RESEARCH ARTICLE

A Descriptive Study of Different Methods of Cervical Cancer Screening among Ever-Married Women in 35-Year and 45-Year Cohorts in Kalutara District, Sri Lanka

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Abstract

   Objective: Screening for cervical cancer in Sri Lankan females with Pap smears (conventional cytology) has shown no marked reduction in cervical cancer incidence over the past two decades. The study aims to compare the efficacy of Pap smear, with other screening tools such as Liquid Based Cytology (LBC) and Human Papilloma Virus/ deoxyribonucleic acid (HPV/DNA) (using cobas 4800) in detection of underlying cervical intraepithelial neoplasia (CIN) and cervical cancer among 35 and 45 year old ever married women in Kalutara districtin Sri Lanka. **Methods:** Women from 35-year cohort and 45-year cohort were selected from all Public Health Midwife areas (n=413) in Kalutara district by random sampling. Pap smear, LBC, and HPV/DNA specimen were collected s from women who attended the Well Woman Clinics (WWC) . Women with positive results from any method were confirmed by colposcopy. **Results:** Of the, 510 and 502 women in the 35-year cohort and 45-year cohort, respectively, included in the analysis, nine women among 35-year cohort (1.8%) and 7 women among 45-year cohort (1.4%) had cytological abnormality (positive results) with Pap smears. Thirteen women among 35-year cohort (2.5%) and 10 women among 45-year cohort (2%) age groups had cytological abnormality (positive results) with Liquid Based Cytology reports. Total of 32 women among 35-year cohort (6.2%) and 24 women among 45-year cohort (4.8%) were positive for HPV/DNA test. Of the women tested positive on screening, colposcopy revealed that HPV/DNA method was superior to Pap and LBC for detecting CIN while the results of latter two were comparable. **Conclusions and Recommendations:** The CIN detection rate by colposcopy was high with HPV/DNA screening with cobas 4800, whereas the detection rate by LBC was insignificantly higher than Pap smears.

Keywords: Cervical cancer- Pap smear- LBC- HPV/DNA

Introduction

   Cervical cancer is the second commonest malignancy among Sri Lankan females. Globocan, 2020 age standardized incidence, mortality and 5-year prevalence rates (per 100,000) were 9.2, 4.9, and 35.08, respectively. A total of1,407 new cervical cancer cases and 780 cervical cancer related deaths were reported from Sri Lanka in 2020 (Globocan, 2020).This shows that almost half the cervical cancer cases die, thereby indicating that they are diagnosed late when they are not amenable to treatment (Kandanearachchi et al., 2021; Vithana et al., 2018).

   Cervical cancer has a unique well-defined pre-invasive/ precancerous state with abnormal epithelial cells at the squamous-columnar junction, known as cervical intraepithelial neoplasia (CIN). This makes screening of this cancer easier as compared to many other cancers (Kandanearachchi et al., 2021). Almost all cervical cancers are associated with Human Papilloma Virus (HPV) infection, which is essentially sexually transmitted (WHO, 2020). HPV 16 and HPV 18 strains are responsible for 70% of cervical cancers and CIN (WHO, 2020). Other than these, 12 pooled HPV types (31, 33, 35,39, 45, 51, 52, 56, 58,59, 66 and 69) are also responsible to a lesser extent for cervical cancer (Perera et al., 2021). Hence, HPV 16, 18 and pooled 12 HPV types are called high-risk HPVs for cervical cancer.

   If HPV infection persists in a woman, it may take up to 10 to 20 years for CIN to develop into invasive cervical cancer (Kandanearachchi et al., 2021) Since CIN precedes over cancer by decades, cervical cancer is largely preventable (WHO, 2021). There are two main cervical cancer screening methods, cervical cytology based screening (Papanicolaou test, Pap smear and liquid based

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cytology [LBC]) and HPV deoxyribonucleic acid (HPV DNA) viral antigen based screening (Kandanearachchi et al., 2021). Evidence from the ATHENA study using HPV as the first-line screening test, and a systematic review (40 studies; N=140,000 women; age between 20 and 70 years) concluded that HPV/DNA testing is more sensitive and specific in detecting CIN than cytology based testing (Koliopoulos et al., 2017; Wright et al., 2015).

The World Health Organization (WHO) 2021 guideline recommends using HPV DNA detection as the primary screening test for general population rather than visual inspection with acetic acid (VIA) or cytology (WHO 2021). A recent study from Sri Lanka reported that the HPV/DNA test was well received by 35-year cohort of ever- married women in Kalutara district and can be a feasible primary cervical cancer screening method for national program (Perera et al., 2021). WHO 2021 further suggests using partial genotyping, colposcopy, VIA orcytology to triage women after a positive HPV DNA test (WHO, 2021). Of these methods for triage, colposcopy is considered the gold standard for confirming CIN/cancer (Pretorius et al., 2007; Perkins et al., 2020).

It has been seen that countries with well-established screening programs, such as United Kingdom (UK), have been able to reduce cancer incidence significantly by almost 75%, since the adoption of national screening program (NSP) (Kandanearachchi et al., 2021). However, despite a NSP, Sri Lanka, has not been able to bring about this significant reduction in cervical cancer burden because of two major drawbacks in the NSP (Perera et al., 2021). One is the use of PAP smear for screening, as it has suboptimal sensitivity (53%) in detecting CIN-II and the other is insufficient NSP coverage (Perera et al., 2021).

The WHO 2021 guideline recommends cervical cancer screening should be started at 30 years and continued until 65 years (WHO, 2021). However, in resource limited setting, WHO, 2021 guidelines recommends that priority should be given to women in age group 30 to 49 years. Currently in Sri Lanka, cervical cancer screening targets two age cohorts; 35-year cohort and 45-year cohort (Kandanearachchi et al., 2021). Therefore, the main objective of this study was to determine the most appropriate cervical cancer screening method in the 35-year cohort and 45-year cohort in Sri Lanka. The study compared all the three methods of screening, Pap smear, LBC and, HPV/DNA to find out the most effective screening tool for detecting CIN in these two age cohorts. The study further compared the percentage of women with positive follow-up colposcopy among those who tested positive by any of these methods.

Materials and Methods

In this Cross-sectional descriptive study, ever married women from 35-year cohort and 45-year cohort were selected from 413 Public Health Midwife (PHM) areas in the Kalutara district. From the 35-year cohort and 45-year cohort, 602 and 592 subjects were chosen by simple random sampling from the 413 PHM areas in the Kalutara district. The mean age of marriage in Sri Lanka is 23.9 years and , it may take up to 10 to 20 years for CIN to

develop into invasive cervical cancer (Kandanearachchi et al., 2021; Perera et al., 2021). Hence, the two chorts were designed as 23.9 + approximately 10 years (35-year cohort) and 23.9 + approximately 20 years (45-year cohort).

Pap smear, LBC, and HPV/DNA specimen were collected from each participant by Medical Officer of Health (MOOH) or Public Health Nursing Sisters (PHNS) in Well Woman Clinics (WWC). Women with frank invasive cervical cancer, per vaginal bleeding and active infection at the time of examination, unmarried women and women who were not residing within the district continuously for ≥ 3 months prior to the date of recruitment, were excluded from the study.

At WWCs a visual inspection of the cervix was done following insertion of a Cusco's speculum. The speculum examination and cervical specimen collection was carried out only by a well-trained MOOH or a PHNS after explaining the procedure to the participants. A HPV/ DNA specimen was obtained from the cervix of each participant using a cervical broom (brush) and placed into an HPV/DNA specimen collection container (preservative medium). The specimen thus collected was used for both LBC and HPV/DNA testing. Also, a specimen was taken for Pap smear by using a wooden spatula. Collected specimens were then transferred with separate referral forms to District General Hospital (DGH) Kalutara laboratory for screening. The polymerase Chain Reaction (PCR) machine, cobas 4800 was used for the HPV DNA testing. All positive subjects from any of the screening methods were referred for colposcopy to Kethumathie Maternity Hospital (KMH) Panadura. Socio-demographic data and data on various laboratory results were collected over a period of six months from 1st February 2019 to 31st July 2019.

Statistical analysis

The statistical package International Business Machines (IBM), Statistical Package for Social Science (SPSS) version 20was used for data entry and correlation analysis of CIN detection by Pap, LBC and HPV/DNA. A chi-square test was used for between group comparisons and a P-value of ≤0.05 was considered as a statistically significant difference. Descriptive statistics using percentage was used to analyze categorical variables.

Results

Baseline characteristics

A total of 602 and 592 ever married women were recruited in the 35-year cohort and 45-year cohort, respectively. Of these, 90.7% women in the 35-year cohort and 90% women in the 45-year cohort attended the WWC for sample collection (Figure 1). After applying the exclusion criteria (Figure 1, Table 1), Pap smear, LBC, and HPV/DNA specimen were collected from each of the 510 women in the 35-year cohort and 502 women in the 45-year cohort. Study participants were mainly Sinhala and Buddhist: in 35-year cohort 97.1% were Sinhala and 97%Buddhist; the corresponding numbers in the 45-year cohort were Sinhala (96.9%) and Buddhist
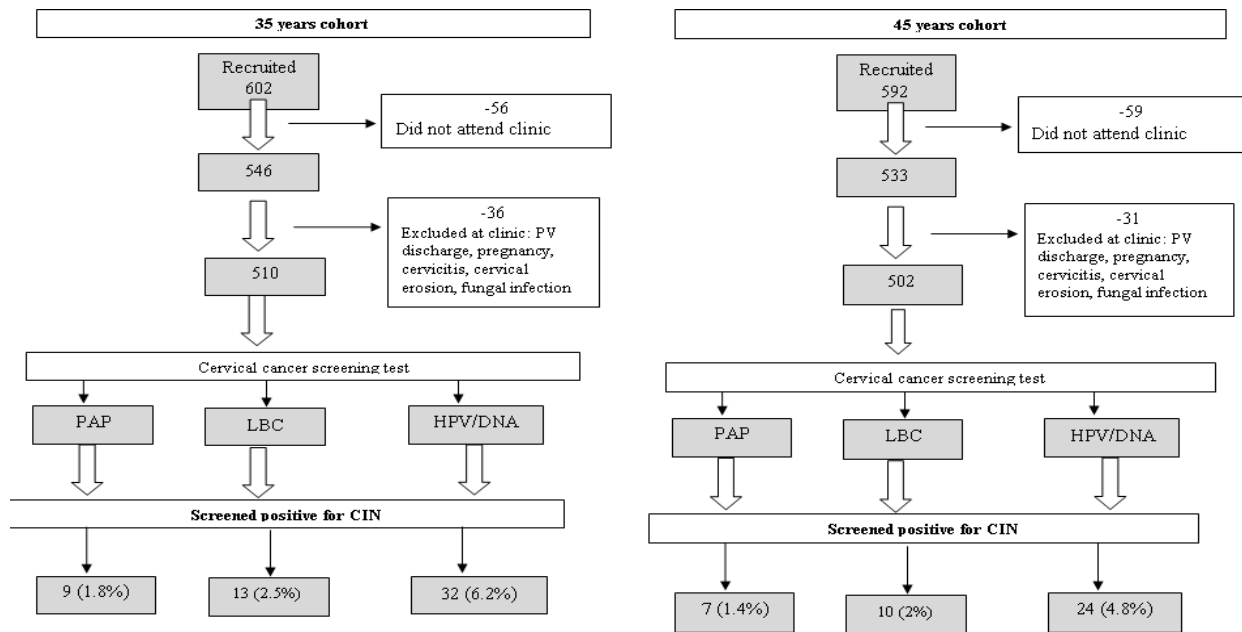
Figure 1. Study Population. Abbreviations: CIN, cervical intraepithelial neoplasia; HPV/DNA, human pappiloma virus/deoxyribonucleic acid viral antigen based screening LBC, liquid based cytology; PAP, Papanicolaou test; PV, per vaginum; HPV/DNA testing by cobas® 4800

(96.6%). Majority were O/L passed (ordinary level as per the General Certificate of Education qualification in Sri Lanka)(58.9% in 35-year cohort and 62.9% in 45-year cohort); 12.2% and 14% of the participants in the 35-year cohort and 45-year cohort respectively, had passed 6-11th grade level and 9% and 9.1%, respectively had not completed school education beyond the 5th grade. Table 2 shows the socio-demographic and economic characteristics of the study participants.

Percentage of participants with positive screening results for Pap smear, LBC or HPV/DNA viral antigen by 35-year cohort and 45-year cohort

HPV/DNA test was positive for typical squamous cells of undetermined significance (ASCUS) in 32 women (6.2%) in the 35-year cohort and 24 women (4.8%) in the 45-year cohort. Pap smear and LBC showing positive results for ASCUS are shown in Table 3. ASCUS detection rate by colposcopy was not significantly different between Pap and LBC positives (P ≥0.5) in both the cohorts. ASCUS detection rate by colposcopy was significantly higher for HPV/DNA screening than LBC and Pap (P <0.5) in both the cohorts.

Table 1. Exclusion Criteria at Clinic Setting

Reason	Number of women aged 35	Number of women aged 45
PV discharge	11	9
Pregnancy	6	0
Cervicitis	8	8
Cervical erosion	6	6
Fungal infection	5	8
Total excluded	36	31

Prevalence of HPV infection among participants in Kalutara district

Overall, HPV/DNA test for HPV genotype infection was positive among 6.3% and 4.8% of 35-year cohort and 45-year cohort, respectively.

Table 4 provides the positivity rates of HPV/DNA test by HPV genotypes 12 pooled HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58,59, 66 and 69), 16, and 18.

Percentage of participants with confirmed CIN by colposcopy after screening positive

Colposcopy and biopsy was done for participants who screened positive by any method. Of the participants who were screened positive by HPV/DNA, confirmed CIN on colposcopy was seen in 2.2% (n=11) and 1.8% (n=9) of participants in the 35-year cohort and 45-year cohort, respectively. Colposcopy confirmed CIN in 35-year cohort and 45-year cohort in participants screened positive by PAP and LBC are shown in Table 5.

CIN detection rate by colposcopy was not significantly different between Pap and LBC positives (P ≥0.5) in both the cohorts.CIN detection rate by colposcopy was significantly higher for HPV/DNA screening than LBC and Pap (P <0.5) in both the cohorts.

Colposcopy and biopsy results among participants with positive screening results

Of the participants who screened positive for CIN, majority of HPV/DNA positive women in 35-year cohort 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. Majority of HPV/DNA positive women in 45-year cohort 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. CIN

Table 2. Socio-Demographic and Economic Characteristics of the Study Population by 35 and 45 Years Age Cohorts

Characteristics	Number of women aged 35 (510)	Percentage %	Number of women aged 45 (502)	Percentage %
Nationality				
Sinhala	495	97.1	486	96.9
Tamil	9	1.7	9	1.7
Muslim	6	1.2	7	1.4
Religion				
Buddhism	494	97	485	96.6
Catholic	6	1.1	6	1.2
Hindu	4	0.7	4	0.8
Islam	6	1.2	7	1.4
Educational level				
No schooling	1	0.2	1	0.2
Grade 1-5	45	8.8	45	8.9
Grade 6-11	62	12.2	70	14
GCE O/Lpassed	192	37.7	200	39.8
GCE A/L passed	151	29.6	139	27.6
Degree & above	59	11.5	47	9.5
Occupational status				
Working women	128	25.2	99	19.8
Non-Working women	382	74.8	403	80.2
Average Monthly Income (SLR)				
≤15,000	39	7.6	49	9.8
>15,000	471	92.4	453	90.2

A/L, advanced level; GCE, General Certificate of Education; O/L, ordinary level; SLR, Sri Lankan Rupee

Table 3. Percentage of Participants with Positive Results by Different Methods of Cervical Cancer Screening

Age of women (Years)	% ofASCUS by each method of cervical cancer screening		
	PAP	LBC	HPV/DNA
35 (n=510)	9 (1.8%)	13 (2.5%)	32 (6.2%)
45 (n=502)	7 (1.4%)	10 (2%)	24 (4.8%)
Total	16	23	56

ASCUS, atypical squamous cells of undetermined significance; DNA, deoxyribonucleic acid; HPV, Human Papilloma Virus; LBC, liquid based cytology; PAP, Papanicolaou test; Chi square test results (both cohorts): Pap vs LBC (P≥0.5); HPV/DNA vs. conventional cytology (Pap/LBC) (P<0.05)

stages detected by clposcopy and biopsy in the 35-year cohort and 45-year cohort in participants screened positive by PAP and LBC are shown in Table 6.

Discussion

The national cervical cancer screening program in Sri Lanka is based on Pap smear which has suboptimal sensitivity in detecting CIN. Hence, we explored the possibility of using other evidence based methods cervical cancer screening. Consequently a pilot study to screen women for cervical cancer was done in Kalutara district using HPV DNA (Perera et al., 2021). In this backdrop, this cross-sectional descriptive study evaluated the suitability of using LBC, and HPV/DNA as cervical cancer screening tool among 35-year cohort and 45-year cohort of ever married women in Kalutara district. The feasibility of LBC and HPV/DNA was compared with that

Table 4. Distribution of High Risk Genotypes According to Cervical HPV/DNA Specimen Results

Cervical HPV/DNA specimen results for HPV genotypes	Number of women aged 35 (n=510)	Percentage %	Number of women aged 45 (n=502)	Percentage %
Negative	478	93.7	478	95.3
Positive	32	6.30%	24	4.8
By HPV genotype				
12 pooled positive	22	4.3	17	3.4
16 positive	9	1.8	5	1
18 positive	1	0.2	2	0.3

DNA, deoxyribonucleic acid; HPV, High risk Human Papilloma Virus

Table 5. Percentage of Participantswith Confirmed CIN by Colposcopy by35 and 45 Year Age Cohorts

Age of women (Years)	% of women with confirmed CIN by colposcopy after screening positive from any method		
	PAP	LBC	HPV/DNA
35(n=510)	8 (1.6%)	6 (1.2%)	11 (2.2%)
45(n=502)	7 (1.4%)	7 (1.4%)	9 (1.8%)

DNA, deoxyribonucleic acid; HPV, Human Papilloma Virus; LBC, liquid based cytology; PAP, Papanicolaou test; Chi square test results (both cohorts): Pap vs LBC (P≥0.5); HPV/DNA vs. conventional cytology (Pap/LBC) (P<0.05)

Table 6. Colposcopy and Biopsy Results: CIN stages seen in the 35 year and 45 year cohort participants with positive HPV/DNAscreening results

Colposcopy and biopsy resultsin n (%)	35 years cohort			45 years cohort		
	Pap+ (n=9)	LBC+ (n=13)	HPV/DNA + (n=32)	Pap+ (n=7)	LBC+ (n=10)	HPV/DNA + (n=24)
Normal	1 (11.1%)	7 (53.8%)	21 (65.7%)	0	3 (30%)	15 (62.5%)
Confirmed CIN	Pap+ (n=8)	LBC+ (n=6)	HPV/DNA + (n=11)	Pap+ (n=7)	LBC+ (n=7)	HPV/DNA + (n=9)
CIN I	6 (75%)	4 (66.7%)	6 (54.5%)	4 (57.1%)	4 (57.1%)	4 (44.4%)
CIN II	1 (12.5%)	2 (33.3%)	3 (27.3%)	3 (42.9%)	2 (28.6%)	2 (22.2%)
CIN III	1 (12.5%)	0	2 (18.2%)	0	1 (14.3%)	2 (22.2%)
Cervical cancer	0	0	0	0	0	1(0.1%)

of Pap smear. The study found that LBC had a slightly higher but insignificant benefit over Pap smear in detecting CIN; and HPV/DNA screening was significantly more likely to detect CIN than Pap and LBC.

Evidence from literature also shows that LBC has an insignificantly higher sensitivity and negative predictive value (NPV) than conventional cytology using Pap test (Nishio et al., 2018). LBC was also found to be better than Pap smears in detecting high-grade CIN in other Asian studies. Another Sri Lankan study assessing the feasibility of HPV/DNA and LBC in 35-year cohort also found that the cervical lesions detection rate by colposcopy was high with HPV/DNA screening, while that of LBC was insignificantly higher than Pap smears (Perera et al.,2021). A study from Thailand reported the prevalence of high-grade CIN from Pap and LBP as 9.5 and 11.9%, respectively.

Asian literature shows that HPV is responsible for 55.6% of the changes seen in colposcopy result (Kaplan, 2020). Another study from Iran showed that HPV DNA was detected in 29.3% of valid LBC samples (Chalabiani et al.. 2017). Just as in our study HPV 16, 12 pooled HPV were found to be responsible for major CIN lesions in the Iranian study (Chalabiani et al., 2017). Hence, HPV/ DNA screening should be helpful in detecting CIN. Pap and LBC are not the ideal primary cervical cancer screening tools as both have comparably sub-optimal CIN detection rates. Both testing methods ultimately depend on additional testing methods in large number of patients for triaging.

It is important to note that the same specimen can be used for both LBC and HPV testing by cobas® 4800HPV/ DNA method (Stoler et al., 2011). So, if LBC is used as a national cervical cancer screening tool, the residual LBC sample of women positive for ASCUS can be used to triage women with HPV, without calling them for an additional office visit (Stoler et al., 2011). This helps to reduce overall costs of cervical cancer screening (Stoler et al., 2011). NCPs should ideally be based on a single effective and

sensitive cancer screening tool that would require fewer referrals for colposcopy. A recent study from Sri Lanka found that HPV/DNA test was a feasible primary cervical cancer screening method in the 35-year cohort as it had higher sensitivity than both Pap and LBC in detecting ASCUS (Perera et al., 2021). Our study too found that HPV/DNA test using cobas 4800 was significantly higher CIN detection rates than Pap or LBC.

HPV-DNA testing has been found to be more cost effective than both conventional cytology and co-testing (Pap/LBC + HPV/DNA), even in resource limited settings (Sankaranarayanan et al., 2009; Vale et al., 2021; Devine et al., 2021). A study from India (N=131,746, ages between 30 and 59 years) showed a single round of HPV/DNA testing in resource limited setting can reduce cervical cancer deaths by approximately 50% within eight years of follow-up (Sankaranarayanan et al., 2009).

However, there are many barriers to the of cervical cancer screening program, especially in women from low-socio-economic strata or in minority population (Gupta et al., 2018). Self-sampling for HPV test is proposed as method to improve participation in NCPs for cervical cancer (Gupta et al., 2018; Yeh et al., 2019). Self-sampling for HPV test has proven to be as accurate as clinician-sampling, especially for assays that use nucleic acid amplification techniques (such as cobas 4800). Industrialized countries have already adopted self-sampling for HPV testing in their NCPs, and many countries are testing its feasibility. This technique can be tested in Sri Lankan NCPs for cervical cancer to see if it improves participation and helps in earlier detection.

Addressing the associated risk factors for any cancer can help reduce the incidence of overt cancer. The risk of HPV infection is higher in Sri Lankan women with poor socio-economic conditions, high parity, high number of vaginal deliveries, low age at 1st pregnancy, long period since last delivery, oral contraceptive pills/hormone usage ≥ 6 months, low age at 1st vaginal intercourse, extramarital sexual exposures of spouse, multiple life

time sex partners and extramarital sexual exposure of the spouse are some important risk factors for developing cervical cancer (Gamage et al., 2012). These risk factors for HPV infection can be mitigated through education and encouragement of safe sexual practices.

Strengths and Limitations of the Study

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

In conclusions, The detection rate of cervical lesions by colposcopy was high with HPV/DNA screening with cobas 4800, whereas the detection rate by LBC was only marginally higher than Pap smears. There was no significant difference between the detection rates of Pap smear and LBC. Hence LBC cannot be recommended to be incorporated into the National Cervical Cancer Screening program as an alternative to Pap smears. However, primary cervical cancer screening with HPV/DNA PCR tests should be assessed for feasibility and affordability.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

Administrative clearance

Administrative clearance was obtained for the study (field and hospital colposcopy component) from the Provincial Director of Health services (PDHS) Western Province, Regional Director of Health Services (RDHS) Kalutara district, Director, National Institute of Health Science, and Director, District General Hospital Kalutara.

Ethics Compliance

Ethical clearance was obtained from the Ethical Review Committee, National Institute of Health Sciences, Kalutara.

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