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Comparative Analysis of ThinPrep and CellSolutions Liquid-Based Cervical Cytology along with Human Papillomavirus DNA Testing: A Study of 412 Cases

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ABSTRACT

Objective: The objective of the study was to compare the effectiveness and feasibility of current cervical cancer screening strategies i.e., CellSolutions and ThinPrep liquid-based cytology (LBC) along with Human Papillomavirus based (HPV) DNA testing in the Indian population for accurate and early detection of cervical cancer.

Methods: ThinPrep (206) and CellSolutions (206) based total of 412 LBC samples were studied, out of which 307 were also used for HPV co-testing. HPV-based DNA testing with hybrid capture 2 followed by PCR was carried out to identify high and low-risk genotypes. The precancerous lesions were reported according to the revised Bethesda classification.

Results: ThinPrep and CellSolutions-based LBC with HPV co-testing showed a significant decrease in the incidence rate of cervical cancer. The detection rate of abnormal smears was 3.88, 2.91, and 10.4% in ThinPrep, CellSolutions, and HPV testing, respectively. Low-grade squamous intraepithelial lesion (LSIL) was the most common abnormality compared to High-grade SILs in both the LBC techniques. The most common high-risk HPV genotypes detected were 16, 18, 56, and 66, while low-risk were 6, 42, 53, 62, 81, and 30, respectively.

Conclusions: Cervical cancer screening strategies evaluated in the Indian population. CellSolutions is comparable to ThinPrep, HPV has the highest detection rate of abnormal smears as compared to LBCs. HPV along with LBC co-testing improves precision, early detection and eliminates unnecessary colposcopy procedures.

Keywords: Liquid-based cytology, Cervical cancer, ThinPrep, CellSolutions, HPV

INTRODUCTION

Cervical cancer is the most common form of genital malignancies in women worldwide and the second most common form after breast cancer in terms of incidence.[1] Over 85% of deaths has been reported in developing countries due to the lack of early detection of cervical cancer.[2] According to 2020 statistics, 604,100 women worldwide have been diagnosed with cervical cancer, of which 341,831 have died.[3] In liquid-based cytology (LBC) as compared to the conventional Papanicolaou test (Pap), cervix samples are immediately rinsed into a vial containing a fixative solution (PreserveCyt® or BestPrep™), instead of layering directly on the glass slides. The vials are transported to the cytopathology laboratory where a single thin layer of cells on the slide is prepared, which drastically improves the smear quality as compared to conventional Pap smear test.[2] The remaining sample in the

LBC vial could also be used for molecular techniques like HPV-DNA testing with the same LBC sample. Molecular and epidemiological studies revealed that Human Papillomavirus (HPV) is the primary cause of cervical carcinoma and is detected in more than 90% of cervical tumors.[4]

Organized screening LBC and HPV co-testing have set a major benchmark to decrease cervical cancer incidence rate. There is a wide range of variations in interpreting Pap smears even among expert cytopathologists. In some women, it indicates a real pathology while in others it represents only a vigorous reactive change that is not malignant. Identifying women at high risk by testing for HPV-DNA avoids unnecessary colposcopy procedures. Two methodologies most widely used for HPV-DNA detection are PCR and Hybrid Capture II.[5] Due to the increase in utility of LBC and HPV co-testing, a new chapter has been added in 2014 The Bethesda System (TBS) for managing the risk of cervical cancer by applying certain combinations of molecular tests, including hc2, southern blot, PCR, and Chromogenic in situ hybridization (CISH).[6] Early detection of precancerous lesions with recent screening strategies and treatment could start before they progress into cervical cancer and become a bigger concern.

In the present study, the effectiveness and feasibility of current screening strategies are compared for the first time in the Indian population. Comparative analysis between CellSolutions and ThinPrep liquid-based cytology with HPV co-testing using 412 samples was performed. The main aim of the study was to compare the effectiveness and feasibility of both the LBC techniques along with HPV co-testing to detect squamous cell and glandular cell abnormalities. Co-testing of HPV and Cytology by LBC is a clinically cost-effective option and allows for better accuracy.

MATERIALS & METHODS

Sample collection and preparation for Liquid Based Cytology (LBC) and Human Papillomavirus co-testing

PAN India hospitals send the samples to the Cytopathology section, Global Reference Laboratory (GRL, Metropolis Healthcare Limited, Mumbai) for cervical cancer detection. The patient age range in this study was 18-85 years. The cervical samples were obtained from the transition zone of the uterine cervix comes in vials containing PreservCyt solution Transport Medium (Hologic, Marlborough, USA) and BestPrep™ solution (CellSolutions 30, Greensboro, USA) specifying whether only LBC or HPV co-test is required. For a uniform thin smear, samples were processed using fully automated ThinPrep 2000 (Hologic, Inc, Marlborough, USA) and CellSolutions 30 processor (CellSolutions 30, Greensboro, USA) using The Bethesda system. [6-8] The same LBC samples were used for HPV tests for a particular genotype on requested samples. After processing, Papanicolaou staining was performed in the same way for both the LBC techniques.[9] If the samples were hemorrhagic, additional cytopreservative (CytoLyt) treatment is given and the slides are further prepared using ThinPrep 2000 automated slide processor and stained with Pap stain to attain optimum squamous cellularity. (Fig. 1) [6,9]

HPV was tested from samples received in ThinPrep and CellSolutions preservative vials. HPV DNA was detected with hybrid capture 2 for high-risk positives followed by nested PCR to identify the specific genotypes in the population. Hybrid capture 2 was performed using a mixture of probes for 13 high-risk HPV types. DNA extraction of high-risk positive samples was carried out using the QIAmp DNA extraction kit (Qiagen, USA), followed by PCR using specific primers to identify the specific genotypes. [9,10] HPV genotypes sequences were submitted at NCBI GenBank and a phylogenetic comparison was done using nBLAST. The precancerous lesions were

reported according to the revised Bethesda classification system. [7,8] All the samples were examined for specimen adequacy with well visualized squamous cells. All the outcomes have been reported by experienced cytopathologists to report LBC. (Fig. 1)

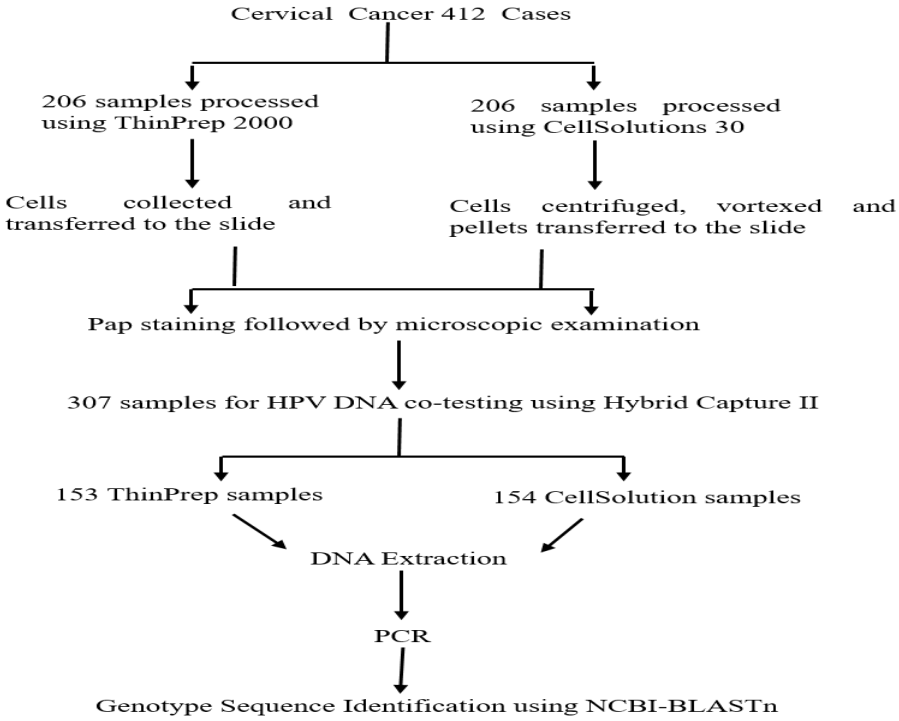

Fig. 1 Sample collection and preparation for Liquid Based Cytology (LBC) and Human Papillomavirus co-testing

RESULTS

Distribution of abnormal, negative smears and comparative analysis of ThinPrep and CellSolutions

Total 412 samples, 206 each for ThinPrep and CellSolutions based cytology were examined. More than 70% of the abnormal smears were found in the 18-70 age range. The distribution of abnormal and negative smears was found to be 94-96% in both the LBCs. The prevalence rate of abnormal and unsatisfactory cytology was 3.88 and 1.9% in ThinPrep, while 2.91 and 0.49% in CellSolutions, respectively (Table 1).

Table 1 Distribution of abnormal and negative smears. Abbreviations: NILM, negative for intraepithelial lesion or malignancy; LBC, liquid-based cytology

No.	Diagnosis	Liquid-based cytology	
		ThinPrep n(%)	CellSolutions n(%)
1.	NILM	195 (94.66%)	199 (96.60%)
2.	Abnormal	8 (3.88%)	6 (2.91%)
3.	Unsatisfactory	4 (1.94%)	1 (0.49%)
4.	Total Cases	206	206

This study demonstrated a slight difference between ThinPrep and CellSolutions LBC abnormal results. The detection rate of abnormal smears was slightly higher in ThinPrep (3.88%) compared with CellSolutions (2.91%). Low-grade squamous intraepithelial lesion (LSIL) was the most common abnormality observed in both the LBC techniques (ThinPrep 2.43% and CellSolutions 2.91%), followed by High-grade squamous intraepithelial lesion (HSIL) (0.97%) in ThinPrep (Table 2).

Table 2 Distribution of abnormal findings in ThinPrep and CellSolutions (n=412). Abbreviations: LSIL, low-grade intraepithelial lesion; HSIL, high-grade intraepithelial lesion; AGC, atypical glandular cells

No.	Abnormality	ThinPrep n (%)	CellSolutions n (%)
1.	LSIL	5 (2.43%)	6 (2.91%)
2.	HSIL	2 (0.97%)	0
3.	AGC	1 (0.48%)	0
4.	Total	8 (3.88%)	6 (2.91%)

HSIL showed clusters of parabasal cells in the background and a sheet like arrangement with significant nuclear size variation and a loss of polarity with overlapping of the nuclei (Fig. 2). LSIL showed mature squamous cells and enlarged nuclei with

variable chromatin and nuclear membrane (Fig. 3). Koilocytosis is also seen in the cytoplasm due to the HPV cytopathic effect. Figure 4 showed atypical glandular cell (AGC), where abnormal cells occurred in sheets with nuclear overcrowding and nuclear to cytoplasmic ratios found to be increased with ill-defined cell borders. Figure 5 showed a negative for intraepithelial malignancy (NILM) with Candida spores and long pseudo-hyphae.

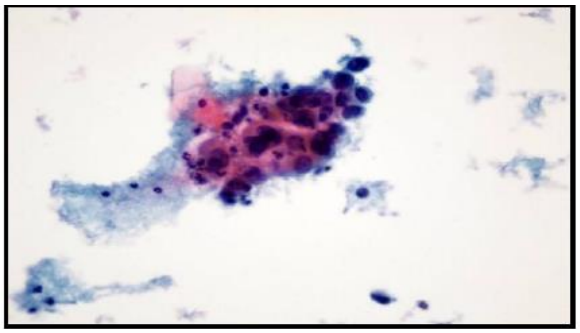

Fig. 2 High-grade intraepithelial lesion-Clusters of parabasal cells in the background and a sheet-like an arrangement with significant nuclear size variation and a loss of polarity with overlapping of the nuclei

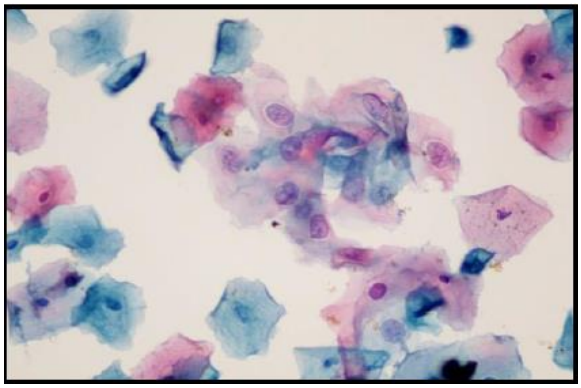

Fig. 3 Low-grade intraepithelial lesion under 40X- Mature squamous cells and enlarged nuclei with variable chromatin and nuclear membrane and koilocytosis is also seen in the cytoplasm due to the HPV cytopathic effect

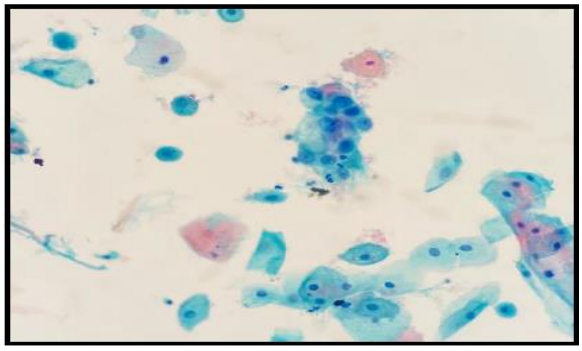

Fig. 4 Atypical Glandular cells under 40X- Abnormal cells occurred in sheets with nuclear overcrowding and nuclear to cytoplasmic ratios increased with ill-defined cell borders

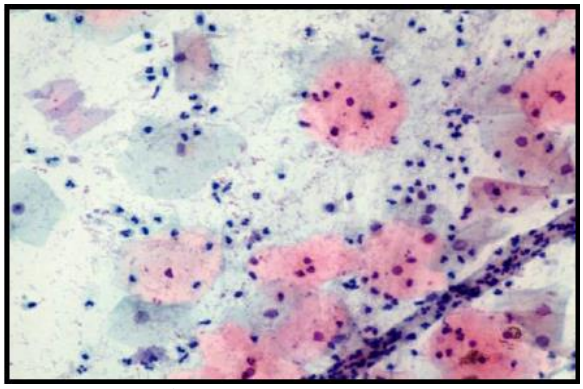

Fig. 5 Negative for intraepithelial malignancy with *Candida species* under 40X- Negative for intraepithelial malignancy (NILM) with *Candida* spores and long pseudo-hyphae

Distribution of HPV positive subtypes and co-testing with ThinPrep and CellSolutions

HPV testing was done for 307 cases and 32 (10.4%) of them were positive for the infection. HPV positive high and low-risk genotypes were seen in 27 (84.3%) and 5 (15.6%) cases, respectively. The most common HPV high-risk genotype detected were 16 (18.75%), 18 (15.62%), 56 (18.75%), and 66 (12.5%); while low risk genotype detected were 6, 42, 53, 62, 81 and 30. Tables 3 and 4 showed the distribution of HPV positive low and high-risk genotypes. The detection rate of HPV-positive cases in ThinPrep was found to be 11.11% (17/153), 82.4% cases showing high-risk genotype, and 17.6% showing low-risk genotype. The most common high-risk genotypes were 16, 18, and 56, and low-risk genotypes were 6, 42, 53, and 62. The detection rate of HPV-positive cases in CellSolutions was found to be 9.74% (15/154), 86.7% cases showing high-risk genotype, and 13.3% showing low-risk genotype. The most common high-risk genotypes were HPV 66 followed by 16, 18, and 56, and low-risk genotypes were 81 and 30. Figure 6 and Figure 7 showed the distribution of high-risk and low-risk genotypes cases reported in HPV, ThinPrep and CellSolutions LBCs.

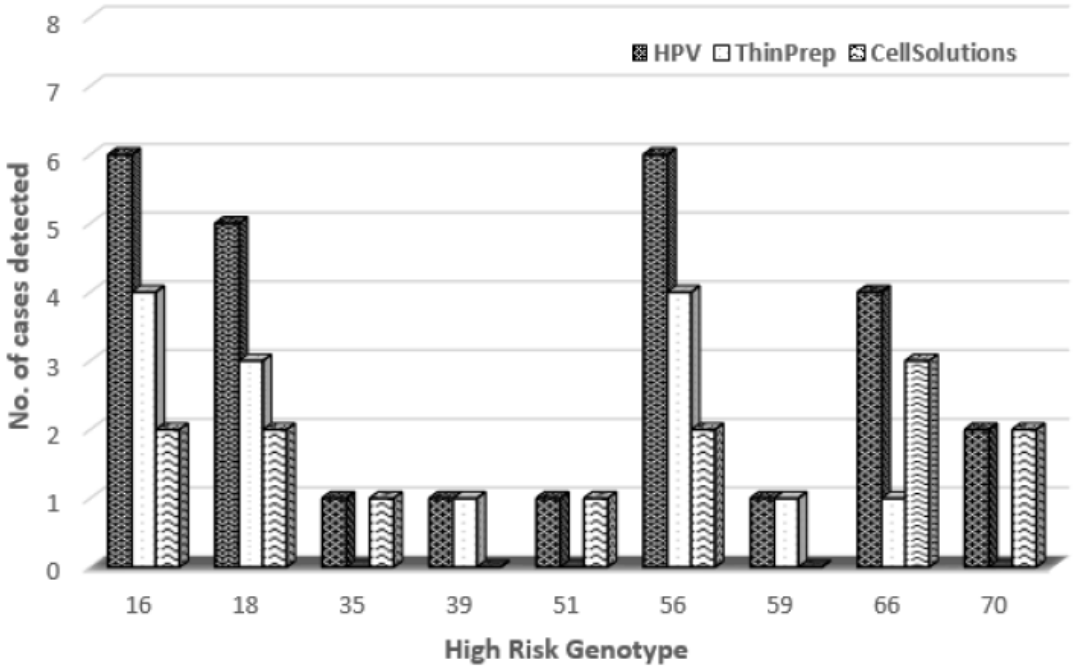

Fig. 6 Number of cases detected in high-risk genotypes in HPV, ThinPrep and CellSolutions. Abbreviations: HPV; Human Papillomavirus

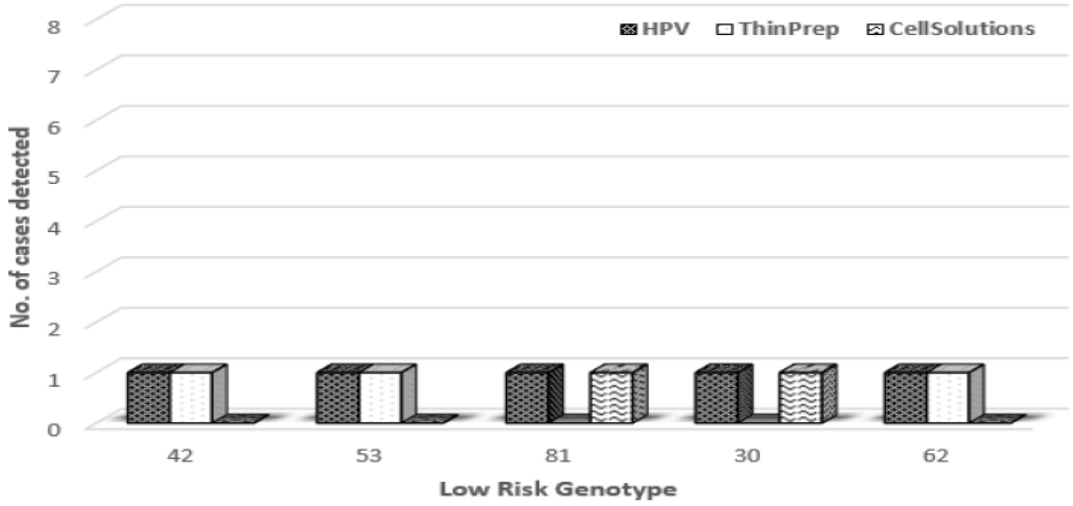

Fig. 7 Number of cases detected in low-risk genotypes in HPV, ThinPrep and CellSolutions. Abbreviations: HPV; Human Papillomavirus

Comparison of HPV testing results with abnormal findings

In this study, 24 NILM cases were HPV-positive, 83.3% of them being high-risk and 16.7% low-risk genotypes. The genotypes detected were 56, 16, 18, 30, 51, 66, 35, 39, 42, 70, 59, 53, 70, and 62. LSIL six cases were HPV positive, 83.3% being high risk and 16.7% were low-risk genotypes. The genotypes detected were 16, 18, 66, and 81. HPV 16 and 18 were the most common type detected in this study. HSIL two cases were HPV positive, both being high-risk type HPV 16 and 18.

DISCUSSION

Discuss findings of your study with relevant reasoning along with proper citations/references. The conventional Pap screening method has shown a decrease in cervical cancer incidence and death rates in some developed countries. However, in developing countries around 80% of all new cases occur in women who never had a Pap smear test. The cervical cancer prevalence rate could be decreased by 90% by using current screening strategies with improved smear quality and good coverage.[11] Proper application of screening programs is

crucial to reduce the incidence and mortality rate of cervical cancer worldwide. The age range in our study was 18-85 years and more than 70% of the abnormal smears were found to be in the age range of 18-70. The age range selected in this study was found to be concordant with other studies from the United Kingdom, India, and France. [11-13] For women aged 30-65 years, USPSTF now recommends cervical screening every 3 years with cervical cytology alone, every 5 years with HPV testing alone, or every 5 years with HPV testing in combination with cytology.[14] This co-test combination is also recommended by ASCCP, ACS, and ACOG as a preferred strategy for screening women over the age of 30. [15,17]

This study showed a slight difference between ThinPrep and CellSolutions LBC systems abnormality results (3.88% and 2.91%), and unsatisfactory smears, varied from 0.49% (CellSolutions) to 1.94% (ThinPrep). Although CellSolutions tended to show a lower unsatisfactory rate than ThinPrep, there was no statistically significant difference. A low unsatisfactory rate can decrease the chance of patient revisiting, thereby lowering the cost of the screening program. Negri et al reported that the LBC test performs significantly better than conventional in follow-up cases with an unclear previous cytological diagnosis because of better sample adequacy.[18] The rate of abnormal findings was 3.88% in ThinPrep smears which were similar to the findings from Bihar (3.87%), India.[19] LSIL (2.43%) was the most common abnormality observed followed by HSIL (0.97%), which were similar to the findings from the USA that showed a lower percentage of ambiguous or borderline cases diagnosed as ASCUS and increased detection of LSIL in the cohort population. Hutchinson et al, found LSIL (2.98%) as the commonest abnormality in their split sample analysis.[20] Carpenter et al, also showed similar data, where the detection rate of LSIL was found to be around 2.6% for ThinPrep.[21] Similar to our study, it was reported that LSIL (2.91%) was also the most common abnormality amongst samples in the CellSolutions.[22]

More than 200 HPV types have been recognized based on DNA sequence, out of which 85 of them are well characterized (Table 3).

Table 5: Prevalence of HPV type and disease association [23] Abbreviations: HPV; Human Papillomavirus

Infection	HPV type
Condyloma acuminata (genital warts)	6, 11, 30, 42, 43, 45, 51, 54, 55, 70
Cervical intraepithelial neoplasia	
Uncertain	30, 34, 39, 40, 53, 57, 59, 61, 62, 64,66, 67, 68, 69
Low-risk	6, 11, 16, 18, 31, 33, 35, 42, 43, 44, 45, 51, 52, 74
High-risk	16, 18, 6, 11, 31, 34, 33, 35, 39, 42, 44, 45, 51, 52, 56, 58, 66
Cervical carcinoma	16, 18, 31, 45, 33, 35, 39, 51, 52, 56, 58, 66, 68, 70

Few HPV infections lead to invasive carcinoma, whereas the majority of the viral infections are benign and can be cleared with the help of the immune system.[24] Women who are positive for high-risk HPV but with negative cytology or an ASCUS result are referred to colposcopy, and those with negative HPV DNA results are asked to undergo a repeat Pap testing at six- and twelve-months duration. If these results are found to be negative, the woman is returned to a routine schedule of screening. [25] Detection of high-risk positives was preferred first by hc2 followed by nested PCR as it could identify the specific genotypes in our population and helpful to design vaccine protocols considering HPV 16 and 18 are currently known and proven to be the most virulent and high-risk genotypes, causing approximately 70% of all invasive cervical cancers.[26] HPV test has much better sensitivity (89.89%) than

cytology (74.47%) in identifying the high-grade cervical lesions with slightly less specificity 96% and 97% and also found to decrease the false-negative rate.[27] In this study, the combined detection rate (ThinPrep+CellSolutions) of HPV was 10.4%. HPV 16 was the commonest genotype (18.75%), followed by HPV 18 (15.62%), similar to a study from India with a detection rate of 11.9%. [28] The overall HPV positivity in ThinPrep was 11.11%, the detection rate of high-risk HPV genotype was 82.4% and low-risk HPV genotype was 17.6%. Similar to this study, the most commonly observed genotypes are HPV 16, 56, 18, and 42. [29] The overall HPV positivity in CellSolutions was 9.74%, the high-risk HPV genotype rate was 86.6% and the low-risk HPV genotype was 13.3%, with HPV type 66 being the most common genotype. The HPV positivity rate for ThinPrep and CellSolutions was found to be comparable.

In this study, 7.82% (24/307) of NILM cases were HPV positive, 83.3% of them being high-risk and 16.7% being low-risk genotypes. The genotypes detected were 56, 16, 18, 30, 51, 66, 35, 39, 42, 70, 59, 53, 70 and 62. Compared with literature, this value falls within the expected range of HPV prevalence for women with normal cytology in the worldwide population varies between 6.1 - 35.5%.[30] A meta-analysis detected HPV 16, 18, 56, 52, and 31, with HPV 16 being the most common type in cervical cancer patients.[31] Similar results were obtained in our study with 6 LSIL cases that were HPV positive, out of which 83.3% were high-risk and 16.7% of low-risk genotypes with HPV 16 and 18 being the most common type detected. A similar study was carried out in a rural setup to understand the association of high-risk HPV with SILs, which showed the highest prevalence of HPV 16 and 18 followed by 66 and 81. [32] HSIL two cases were HPV positive, both being high-risk type HPV 16 and HPV 18. Similar results were obtained in a study that showed more prevalence of HPV type 16 and 18 in HSIL. [33] Evidence suggests that cytology has lower sensitivity than HPV to detect treatable lesions. In this study, 24 cases of NILM were HPV positive, 83.3% being high risk and 16.7% being low-risk genotypes. This indicated that the above cases could have been missed if only one of the two tests were done. Thrall et al investigated the clinical use of co-testing for women with negative cytology results and found out few high-grade cervical lesions by colposcopy immediately following a NILM HPV positive result.[34]

CONCLUSION

Current cervical cancer screening strategies were compared with respect to the Indian population for accurate and early detection. The detection rate of abnormal smears is maximum in HPV as compared to liquid-based cytology. CellSolutions is comparable to ThinPrep LBC techniques and has almost similar detection rates for cytological abnormalities. Co-testing of HPV and LBC-based cytology gives more precision and avoids unnecessary colposcopy procedures. It improves sensitivity and specificity and helps reduce ambiguous results, thereby helping the clinician to take better treatment and follow-up decisions.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Ethical Approval: Approved

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