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Chapter 6

Descriptive Study of Different Methods of Cervical Cancer Screening Among Ever Married Women Aged 35 And 45 Years in Kalutara District: A Cross Sectional Study

Mapitigama N[1]; Beneragama BVSH[2]; Moonesinghe L[3]; Punchihewa R[4]; Perera KCM[5]*

[1]Consultant Community Physician, Family Health Bureau, Sri Lanka.

[2]Deputy Director General, Laboratory Services, Ministry of Health.

[3]Consultant Community Physician, Family Health Bureau, Sri Lanka.

[4]Consultant Histopathologists, National Hospital of Respiratory Diseases.

[5]Senior Registrar in Community Medicine, Directorate of Non-Communicable Diseases, Ministry of Health, Sri Lanka.

****Correspondence to: KCM Perera,** Senior Registrar in Community Medicine, Directorate of Non-Communicable Diseases, Ministry of Health, Sri Lanka.*

Email:chithranganieperea@yahoo.com

Abstract

Background One of the major drawback of the present cervical cancer screening programme in Sri Lankla is the suboptimal sensitivity (53%) of the pap smear to detect Cervical Intraepithelial Neoplasia (CIN). The sensitivity of LBC and HPV/DNA test to detect CIN II+ is 79.1% and 92.9% respectively. The objective of the study was to describe results of HPV/DNA screening test, conventional cytology and Liquid Based Cytology (LBC) among 35 and 45 year old women cohorts in Kalutara district.

Method Two women from each 35 and 45 year old women cohorts were selected from all Public Health Midwife areas (n=413) in Kalutara district by random sampling technique. The eligible families register/s were used as the sampling frame.Total number of 510 subjects from 35 age cohort and 502

subjects from 45 age cohort were subjected to cervical and pap smear specimen collection at community Well Woman Clinic (WWC) setting by public health staff called Medical Officers of Health or Public Health Nursing Sisters. HPV/DNA and conventional cyto-screening was done at District General Hospital Kalutara, while LBC was done by a Consultant Histopathologist. Screen positive women from any of methods were referred to colposcopy.

Results Response rate of 35 and 45 age cohort women was 90.7% and 90% respectively. Total of 32 women (6.2%) among 35 and 24 women (4.8%) among 45 year were positive for HPV/DNA test. Nine women (1.8%) among 35 year and 7 women (1.4%) among 45 year had cytological abnormality with conventional cytology. Total of 13 women (2.6%) among 35 year and 10 women (2%) among 45 year had cytological abnormality with LBC. Prevalence of Cervical Intraepithelial Neoplasia by colposcopy and biopsy among 35 years and 45 years women were 2.2% (n=11) and 1.8%(n=09) respectively.

Conclusions Liquid Based Cytology is not feasible to be incorporated into the National Cervical Cancer Screening programme as an alternative to conventional cytology. However to improve the quality of the programme in Sri Lanka, primary cervical cancer screening with HPV/DNA test should be assessed with LBC for only screen positive follow-up.

Keywords: Cervical cancer, Screening Methods, HPV/DNA test, LBC, Conventional Cytology.

Abbreviations: LBC: Liquid based Cytology; HPV/DNA: Human Papillomavirus/DNA**;** WWC: Well Woman Clinic**;** MOH: Medical Officer of Health**;** PCR: Polymerase Chain Reaction; PHM: Public Health Midwife; PHNS:Public Health Nursing Sister**;** HR-HPV; High risk human papillomavirus.

1. Background

Cervical cancer is a cancer that begins in the cervix of the uterus from the vagina. Cervical cancer is the second commonest among the Sri Lankan females, which accounts for nearly 10% of all female cancers. There was no marked reduction in age specific incidence rates of cervical cancer in Sri Lanka from 2006 to 2010 (eg. Age specific incidence rate for 50-54 age group in 2006 was 23, while in 2010 it was 22.5 per 100,000 women population) [1]. Comparison of age specific incidence rates between 55 and 75 age group females in Sri Lanka, across the other areas within the Southeast-Asian region and the rest of the world had shown an increasing trend according to the 2012 estimates [2]. Moreover deaths due to cervical cancer in Sri Lanka from 2000 to 2012 almost remained unchanged [3].

In 1998, Sri Lanka took a initiative to include screening for cervical cancer with conventional papaniculaou (pap) smear in the Well Woman Clinics (WWCs). However, even after 20 years of cervical cancer screening (with pap smears), there is no marked reduction

in incidence, morbidity and mortality of cervical cancer in Sri Lanka. Two major drawbacks of the present programme are, the suboptimal sensitivity (53%) [4] of the pap smear to detect Cervical Intraepithelial Neoplasia (CIN) and the low coverage [5] of the cervical cancer screening programme.

All cervical cancers are virtually associated with Human papillomavirus infection (HPV). There are high risk and low risk HPVs. Not all of the 40 sexually transmitted HPV virus genotypes cause serious health problems. High-risk HPV strains include HPV 16 and 18, which cause about 70% of cervical cancers. Other high-risk HPV viruses include 31, 33,35, 39 45, 51, 52, 56,58, 59,66 and 68. Persistent infection with carcinogenic HPV types is the cause of most cervical cancer [6].

There are some popular screening methods now used in the world for cervical cancer screening; visual inspection with Lugol's iodine (VILI), visual inspection with acetic acid (VIA) or visual inspection with a magnifying device (VIAM), conventional papcytology, liquid-based cytology and HPV/DNA screening test [7]. Visual Inspection is a suitable subjective screening method for low resource settings that can be used in women whose squamo-columnar junction (SCJ) is visible, typically in those ≤ 50 years, as SCJ graduallyprecedes into the endocervical canalwith menopause, which can lead to the missing of lesions [3].

Liquid based cytology (LBC) is used as a cervical cancer screening method in some developed countries, where more resources are available. In LBC a sample is taken by using a brush or a spatula and placed in a transport medium and then sent to the laboratory for microscopic examination and the major advantage is it's high sensitivity (79.1%) [4]. Supplies and laboratory facilities are more expensive in LBC than for conventional pap smear cytology [7].

The sensitivity of the HPV/DNA test is very high (92.9%) [8]. HPV/DNA screening is used in combination with cytology (co-test), as a triaging test for borderline cytology (ASC-US cytology with HPV/DNA test triage) or as a primary screening method followed by cytology i.e. HPV/DNA test with cytology triage [9]. In primary screening, only HPV/DNA positive women with 'Atypical Cells of Undetermined Significance (ASC-US) cytology need to be referred for colposcopy. Hence, there is a marked reduction in the number of referral for colposcopies.

Cervical cancer screening programme in Sri Lanka needs to review with special attention. The objective of the study was to describe results of HPV/DNA screening test, conventional cytology and LBC among 35 and 45 year old women cohorts in Kalutara district and determine the prevalence of cervical Intraepithelial Neoplasia(CIN) by colposcopy.

2. Methods

A community based cross-sectional study was conducted from 1st of February 2019 to 31st of July 2019. The study population comprised of ever married women in 35 and 45 years age cohorts in Kalutara district. Women with diagnosed invasive cervical cancer, per vaginal bleeding, active infection at the time of examination evidenced by medical records or by visual inspection, who were currently on treatment for HPV infection and women, who are not resident within the district continuously for ≥ 3 months prior to the date of the survey.

For the calculation of the sample size we assumed that the expected prevalence of HPV as 3.3% [6]and degree of accuracy desired specified as 0.016 (3.3/100x2) as the prevalence of ASCUS cytology was 4.1%[10]. Therefore we needed 435 women. Further adjustment to the sample size was made by considering the non-response rate (10%) in Kalutara district and the final required sample size was 485.

A Random sampling technique was adopted. There were 15 Medical Officer of Health (MOOH) areas in Kalutara district and 413 Public Health Midwife (PHM) areas. Two subjects each were chosen from all 413 PHM areas from each of the two separated age cohorts by random sampling technique from the relevant area eligible couple register/s. Information regarding Medical Officer of Health (MOH) area wise population in Kalutara district together with respective population were obtained from the 2017 census data. First author recruited eligible subjects to the study to avoid the bias could be made by PHM as they were care givers in field setting. Total number of 602 women in 35 age cohort and 592 women in 45 age cohort were recruited to the study after applying exclusion criteria at field setting. Arrangements for clinics were made with the help of the relevant MOH close to each PHM area. In a case those who were requested to change the clinic appointment for a special reason was given an appointment to the next closest clinic session.

Cervical specimen collection was carried out only by MO/MOH or Public Health Nursing sister/PHNS at WWCs. Cusco's speculum was inserted to visualize cervix before obtaining cervical specimen. Cervical specimens obtained (35y, n=51045y, n=502)from the cervix using a special broom-like devices were separately placed into cervical specimen collection containers with cell collection media/thin prep (20ml) were used for both HPV/DNA test and LBC. Pap smear collection was done for each women in both cohorts by using spatula. Cervical specimens and pap smears were packed and transported to the laboratory District General Hospital, Kalutara along with separate referrals. Prepared guidelines were strictly adhered during data collection, barcoding and preparation for transport.

HPV/DNA screening was done by well trained cyto-screeners with cobas 4800 HPV/DNA automated PCR machine, which consists of cobas 4800x instrument and cobas analyzer. Cobas 4800 HPV/DNA screening machine was included several quality control mechanisms

such as internal quality control, external quality control and contamination control. The test sensitivity and specificity to detect ≥Cervical Intraepithelial Neoplasia (CIN) II is 92.9% and 71% respectively [8]. It detects 14 high risk carcinogenic HPV genotypes, such as; 16,18 and 12 pooled high risk (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). Following the HPV/DNA screening cervical specimens were transported to a specialized laboratory in Colombo with a referral to LBC. Pap screening was carried out by two cytoscreeners at DGH Kalutara, while LBC was carried out by a Consultant Histopathologists in a specialized laboratory.

Public Health Midwives (field guides) were uniformly trained to locate households. A self administered questionnaire were given to participants by field guides at field setting. Once a questionnaire was completed, participant was given a clinic appointment card with a reference number and invited to attend the clinic.

All positive subjects from any of the screening methods were referred for colposcopy at colposcopy clinic Family Health Bureau, Colombo. All categories of staff including colposcopist were received uniform training to ensure the quality of performance. Training of Trainers (MOHs, Colposcopist, PHNS and Cytoscreeners) was done by relevant area specialists (e.g. - Consultant VOGs, Consultant Pathologists).

Follow-up of all positive clients was done by each relevant area MOH. Positive follow-up register at MOH office was used for that. This register was available at each relevant MOH office and a copy of the list was given to each relevant area PHM. Relevant area MOH was responsible for all referrals.

Data entry by using statistical package IBM SPSS version 20.Descriptive statistics was used in data analysis. Overall prevalence of the cervico-vaginal HPV infection and subgroup analysis (HPV genotype 16, 18 and 12 pooled risk) with 95%CI among 35 and 45 year old ever married women were estimated. Overall prevalence of ASCUS cytology in LBC vs. conventional cytology estimated. Overall prevalence of CIN by colposcopy among 35 and 45 age cohort women were calculated. The technical and operational feasibility of incorporating liquid based cytology (LBC) into National Cervical Cancer Screening programme in Sri Lanka as an alternative to conventional cytology was assessed.

3. Results

Response rateof 35 year old women attended the community WWCs to participate in the study was 90.7%. Six recruits were excluded at clinic setting from the study, as they were pregnant (16.7%), while others were due to vaginal discharge (30.5%), cervicitis (16.7%), fungal infection (13.9%) and cervical erosion (16.7%). (**Figure 1**).

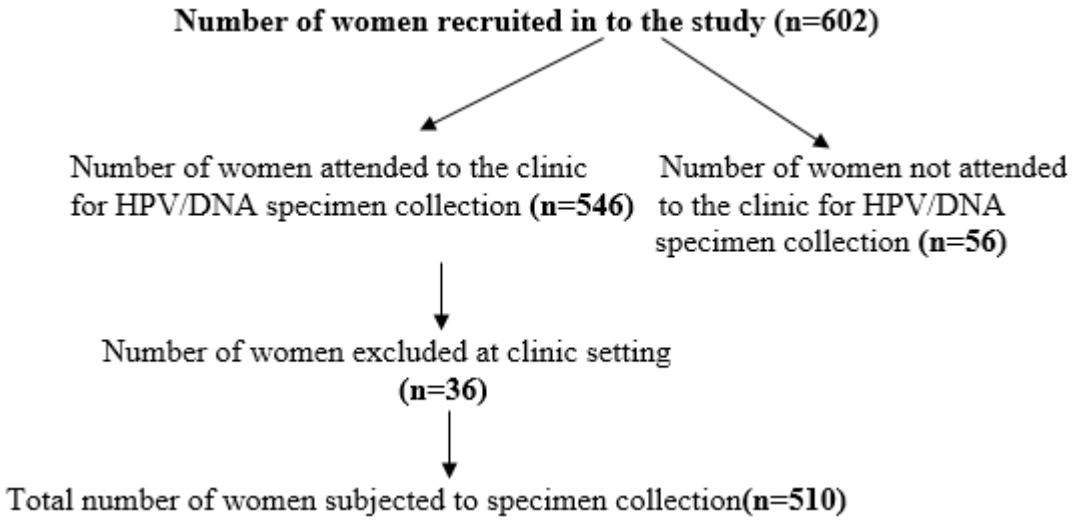

Figure 1

Majority of women who participated in the study were Sinhala (n=485, 97.1%) and Buddhist (n-484, 97%), Out of the total subjects 9% (n=46) had not completed years of school education beyond the 5thgrade level of education and another 12.2% (n=62) of the subjects remained at 6-11th grade level of education. Majority (58.9%, n=300) were educated up to O/L passed level of education (**Table 1**).

Table 1: Distribution of 35 year old participants according to socio-demographic and economic characteristics.

Characteristics	Number of women (n)	Percentage %
Nationality		
Sinhala	495	97.1
Tamil	09	1.7
Muslim	06	1.2
Religion		
Buddhism	494	97.0
Catholic	06	1.1
Hindu	04	0.7
Islam	06	1.2
Educational level		
No schooling	1	0.2
Grade 1-5	45	8.8
Grade 6-11	62	12.2
O/L* passed	192	37.7
A/L** passed	151	29.6
Degree & above	59	11.5
Occupational status		
Working women128 25.2, Non-Working women382 74.8		
Average Monthly Income (Rs)		
≤15,000	39	7.6
>15,000	471	92.4
Total	**510**	**100.0**

*General Certificate Examination Ordinary Level

** General Certificate Examination Advance Level

Response rate of 45 year old women was 90%. Nine recruits were excluded due to vaginal discharge (29%), while others were due to cervicitis (25.8%), cervical erosion(19.4%) and fungal infection (25.8%) **(Figure 2).**

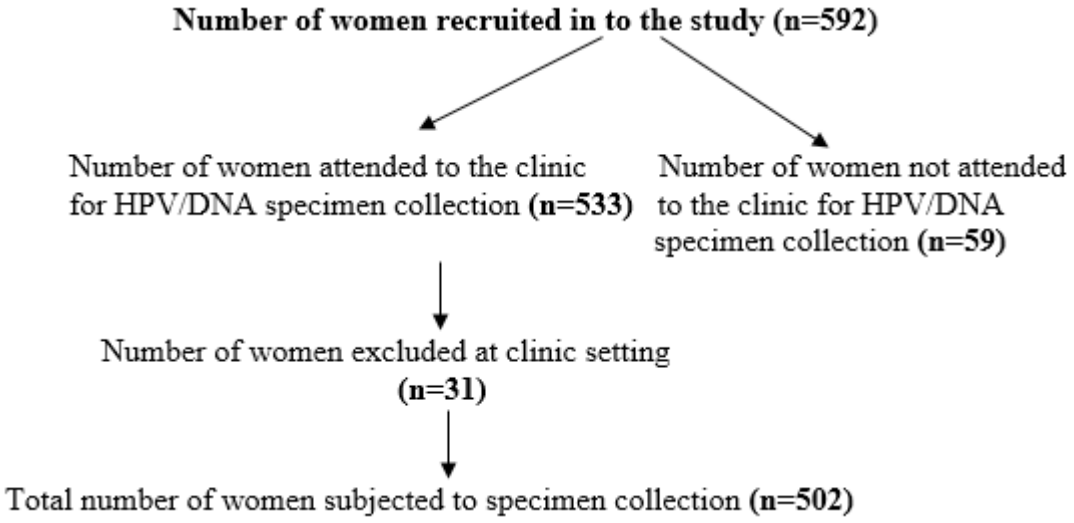

Figure 2

Majority of women who participated in the study were Sinhala (n=486, 96.9%) and Buddhist (n=485, 96.6%). Out of the total subjects 9.1%(n=46) had not completed years of school education beyond the 5thgrade level of education and another 14% (n=70)of the subjects remained at 6-11th grade level of education. Majority (n=316, 62.9%) were educated up to O/L passed level of education **(Table 2).**

Table 2: Distribution of 45 year old participants according to socio-demographic and economic characteristics.

Characteristics	Number of women (n)	Percentage %
Nationality		
Sinhala Tamil Muslim	486 09 07	96.9 1.7 1.4
Religion		
Buddhism Catholic Hindu Islam	485 06 04 07	96.6 1.2 0.8 1.4
Educational level		
No schooling Grade 1-5 Grade 6-11 O/L* passed A/L** passed Degree & above	1 45 70 200 139 47	0.2 8.9 14.0 39.8 27.6 9.5
Occupational status		
Working women9919.8, Non-Working women40380.2		
Average Monthly Income (Rs)		
≤15,000 >15,000	49 453	9.8 90.2
Total	**502**	**100.0**

*General Certificate Examination Ordinary Level

** General Certificate Examination Advance Level

Total number of 32 women (6.2%) among 35 age cohort and 24 women (4.8%) among 45 age cohort were positive for HPV/DNA test. Total number of 9 women (1.8%) among 35 age cohort and 7 women (1.4%) among 45 age cohort had cytology ≥ASCUS in conventional cytology. Total number of 13 women (2.5%) among 35 age cohort and 10 women (2%) among 45 age cohort had cytology ≥ in LBC **(Table 3).**

Table 3: Prevalence of cervical cancer precursors by each method of cervical cancer screening

Age of women (Years)	% of Cervical cancer precursors by each method of cervical cancer screening		
	Conventional Cytology	LBC	HPV/DNA
35	1.8% (n=9)	2.5% (n=13)	6.2% (n=32)
45	1.4% (n=7)	2% (n=10)	4.8% (n=24)

Overall prevalence of the high risk HPV genotype infection among 35- year- age cohort ever- married women in Kalutara district was 6.2%(95%CI:6.18-6.22), while the prevalence of high risk HPV(HR-HPV) genotypes 16 and 18 was 2%(95%CI:1.99-2.01). The prevalence of HPV 12 pooled genotypes was 4.3%(95%CI:4.29-4.31) **(Table 4).**

Table 4: Distribution of 35 year old participants according to cervical HPV/DNA specimen results for high risk genotypes.

Cervical HPV/DNA specimen results for HR-HPV genotypes	Number of women	Percentage%	95% CI for percentages %
Negative	478	93.7	
12 pooled positive	22	4.3	4.29-4.31
16 positive	09	1.8	1.79-1.81
18 positive	01	0.2	0.19-.21
Total	**510**	**100.0**	

Overall prevalence of the high risk HPV genotype infection among 35- year- age cohort ever- married women in Kalutara district was 4.8%(95%CI:4.79-4.81), while the prevalence of high risk HPV(HR-HPV) genotypes 16 and 18 was 1.3%(95%CI:1.29-1.31). The prevalence of HPV 12 pooled genotypes was 3.4%(95%CI:3.39-3.41) **(Table 5)**.

Table 5: Distribution of 45 year old participants according to cervical HPV/DNA specimen results for high risk genotypes.

Cervical HPV/DNA specimen results for HR-HPV genotypes	Number of women	Percentage%	95% CI for percentages %
Negative	478	95.3	
12 pooled positive	17	3.4	3.29-3.41
16 positive	05	1	0.99-1.01
18 positive	02	0.3	0.29-0.31
Total	**502**	**100.0**	

Overall prevalence of colposcopy confirmed CIN among 35 and 45 year old women in Kalutara district were 2.2% (n=11) and 1.8% (n=9) respectively and they all were screen positive for HPV/DNA test. Colposcopy confirmed CIN among 35 and 45 year old women by

conventional cytology and LBC (≥ASCUS) were 1.6% (n=8), 1.2% (n=6) and 1.6% (n=8), 1.4% (n=7) **(Table 6)**.

Table 6: Percentage of women with confirmed CIN by colposcopy (gold standardfor CIN) from any method among 35 and 45 year age cohorts.

Age of women (Years)	% of women with confirmed CIN by colposcopy (gold standardfor CIN) from any method among 35 and 45 year age cohorts		
	Conventional Cytology	LBC	HPV/DNA
35	1.6% (n=8)	1.6% (n=8)	2.2% (n=11)
45	1.2% (n=6)	1.4% (n=7)	1.8% (n=9)

Majority of HPV/DNA screen positive 35 year age cohort women had normal colposcopy results(65.7%), while 18.7%, 9.3% and 6.3% were positive for CIN I, CIN II and CIN III respectively (**Table 7**). Majority of HPV/DNA screen positive 45 year age cohort women had normal colposcopy results(62.5%), while 16.7%, 8.3%, 8.3% and 4.2% were positive for CIN I, CIN II,CIN III and cervical cancer respectively (**Table 8**).

Table 7: Distribution of 35 year old participants with HPV/DNA screen positive results by colposcopy and biopsy results.

Colposcopy and biopsy results	HPV/DNA screen positive results	Percentage%
Normal	21	65.7
CIN I	06	18.7
CIN II	03	9.3
CIN III	02	6.3
Cervical Cancer	0	0
Total	**32**	

Table 8: Distribution of 45 year old participants with HPV/DNA screen positive results by colposcopy and biopsy results.

Colposcopy and biopsy results	HPV/DNA screen positive results	Percentage%
Normal	15	62.5
CIN I	04	16.7
CIN II	02	8.3
CIN III	02	8.3
Cervical Cancer	1	4.2
Total	**24**	

There were no invalid or unsatisfactory reports of LBC. Cell collection media (thinprep) in HPV/DNA specimen collection instrument was used for LBC and screened by a machine. Management adherence of the colposcopy after one month of the initial referral following LBC screen positive results was 86.7%(n=20). There was no significant difference ($p \geq 0.5$) between the detection of CIN by colposcopy between conventional cytology and LBC and the difference is only marginally. Detection rate of CIN by colposcopy was significantly higher ($p < 0.5$) for HPV/DNA screening than LBC and conventional cytology.

4. Discussion

Cervical cancer is the 2nd leading cause of female cancer in Sri Lanka[2]. Hence in 1998, Sri Lanka took a initiative to include screening for cervical cancer with conventional papaniculaou (pap) smear in the WWCs. After 20 years of existence of the cervical cancer screening programme, in contrast to the vigorous preventive measures there is no marked reduction of incidence, morbidity and mortality of cervical cancer in Sri Lanka. Therefore, cervical cancer prevention programme needs to be reviewed with special attention.

In Sri Lanka, the target cohorts for cervical cancer are women aged 35 and 45 years. Even though screening two age cohorts gives an evidence of well organized screening programme, the coverage for 35 years age cohort in 2017 in Sri Lanka is only 53.6%[11]. One of the major disadvantages of the pap smear screening is the suboptimal sensitivity to detect cervical lesions and its sensitivity to detect Cervical Intraepithelial Neoplasia (CIN) 2+ is only 53% and the specificity is 96.3% [4]. Liquid Based Cytology (LBC) is a more sensitive method of diagnosing cervical cancer and its sensitivity to detect CIN 2+ is 79.1% and the specificity is 78.8% [4].

However, HPV/DNA testing is the most sensitive screening tool available at this time for the detection of underlying CIN and cervical cancer [12]. In cobas 4800 HPV/DNA test the sensitivity to detect ≥CIN 2+ is 92.9% and the specificity is 71%.In 2009, a randomized controlled trial of over 130, 000 women in India showed that a single round of HPV/DNA testing canreduce cervical cancer deaths by about 50% within eight years of follow-up [13].

All cervical cancers are virtually associated with cervico-vaginal HPV infection. There was a marked elevation of the prevalence of the cervico-vaginal HPV infection from 2009 (3.3%) to 2020 (6.2%) among ever married women population in Sri Lanka. More over high risk genotypes 16 and 18 prevalence were elevated from 1.2%[6] to 2% within the same duration. HPV 16 and 18 are associated with approximately 70% of all cervical cancers. It was obvious that the prevalence of other high risk HPV genotypes (except genotype 16 and 18) were too markedly elevated from 2.1% to 4.3% in 2020. In the study carried out in 2009, the age group screened for HPV/DNA was 20-59 year ever married women in Gampaha district. Usually transient HPV infection rate was high among sexually active women ≤ 30 years of age[3], so the absolute prevalence rates of HPV infection at 35 year age cohort in 2009 may be even smaller to the mentioned data.

This is the first study carried out to assess the prevalence of cervico-vaginal infection among 45 years age cohort women in Sri Lanka. Further, subgroup analysis among the 45 year age cohort was too carried out. When the proportion of women tested positive for high risk HPV/DNA in a country are at least 1%, it indicates a good quality standard for the HPV/DNA screening test as a cervical cancer screening method [14], therefore HPV/DNA screening test

can be considered to be incorporated in to the National Cervical Cancer Screening programme in Sri Lanka as the prevalence≥1%.

Detection rate of CIN by colposcopy among 35 and 45 year women was only marginally higher by LBC than conventional cytology (pap smears) and it's not significant($p<0.05$). Detection rate of CIN by colposcopy was significantly high for HPV/DNA screening($p\geq0.05$) in comparison with LBC and conventional cytology. Most of the detected CIN among 35 and 45 year old women cohorts were remain at stage I, which was a good indicator for timely intervention.

This study was restricted to one district out of 25 districts in Sri Lanka due to logistic constrains. The population characteristics and the public health infrastructure of the district favored generalizability of the research findings to the whole country.

5. Conclusions and Recommendations

Detection rate of CIN by colposcopy was only marginally higher by LBC than conventional cytology (pap smears), therefore LBC cannot be recommended to be incorporated in to the National Cervical Cancer Screening programme as an alternative to conventional cytology. To improve the quality of the National Cervical Cancer Screeningprogramme in Sri Lanka, HPV/DNA PCR test as a primary cervical cancer screening methodwith LBC for only screen positive follow-upshouldbeassessed for feasibility.

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8. Availability of data and materials

The datasets used to analyze in this study is available at corresponding author on reasonable request.

9. Authors contribution

KCMP was participated in the design of the study, coordinated data collection performed

the statistical analysis and drafted the version of the manuscript. NM were participated in the design of the study. KCMP was performed the statistical analysis and interpreted data. Both NM and LM were helped to draft the manuscript. All five authors were read and approved the final manuscript.

10. Ethical approval and consent to participate

Ethical clearance was obtained from the Ethics Review Committee (ERC), National Institute of Health Science (NIHS), Kalutara, Sri Lanka (ref number NIHS/ERC/18/85R). Informed written consent was obtained from each of the selected participants at the field during the study. Confidentiality was highly maintained, while handing over individual HPV/ DNA, conventional cytology and LBC result reports. Administrative clearance to conduct the study was obtained from Provincial Director of Health Services/Western Province, Regional Director of Health Services/Kalutara district, Director/ District General Hospital Kalutara and Director /National Institute of Health Science Kalutara.

11. Consent to publish

Not applicable

12. Competing interests

Authors were declared that they have no competing interests

13. References

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