<sup>10</sup>. Therefore, it is important to know the prevalence and trend of epithelial cell abnormality in the Pap smear cytology and highlight the implication of cervical cancer screening in a developing country like Nigeria.

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**Conflict of Interest:** None Declared

## Subjects and Methods

This retrospective study was designed to review cervical cytology reports performed in the Pathology laboratory of National Hospital Abuja, Nigeria over a 10-year period from January 2008 to December 2017 using clinical and Pathology records. All cases of Cervical Pap Smear carried out within the study period were included. There were 5850 cervical smear cytology during the period.

The Cervical Pap Smear was done using conventional smears (PAP Smear) and Revised Bethesda System of 2001 was used in reporting. Smears were categorized as “satisfactory” when an adequate number of epithelial cells were clearly visualized, as per the guidelines of the Bethesda system.

The following categories were used: Negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells (ASC) includes ASC-US (ASC of undetermined significance) and ASC-H (ASC, cannot exclude high grade squamous intraepithelial lesions), Low-grade squamous intraepithelial lesions (LSILs), High-grade squamous intraepithelial lesions (HSILs), and carcinomas. Epithelial cell abnormalities comprising of ASCs, LSILs, HSILs and atypical glandular cells (AGC) were considered as cervical precursor lesions.

Data management, analysis and graphical presentation were completed using the Statistical Package for the Social Sciences (SPSS), Version 18 (IBM Corp., Chicago, Illinois, USA). Descriptive statistics were presented as numbers, percentages and means  $\pm$  standard deviations. The normal Z-test was used to test the difference in proportions and the Chi-squared test was used to determine if there was any trend in the proportion of cases over the 10-year period. The two-tailed probability value  $P < 0.05$  was considered statistically significant.

The study was conducted after obtaining approval from National Hospital Research and Ethics Committee/Board.

## Results

The trend of cervical smear cytology was reviewed over a period of 10 years. There were 5850 cervical smear cytology during the period.

Due to cases of inadequate documentation and incomplete/missing results 638 (10.9%), only 5212 (89.1%) were analyzed for the study.

Table 1 showed that the mean age of participants for the different years under study ranges from  $40.6 \pm 9.5$  years to  $44.1 \pm 10.0$  years. The variations of the mean age at different years were statistically significant ( $F = 7.136$ ,  $P < 0.0001$ ). The most frequent age range was found to be 35-44 yrs accounting for 39.6% followed by 45 to 54 yrs (27.1%) only 21.8% were below 35 yrs. (Fig 1)

Table 2 shows the pattern of cytology results between 2008 – 2017. Highest number of Pap smear was carried in 2008. Subsequently, there was a steady decline in the number of smears done over the years. Majority 4484 (86.0%) of the smears were negative (Negative Intraepithelial Lesion and Malignancy). Smear unsatisfactory for interpretation accounted for 398 (7.6%) followed by ASCUS -180 (3.4%), LSIL-113 (2.2%), HSIL-19 (0.4%), malignancy – 16 (0.3%), ASC-H – 5 (0.1). (Table 3)

As shown in table 4, the prevalence of abnormal PAP Smear was found to be 6.5% (CI 5.8% - 7.1%). ASCUS accounted for the highest abnormal epithelial cells -180 (54.1%) followed by LSIL (33.9%), HSIL – 19 (5.7%), malignancy – 16 (4.8%) and ASC-H – 5 (1.5%). Out of the 16 malignant cases recorded, 14 (87.5%) were squamous cell carcinoma while only 2 (12.5%) were Adenocarcinoma. (Table 5)

The highest rate of abnormal cells was recorded in 2008 accounting for about 62.7% of the total smears reviewed in 2008 after which a steady decline was noticed in successive 3 years. However, there was moderate increase in LSIL in 2012 and 2013. In the last 4 years, the rate of LSIL increased from 3.5% to 17.9% ( $p < 0.0001$ ). HSIL increased from 15.8% in 2013 to 21.1% in 2015 but had a sharp decline afterwards. Malignant cytology rate fluctuated over the years without a specific pattern

The mean age women with malignant smear was  $51.2 \pm 10.0$  years; compared to  $42.4 \pm 10.7$  and  $46.4 \pm 13.4$  years for LSIL and HSIL respectively.

**Table 1:** Mean and Median ages of participants (2008-2017)

Year	Mean age (years)	Median age (years)	N	Std. Deviation	Minimum age (years)	Maximum age (years)	ANOVA (F); P
2008	40.6	40.0	879	9.5	27.0	75.0	
2009	42.1	41.0	700	9.7	28.0	70.0	
2010	42.0	41.5	620	9.8	28.0	77.0	
2011	41.7	41.0	506	10.1	25.0	77.0	
2012	42.8	42.0	471	10.5	25.0	71.0	
2013	42.4	42.0	480	9.6	23.0	72.0	
2014	43.9	44.0	341	10.0	25.0	73.0	
2015	44.1	44.0	424	10.0	24.0	73.0	
2016	44.0	43.0	391	10.2	23.0	77.0	
2017	42.9	42.5	400	9.7	25.0	62.0	
<b>Total</b>	<b>42.386</b>	<b>42.000</b>	<b>5212</b>	<b>9.9</b>	<b>21.0</b>	<b>77.0</b>	<b>7.136; &lt;0.0001</b>

**Table 2:** Pattern of cytology procedure from 2008- 2017

Year	NILM N (%)	LSIL N (%)	HSIL N (%)	Malignant N (%)	ASCUS N (%)	ASC-H N (%)	Smear unsatisfactory for interpretation N (%)	Total
08	717 (16.0)	24 (21.2)	2(10.5)	3(18.8)	22(12.2)	0 (0.0)	111 (27.9)	879 (16.9)
09	593 (13.2)	16 (14.2)	1 (5.3)	2(25.0)	14 (7.8)	0 (0.0)	72 (18.1)	700 (13.4)
10	581 (13.0)	3 (2.7)	1 (5.3)	1 (6.2)	13 (7.2)	0 (0.0)	21 (5.3)	620 (11.9)
11	455 (10.2)	7 (6.2)	2(10.5)	0 (0.0)	11 (6.1)	0 (0.0)	31 (7.8)	506 (9.7)
12	383 (8.5)	12 (10.6)	2(10.5)	4(25.0)	23(12.8)	0 (0.0)	47 (11.8)	471 (9.0)
13	386 (8.6)	17 (15.0)	3(15.8)	0 (0.0)	40(22.2)	0 (0.0)	34 (8.5)	480 (9.2)
14	290 (6.5)	4 (3.5)	3(15.8)	0 (0.0)	27(15.0)	0 (0.0)	15 (3.8)	341 (6.5)
15	365 (8.1)	5 (4.4)	4(21.1)	3(18.8)	14 (7.8)	2 (40.0)	30 (7.5)	424 (8.1)
16	361 (8.1)	5 (4.4)	1 (5.3)	1 (6.2)	6 (3.3)	3 (60.0)	17 (4.3)	391 (7.5)
17	350 (7.8)	20 (17.7)	0 (0.0)	0 (0.0)	10 (5.6)	0 (0.0)	20 (5.0)	400 (7.7)
<b>Total</b>	<b>4481(100.0)</b>	<b>113(100.0)</b>	<b>19(100.0)</b>	<b>16(100.0)</b>	<b>180(100.0)</b>	<b>5(100.0)</b>	<b>398(100.0)</b>	<b>5212(100.0)</b>

**Table 3:** Mean and Median ages of participants by Pap smear test result (2008-2017)

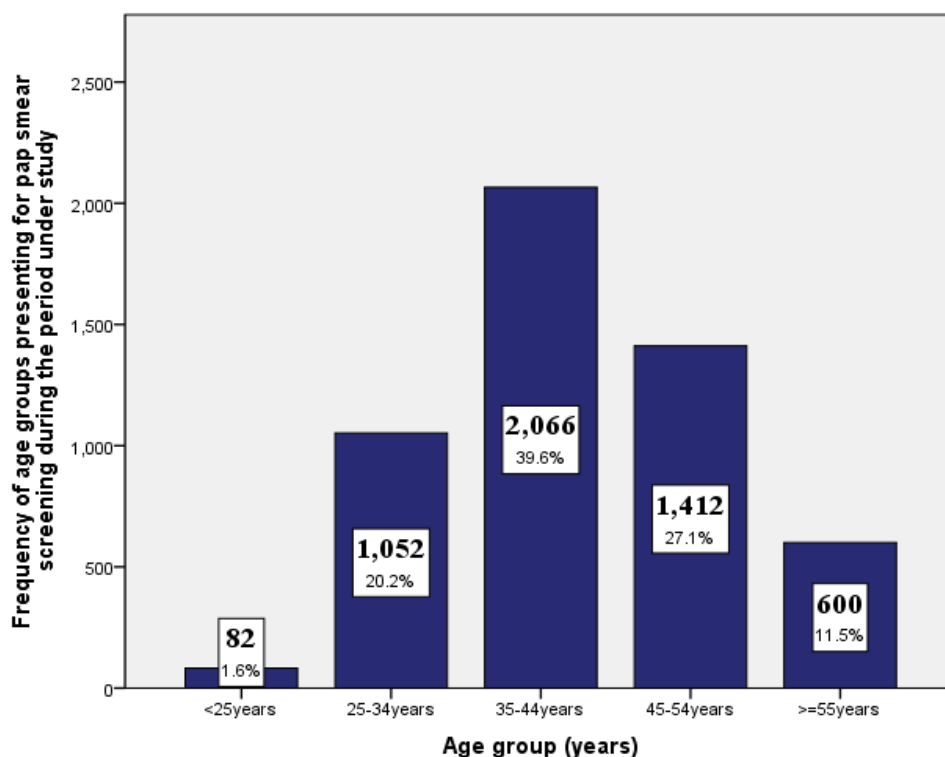
Diagnosis	Mean age (years)	Median age (years)	N (%)	Std. Dev.	Min age (years)	Max age (years)	ANOVA (F); P
NILM	42.3	42.0	4481 (86.0)	9.9	25.0	69.0	
LSIL	42.4	40.0	113 (2.2)	10.7	21.0	75.0	
HSIL	46.4	46.0	19 (0.4)	13.4	29.0	77.0	
Malignant	51.2	51.0	16 (0.3)	10.0	34.0	69.0	
ASC-H	41.4	43.0	5 (0.1)	10.1	25.0	82.0	
ASCUS	44.1	43.5	180 (3.5)	10.1	20.0	73.0	
Cervical smear: unsatisfactory for interpretation	42.2	41.0	398 (7.6)	9.7	30.0	72.0	
<b>Total</b>	<b>42.4</b>	<b>42.0</b>	<b>5212 (100.0)</b>	<b>9.9</b>	<b>21.0</b>	<b>82.0</b>	<b>3.733; 0.001</b>

**Table 4:** Prevalence of abnormal epithelial cells (2008-2017)

Types of abnormality	Group frequency n=333	Group %	95% Confidence Interval	Overall percentage (95%CI) n=5212
LSIL	113	33.9%	29.5% -39.2%	2.2% (1.8%-2.6%)
HSIL	19	5.7%	3.7%-8.7%	0.4% (0.3%-0.6%)
Malignancy	16	4.8%	3.0%-7.7%	0.3% (0.1% -0.4%)
ASCUS	180	54.1%	48.7%-59.3%	3.4% (3.0% - 4.0%)
ASC-H	5	1.5%	1.5% 0.6%-3.5%	0.1% (0.04%-0.023%)
<b>Total</b>	<b>333</b>	<b>100.0%</b>		<b>6.4% (5.8% -7.1%)</b>

**Table 5:** Types of Malignancy

Types of Malignancy	Frequency	Percentage	95% Confidence Interval
Squamous cell carcinoma	14	87.5%	64.0% - 96.5%
Adeno Carcinoma	2	12.5%	3.5% - 36.2%
<b>Total</b>	<b>16</b>	<b>100%</b>	



**Fig 1:** Presentation for screening vs. age group (years)

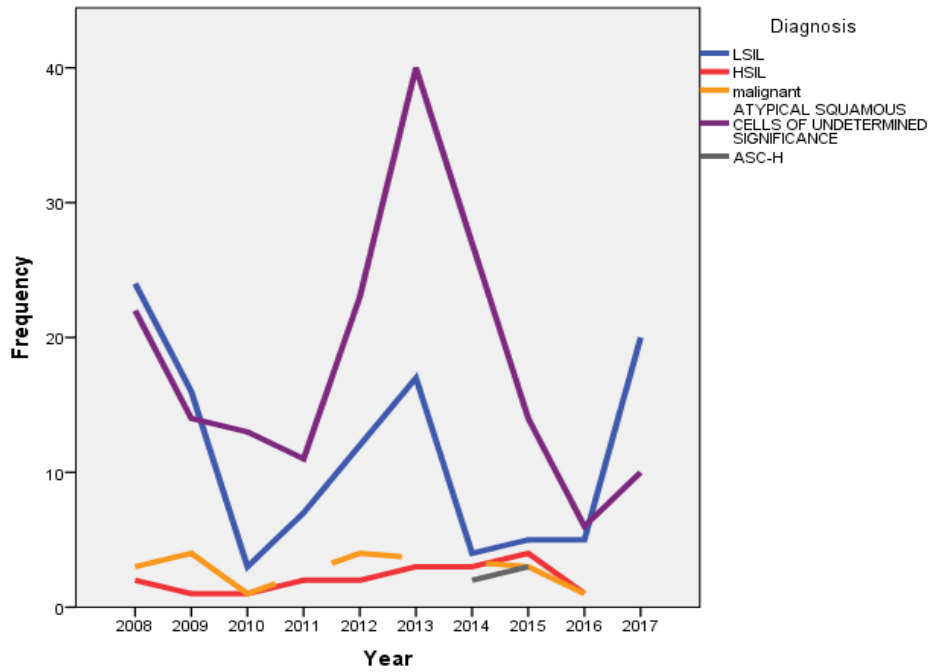


Fig 2: Pattern of abnormality at different years

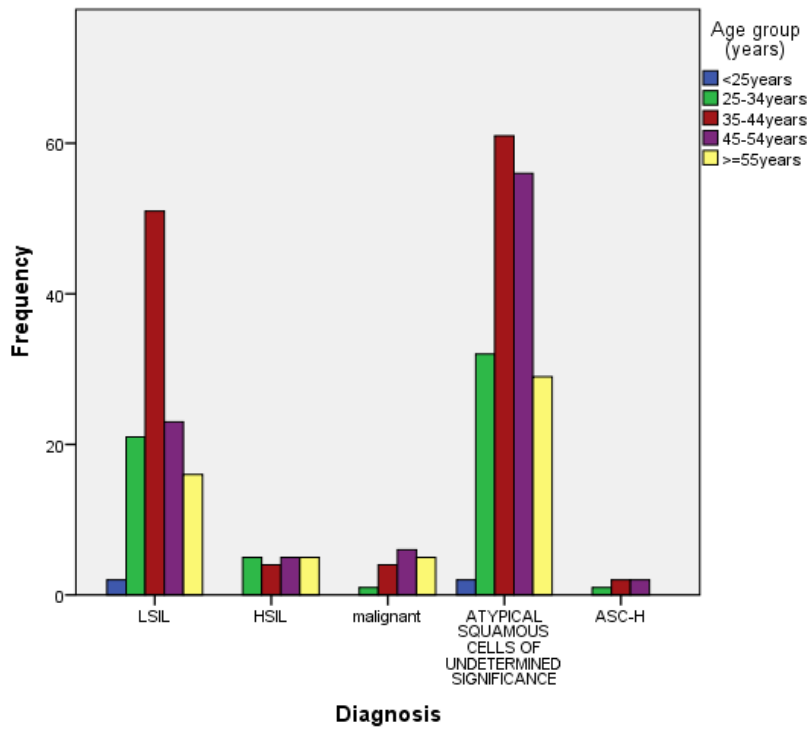


Fig 3: Distribution of diagnosis vs. age group

## Discussion

In this study, the mean age of participants for the different years was  $40.6 \pm 9.5$  years to  $44.1 \pm 10.0$  years. This showed that mostly women in their late reproductive years present for cervical cancer screening in our Center. Unfortunately, only 21.8% of the study population were below 35 years, implying a gross under-utilization of Pap smear screening among the young reproductive age group. There is need for increased awareness of benefits of early detection of cervical premalignant stage through Pap smear.

Majority 4484 (86.0%) of the smears were negative (Negative for intraepithelial lesion or malignancy). Prevalence of abnormal epithelial cells were found to be 6.4% (CI 5.7% - 7.0%). This is similar to a study carried out in Sokoto where 6.8% (39/577) of the cytology results were positive for intraepithelial lesions<sup>7</sup>. In studies done in Kuwait and India, the rate of epithelial cells abnormalities were 4.43%, 3.22% and 5.46% respectively.<sup>11,12,13</sup> However, while the Kuwait study used both convention PAP smear and thin Prep (Liquid based cytology), in India studies, only conventional Pap smear was used. Studies have shown that liquid based cytology (LBC) reduces the rate of unsatisfactory smear when compare with conventional Pap smear however, its superiority over conventional Pap smear in detection of premalignant and malignant cervical tumour is still controversial.<sup>13,14,15,16,17,18</sup> In our study, conventional Pap smear was used as in most developing countries.

In the present report, ASCUS accounted for the highest among the abnormal epithelial cells. This is similar to other reports<sup>11, 12</sup>. In one report from Saudi Arabia, the most common abnormality presenting in all age groups was ASCUS (65%), followed by LSIL (20%)<sup>19</sup>. In our report, however, follow up information was lacking.

Despite the decline in the number of smears in the last 4 year, there was a steady increase in the number of LSIL from 3.6% to 17.9% ( $p < 0.0001$ ). This is similar to a report from Norway in which patterns in the incidence of CIN2, CIN3 and AIS was analyzed by age and histology during the period 1992–2016. That report showed an increasing trend in the incidence of all precancerous lesions in most age groups<sup>20</sup>. A similar increase in precancerous lesions were also reported in Denmark<sup>21</sup>.

Changing sexual practice is exposing more young girls to HPV infection which is a known causative agent of cervical cancer<sup>1,22</sup>. Age at first sexual intercourse has decreased, while number of lifetime sexual partners has increased, leading to higher exposure to sexually transmitted infections, including HPV<sup>20,23</sup>. Furthermore, a report from sub-Saharan Africa has shown that cervical cancer trends are on the rise in the past two decades because of HIV, resulting in an increase in cervical cancer cases among young women<sup>24</sup>. The urgent need for HPV vaccine cannot be overemphasized. Despite the high prevalence of cervical cancer in Nigeria, there is neither an organized national HPV vaccine immunization programme nor government

subsidized cost intervention to provide for primary prevention of the disease. There is need for urgent intervention in low income countries like ours where HPV vaccine is expensive. There's reported marked reduction in the incidence of precancerous lesion in areas with efficient screening programme and good vaccination coverage. Studies in the United States have shown marked reduction in the incidence of precancerous lesions<sup>25, 26, 27</sup>. However, in a report from Kuwait, the distribution of epithelial cells abnormalities (ECAs) in 140,404 cervical cytology smears analyzed over a 21-year period did not show any significant change in LSIL, HSIL or carcinoma cases<sup>11</sup>.

The mean age of women with malignant smear over the 10-year study period was  $51.2 \pm 10.0$  years compared to  $42.4 \pm 10.7$  and  $46.4 \pm 13.4$  years for LSIL and HSIL respectively. In reports from India, the incidence of cervical cancer was noticed to significantly rise around the age of 45 years and peaks at 55 years of age<sup>12, 13</sup>. In Ethiopia, women aged 40–49 years had 2.4-fold higher odds of precancerous lesions compared to those aged 30–39 (Adjusted Odds Ratio = 2.4, 95% Confidence Interval: 1.27–4.54)<sup>28</sup>. However, in a report from Norway, the highest incidence of CIN2, CIN3 and AIS was observed in the age group 25–29 years<sup>20</sup>.

In the present report, out of the 16 malignant cases recorded, 14 (87.5%) were squamous cell carcinoma and 2 (12.5%) Adenocarcinoma. Squamous cell carcinoma has always been the dominant lesion in cancer of the cervix. In recent times, there are reports of increasing incidence of adenocarcinoma. This has been attributed to efficient cervical screening. In a report from Denmark, the incidence of SCC was reported to have decreased significantly, especially in women aged  $\geq 45$  years [EAPC:  $-3.1\%$  (95% CI  $-4.3$  to  $-2.5$ )] due to efficient Danish screening program. Whereas the incidence of adenocarcinoma increased significantly, from 2.4 to 3.1/100,000 primarily due to increases in women aged  $\leq 44$  years<sup>21</sup>. In low income countries like ours where there is almost no organized screening program, the predominant lesion is still Squamous cell carcinoma.

Some potential limitations of this study should be considered. The study is a one-center study. There is need for a well-organized nation-wide study on the trends of epithelial cell abnormalities on Pap smear. Also, the management and outcome of the patients with abnormal epithelial cells were not included in the study. Documentation on patient's follow-up is very important. Thus, the need for proper training of staff on data management cannot be overemphasized.

## Conclusion

Given the increasing rate of LSIL in this setting and late commencement of cervical screening among our women, there is an urgent need to increase the awareness of the benefits of early detection of cervical cancer using pap smear. There is also need for a well-organized cervical screening program supplemented by larger

national studies on the pattern of cervical abnormalities in this country.

### Author Contributions

All the authors contributed to the conception and design of the study, literature review, collection, analysis and interpretation of data and revising the manuscript. All authors approved the final manuscript.

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### Conflicts of interest

The authors have no conflict of interest

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