Community-based Cervical Cancer Screening Using Cobas Human Papillomavirus (HPV) Test and Liquid Based Cytology (LBC) in Married Women Living in North Okkalapa Township, Yangon

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Cervical cancer is caused by persistent infection with high-risk human papillomavirus (hrHPV) types. This study aimed to perform the community-based cervical cancer screening using Cobas HPV test and liquid-based-cytology (LBC) in married women by a cross-sectional descriptive method. A total of 312 married women were screened using LBC in 2017. Among them, 220 women aged between 30-49 years were also investigated using Cobas HPV test. Cervical cells were obtained from the cervix by sterile disposable cytobrush and collected in Cobas PCR-cell-collection-media. HPV DNA testing was performed by Cobas HPV Test. It is an automated, polymerase-chain-reaction and nucleic-acid-hybridization test for the detection of 14 hrHPV types in a single analysis. It identifies HPV-16 and HPV-18 specifically which are associated for over 70% of cervical cancer while concurrently detecting other 12 hrHPV types (-31,-33,-35,-39,-45,-51,-52, -56,-58,-59,-66-and-68) as pooled-12-hrHPV. In this study, hrHPV was identified in 5.5% (12/220) of women in general population of Kyauk Ye Twin Ward. Among HPV positive cases, pooled-12-hrHPV types were 66.7%, HPV-16 (25%) and HPV-18 (8.3%). Using LBC (Bethesda-system), negative-for-intraepithelial-lesion-or-malignancy (NILM) was 79.5% (248/312). Epithelial cell abnormalities such as atypical-squamous-cells and/or atypical-glandular-cells (ASC/AGC), low-grade-squamous-intraepithelial-lesion (LSIL) and high-grade-squamous-intraepithelial-lesion (HSIL) were detected 11.9% (37/312), 7.4% (23/312) and 1.3% (4/312), respectively. Women with positive HPV-16 or HPV-18 and/or epithelial cell abnormalities were referred to North Okkalapa General Hospital for colposcopy, histopathology and treatment. Positive pooled-12-hrHPV types with NILM were instructed to screen/follow up after one year. This study highlighted that all women with positive hrHPV types and/or epithelial cell abnormalities had no previous history of cervical cancer screening. To reduce the incidence and mortality of cervical cancer in Myanmar, well-organized National Cervical Cancer Screening Program (NCCSP) should be established as a priority. If the primary HPV testing in NCCSP is used, the most-highest risk women for cervical cancer can be ruled out. In addition, refer to hospital for appropriate management and/or follow-up and burden of health care providers will be certainly reduced.

Keywords: Cervical cancer screening, HPV DNA testing, Cytology

INTRODUCTION

Worldwide, cervical cancer is the fourth most common cancer among women worldwide, with an estimated 604,127 new cases and 341,831 deaths in 2020 (GLOBOCAN 2020). In Asia (SEA) incidence and mortality of cervical cancer are about 68,623 cases

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and 38,530 deaths, respectively.[1] In Myanmar, cervical cancer is the most common female cancer and the first leading cause of cancer deaths in women aged 15 to 44 years (IARC 2021). Age standardized incidence rate of cervical cancer were 22.6% in Myanmar, 17.8% in Southeast Asia and 13.3% in the world. Age standardized mortality rate of cervical cancer were 14.4% in Myanmar, 9.9% in South East Asia and 7.3% in the world.[2]

Human papillomavirus (HPV) is one of the commonest sexually transmitted infections. In South-Eastern Asia, 7.3% of women in the general population are estimated to harbour cervical HPV infection at a given time. About 3.0% of women in the general population and 73.0% of invasive cervical cancers are attributed to HPV-16 or 18.[2] Up to 80% of sexually active women are infected at some point in their lives and 10-20% develops persistent infection.[3]

It is now well-established and widely accepted that almost all cervical cancer and its precancerous lesions arise from persisting cervical infections by approximately 15 (high-risk) human papillomavirus (hrHPV) genotypes.[4] The most important of these HPV genotypes are HPV16 and HPV18, which account for more than 70% of all invasive cervical cancers.[5] A new paradigm of cervical carcinogenesis replaces an older model of stepwise progression from low-grade to high-grade morphological changes and can now be summarized as four reliably measured stages: 1) HPV acquisition, 2) HPV persistence (*vs.* clearance), 3) progresssion of a persisting infection to cervical pre-cancer (with incidental co-occurrence of both conditions), and 4) invasion.[6, 7]

WHO (2021 Guideline) recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV. Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of the inherent challenges with quality assurance. WHO suggests using an HPV DNA primary screening test either with triage or without triage to prevent cervical cancer among the general population of women. In a screen-and-treat approach using HPV DNA detection as the primary screening test, WHO suggests treating women who test positive for HPV DNA among the general population of women. In a screen, triage and treat approach using HPV DNA detection as the primary screening test among the general population of women, WHO suggests using partial genotyping, colposcopy, VIA or cytology to triage women after a positive HPV DNA test.[8]

The Cobas HPV Test is the clinically validated, US-FDA approved cervical cancer screening test that allows 14 high-risk HPV (hrHPV) genotypes in a single analysis. It individually identifies HPV-16 and HPV-18 while simultaneously detecting 12 other high risk HPV genotypes as pooled. It is an automated qualitative *in vitro* test for the detection of human papillomavirus (HPV) DNA in patient specimens. The tests utilize amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of. [9]

In Myanmar (2017), HPV vaccination program as well as cervical cancer screening program are not started yet. But, the stakeholders are now planning the guidelines to establish it. Previously, hrHPV infection and genotypes were investigated in cervical pre-cancer and cancer cases but they are not identified in the general population in Myanmar yet. Before the introduction of HPV vaccination program, it is very important to determine the baseline HPV prevalence and genotypes in the general population in Myanmar. This study aimed to perform the pilot community-based cervical cancer screening using Cobas HPV test and liquid based cytology (LBC) in married women residing in Kyauk Ye Twin Ward, North Okkalapa Township, Yangon in 2017.

MATERIALS AND METHODS

Study population and design

This study was a community-based cross-sectional descriptive study. A total of 312 married women (mean age 45 years; range 30-64) residing in Kyauk Ye Twin Ward, North Okkalapa Township, Yangon were screened using liquid based cytology (LBC) in 2017. Among them, 220 women aged between 30-49 years were enrolled for the detection of hrHPV using Cobas HPV test.

After obtaining a written informed consent, a thorough history was taken using structured-proforma. Then, speculum examination was performed under good light source. Cervical cells were obtained from the cervix by sterile disposable cytobrush and collected in Cobas PCR-cell-collection-media solution. The samples were sent to the Technology Development Division, Department of Medical Research (DMR), Yangon at room temperature. Then, those samples were stored in 4°C prior to testing for LBC and Cobas HPV test.

Laboratory testing

Human papillomavirus testing using Cobas HPV test

The Cobas HPV test is an automated, polymerase-chain-reaction and nucleic-acid-hybridization test. It was performed on the Cobas® 4800 System, which offers the automation of nucleic acid extraction and purification, as well as real-time PCR based amplification and detection. This HPV test simultaneously detects a total of 14 hrHPV types in a single analysis: HPV 16 individually, HPV 18 individually and pooled-12-hrHPV genotypes (-31,-33,-35, -39,-45,-51,-52,-56,-58,-59,-66-and-68). All tests were performed according to the manufacturer's instructions. One ml of each specimen from liquid based cytology vials was directly processed on this system. Twenty-two samples with two controls, i.e. HPV positive and HPV negative control were tested in each run. Each sample was tested for the human ß globin gene. The system was completed by the software which integrates sample preparation, amplification and detection, and result management.[9]

Liquid based cytology (LBC)

One ml of the samples was taken and added in 1.5ml tube and then centrifuged at 8000 rpm for 3 minutes. The cell deposits were placed over the glass slide and the cervical smear were made. Then, fixative spray was applied over the cervical Pap smear. Pap staining was done to the cervical smear slides using modified Papanicolaou staining method. Cytological screening was performed using Bethesda system.[10]

Data analysis

All study data were double-entered using Microsoft Excel. Statistical analysis of the data were performed by using Statistical Package for Social Sciences (SPSS-16.0) (http://en.softonic.com/s/spss-16-full-version-free-download/).

RESULTS

A total of 312 married women residing in Kyauk Ye Twin Ward, North Okkalapa Township, Yangon were screened using liquid based cytology (LBC) in 2017.

Regarding the baseline characteristics of women who participated in this community-based cervical cancer screening, most of the women were 40-49 years (39.7%) of age group, followed by 30-39 years (32.1%), 50-59 years (23%) and =/>60 years (20.8%). The mean age was 45 years (±SD, 8.4 years, Range-30-64) and 24% were postmenopausal. The mean age of first marriage was 23 years (±SD, 5.4 years, Range-15-42) and of menarche was 14 years (±SD, 1.6 years Range-11-19). Education of those women was graduated (21.3%), high school level (26.8%), middle school level (32.3%), primary school level (18.6%) and illiterate (0.5%). Only 8% of women had previous history of cervical cancer screening. Also only 3.5 % had been vaccinated against HPV.

Liquid based cytology (LBC)

Among 312 women who had been screened by LBC (Bethesda-system), 79.5% (248/312) of the women were negative-for-intraepithelial-lesion-or-malignancy (NILM). Women who had cervical epithelial cell abnormalities such as atypical-squamous-cells and/or atypical-glandular-cells (ASC/ AGC), low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) were 11.9% (37/312), 7.4% (23/312) and 1.3% (4/312), respectively (Fig. 1).

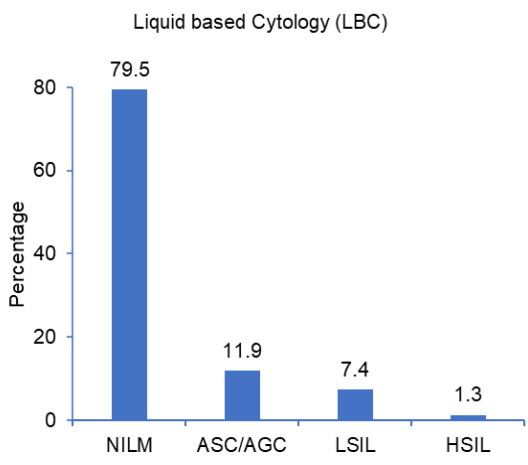

Fig. 1. Prevalence of cervical epithelial cell abnormalities using LBC in women residing at Kyauk Ye Twin Ward, North Okkalapa Township, Yangon

Human papillomavirus testing

Among a total of 312 screened women, 220 women aged between 30-49 years were enrolled for HPV testing using Cobas HPV test. In this study, hrHPV was identified in 5.5% (12/220) of women in general population of Kyauk Ye Twin Ward (Fig. 2a). Among HPV positive cases, pooled-12-hrHPV genotypes were 66.7%, HPV-16 (25.0%) and HPV-18 (8.3%) (Fig. 2b).

In this study, hrHPV was identified in 33.3% of HSIL, 27.3% of LSIL, 9.1% of ASC/ AGC, and 1.7% of NILM. Among the hrHPV positive women, 75% of them had cervical epithelial cell abnormalities in liquid based cytology (LBC) but 25% were NILM. Most of the hrHPV positive women had LSIL (50%) followed by ASC/AGC (16.7%) and HSIL (8.3%) (Table 1).

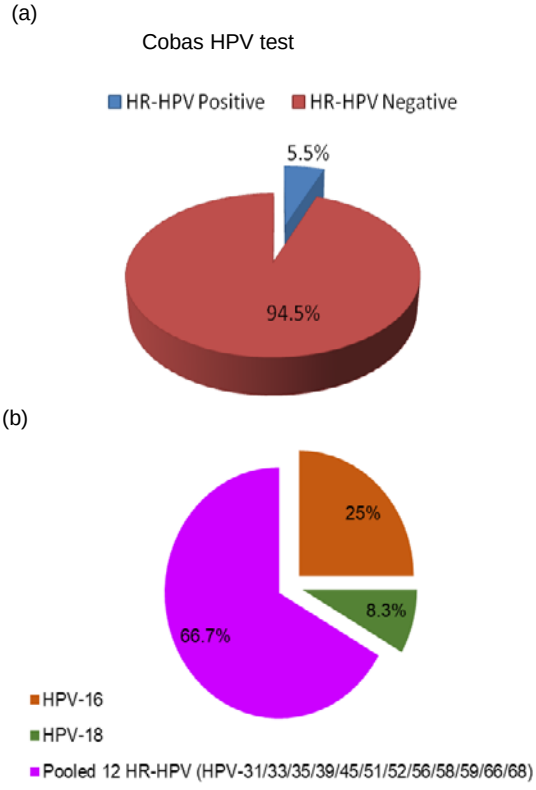

Fig. 2. Proportion of (a) hrHPV infection and (b) hrHPV genotypes using Cobas HPV test in women residing in Kyauk Ye Twin Ward, North Okkalapa Township, Yangon

Among HPV-16 positive women, all of them had cervical epithelial cell abnormalities in LBC comprising 33.3% of each had ASC/AGC, LSIL and HSIL (Fig. 3a). All HPV-18 positive cases were LSIL (Fig. 3b).

Of the pooled-12-hrHPV genotypes positive women, 62.5% of them had cervical epithelial cell abnormalities in LBC which were 50% LSIL and 12.5% ASCUS. However, 37.5% had no epithelial cell abnormalities in LBC (Fig. 3c). All women who had positive hrHPV and/or epithelial cell abnormalities had no previous history of cervical cancer screening.

Table 1. Proportion of hrHPV in association with liquid based cytology in women residing at Kyauk Ye Twin Ward, North Okkalapa Township, Yangon

Liquid based Cytology		Cobas HPV test		Total
		HR-HPV positive	HR-HPV negative	
Negative for intraepithelial lesion or malignancy (NILM)	Count	3	170	173
	% within LBC	1.7%	98.3%	100%
	% within CobasHPV test	25%	81.7%	78.6%
Atypical squamous cell and/or atypical glandular cell (ASC/AGC)	Count	2	20	22
	% within LBC	9.1%	90.9%	100%
	% within CobasHPV test	16.7%	9.6%	10%
Low grade squamous intraepithelial lesion (LSIL)	Count	6	16	22
	% within LBC	27.3%	72.7%	100%
	% within CobasHPV test	50%	7.7%	10%
High grade squamous intraepithelial lesion (HSIL)	Count	1	2	3
	% within LBC	33.3%	66.7%	100%
	% within CobasHPV test	8.3%	1%	1.4%
Total	Count	12	208	220
	% within LBC	5.5%	94.5%	100%
	% within CobasHPV test	100%	100%	100%

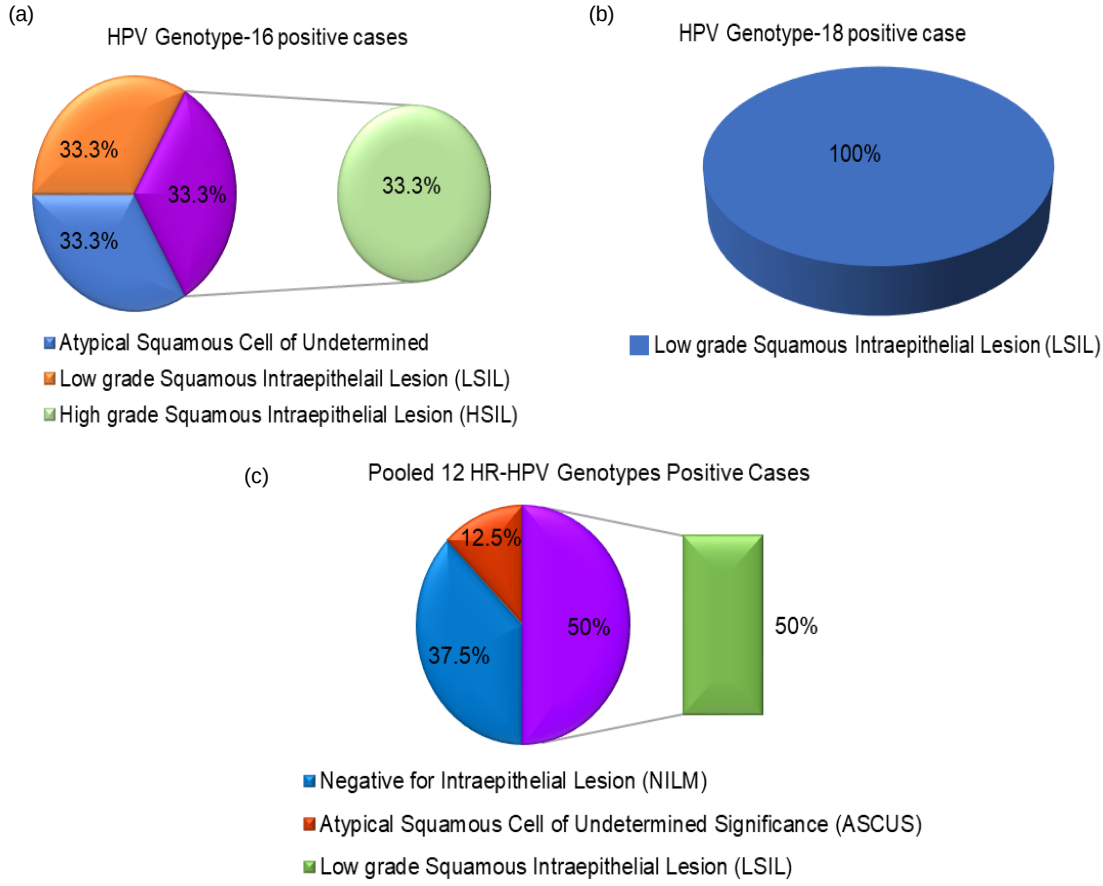

Fig.3. Prevalence of cervical epithelial cell abnormalities in LBC among (a) HPV-16 positive (b) HPV-18 positive (c) Pooled-12-hrHPV positive women residing in Kyauk Ye Twin Ward, North Okkalapa Township, Yangon

DISCUSSION

For reducing morbidity and mortality of cervical cancer, a three prong strategy i.e, HPV vaccination, screening and cancer management should be a global health priority. In low-and middle-income countries, there is limited access to these preventative measures and cervical cancer is often not identified until it has further advanced and symptoms develop. In addition, access to treatment of cancerous lesions may be limited, resulting in a higher rate of death from cervical cancer in these countries.[11]

Recent years, it has been well documented that providing quality assured and effective cervical cytology screening is a challenging task and cytology screening programs have been less successful in reducing cervical cancer burden in LMICs.[12] The challenges in introducing high-quality, frequently repeated cytology screening and the well documented low sensitivity of cytology to detect cervical cancer and its precursors, cervical intra-epithelial neoplasia (CIN) 2 and CIN3 lesions in various settings have led to the evaluation of alternative screening approaches such as HPV testing-based screening.[13, 14]

A number of countries are currently considering a transition to primary HPV testing for cervical screening, underpinned by evidence from a number of large-scale randomized trials and longitudinal cohort studies, which, taken together, show improved early detection of high-grade precancerous disease (CIN2/CIN3), lower cumulative incidence of CIN3 and invasive cervical cancer in HPV negative compared to cytology negative women, and, following treatment of detected CIN2/3, subsequent improved long-term protection against CIN3 and invasive cervical cancer in HPV-screened women compared to those screened with cytology.[15-17]

In 2017, according to American Society of Clinical Oncology (ASCO)'s Resource-Stratified Clinical Practice Guideline, HPV DNA testing is recommended in all resource settings; Recommended age ranges and frequencies by setting are as follows: maximal setting: ages 25 to 65, every 5 years; enhanced setting: ages 30 to 65, if two consecutive negative tests at 5-year intervals, then every 10 years; limited setting: ages 30 to 49, every 10 years; and basic setting: ages 30 to 49, one to three times per lifetime.[18] In this study, a total of 312 married women (mean age-45-years; range 30-64) residing in Kyauk Ye Twin Ward, North Okkalapa Township, Yangon were screened using liquid based cytology (LBC) in 2017. But 220 women aged between 30-49 years were enrolled for HPV testing using Cobas HPV test as the limited resource setting.

Prevalence of HPV among women with normal cervical cytology in Asia was 9.7-29.9% in China, 2.3-36.9% in India, 3.1-46.7% in Malaysia, 3.3-40.6% in Thailand, and 1.5-10.2% in Vietnam.[19] Muangto T, *et al* (2016) showed that prevalence of HPV among Thailand women attended the gynaecologic clinic was 19.7%. Majority of cases of abnormal cytology was ASC-US.[20] Tangjitgamol S, *et al* (2016) reported that abnormal cytology and positive HRHPV among Bangkok Metropolitan women were found in 6.3% and 6.7%, respectively. Rates of HRHPV detection were 5.4% among normal cytology and 13.0%, 39.5%, 56.3% and 100.0% among ASCUS, LSIL, HSIL, and SCC, respectively. The most common hrHPV genotype was HPV 16 (1.4%) followed by HPV 52 (1.0%), HPV 58 (0.9%), and HPV 18 and HPV 51 at equal frequency (0.7%).[21]

Van SN, *et al* (2017) reported that hrHPV were detected in 9.5% of women residing in two districts of Vietnam. The proportion of high-risk genotypes other than 16 and 18 was relatively high.[22] Chatzistamatiou K, *et al* (2017) reported that HR-HPV prevalence of women attending at the family planning centers, Germany was 17.7%. In Cytology, ASC-US/LSIL was in 7.6% and HSIL was detected in 1.6%. Sensitivity of cytology (ASCUS or worse) and HPV DNA testing for the detection of CIN2+ was 50.0 and

100%. HPV testing represents a more sensitive methodology for primary cervical cancer screening compared to cytology.[23]

In the ATHENA HPV study (USA) using Cobas HPV test and LBC, a total of 47,208 women were enrolled. The prevalence of cytological abnormalities was 7.1%. Overall prevalence of ASCUS, LSIL and HSIL were 4.1%, 2.3% and 0.3%, respectively. Pooled 12 hrHPV, HPV-16 and HPV-18 were detected in 12.6%, 2.8% and 1.0% of women, respectively. HPV-16 was identified in 12.8% of CIN1, 29.7% of CIN2, and 51.2% of CIN3.[24]

The present study using Cobas HPV test and LBC was based on general population in North Okkalapa Township, Myanmar. hrHPV was identified in 5.5% of women residing in Kyauk Ye Twin Ward. It was consistent with above studies from India, Malaysia, Thailand and Vietnam. The prevalence of cytological abnormalities was 20.5% which was higher than those of developed countries which had well organized cervical prevention programs since decades ago. Overall prevalence of ASC/AGC, LSIL and HSIL were 11.9%, 7.4% and 1.3%, respectively. The majority of abnormal cervical cytology cases were ASC/ AGC in the general population which was similar with above studies.

Mu Mu Shwe, *et al* reported that using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, hrHPV was identified 60% of ASCUS, 86.7% of LSIL in women attending Cervical Cancer Screening Clinic, DMR, Yangon[25], 44% of CIN-1, 63% CIN-2, 71% CIN-3, 74.1% of women with SCC attending Sanpya General Hospital, Yangon.[26] Those studies were performed in hospital-based and clinic-based population. The variation in HPV prevalence among the studies may be due to the difference of clinic-based and population-based, geographic variations, and HPV detection technologies.

In meta-analysis of South-east Asia studies (2017), prevalence of HPV-16 and/or HPV-18 among women with HSIL, LSIL and normal cytology was 33.4%, 27.4%, and 3.0%.[2] In this study, the detection of hrHPV in the general population was directly associated with severity of abnormal cytology: 33.3% of HSIL, 27.3% of LSIL, 9.1% of ASC/AGC, and 1.7% of NILM which was consistent with above studies. The proportion of high-risk genotypes other than 16 and 18 was relatively high in the general population which was similar to Van SN, *et al*.

In this study, among HPV-16 positive women, all women had abnormal cytology comprising 33.3% of each had ASC/AGC, LSIL and HSIL. All HPV-18 positive cases were LSIL. Of the pooled-12-hrHPV positive women, 62.5% had abnormal cytology comprising 50% LSIL and 12.5% ASCUS. Therefore, primary HPV testing and co-testing with cytology takes very crucial role for the early detection of cervical cancer. Those abnormality on either LBC or Cobas HPV tests were referred for colposcopy and/or directed biopsies (CDB) and early management. Further follow up studies using colposcopy, histopathology and HPV testing will be continued.

Currently, HPV testing alone or with cytology triage is increasingly being used as a primary screening approach for cervical neoplasia. Whilst HPV tests are less likely to miss cases of cervical pre-cancer and cancer, primary HPV screening test is very useful which don't lead to more unnecessary referrals. Negative HPV test is more reassuring than a negative cytological test, as the cytological test has a greater chance of being falsely negative, which could lead to delays in receiving the appropriate treatment.

Conclusion

This is the first report of hrHPV in general population in Myanmar. This study high-lighted that all women who had positive hrHPV and/or cervical epithelial cell abnormalities had no previous history of cervical cancer screening. To reduce the incidence and mortality of cervical cancer in Myanmar, well-organized National Cervical

Cancer Screening Program (NCCSP) should be established as a priority. If HPV testing is used as a primary screening test in NCCSP, the women with the highest risk of developing cervical cancer can be ruled out. In addition, hospital referral for appropriate management and/or follow up and burden of health care providers will be certainly reduced.

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