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Prevalence and Factors Associated with Cervical Premalignant Lesions in Women 25-65 Years Attending Gynaecology Clinic at Kampala International University Teaching Hospital

Richard Mulumba*[1], Herman Lule[2], Collins Atuhaire[3], Ivan Bonet[1], Anaya Amnia Diaz[4]
[1]Department of Obstetrics & Gynaecology, Kampala International University Western Campus, Uganda
[2]Departments of Global Health & Infectious Diseases, the University of Edinburgh (Scotland) & Surgery, Kampala International University Teaching Hospital Uganda
[3]Department of Epidemiology & Biostatics, Kampala International University Western Campus, Uganda
[4]Department of Pathology, Kampala International University Teaching Hospital, Uganda

Original Research Article

***Corresponding author**
Richard Mulumba

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Abstract: The prevalence of cervical premalignant lesions and factors associated with progression into cervical cancer are poorly documented in Uganda. Knowledge of those at risk is mandatory to guide clinical practice and preventive policy formulation. In this Cross-sectional descriptive and analytical study of consecutively recruited participants, we determined the prevalence and factors associated with cervical premalignant lesions amongst women aged 25-65 years attending the gynecology clinic at Kampala International University Teaching Hospital, using investigator administered survey questionnaire between February 2017 and May 2017. We cysto-pathologically analyzed Pap smear samples obtained from study participants for positivity and grades of cervical premalignant lesions. We then conducted bivariate and multivariate analyses using STATA 14.0, to determine factors significantly associated with positivity and different grades of cervical premalignant lesions. Ethical clearance was obtained from Mbarara University of Science and Technology Research and Ethics Committee (IRB N0. 09/10-16).Of 315, cervical premalignant lesions were prevalent in 22% (n=69) with high grade squamous intra epithelial lesions (HSIL) comprising 13%. Those with history of tobacco smoking were twice more likely to test positive for cervical premalignant lesions (aPR 2.12; 95% CI [1.03-4.39]). Females who had ever screened before for cervical premalignant lesions were 1.7 times more likely to turn out positive compared to those who had never (aPR 1.71; 95%CI [1.01-2.91]). Participants with presumed financial ability to pay for a pap test were 65% less likely to test positive for cervical premalignant lesions as compared to those who were financially not able to pay for pap test (aPR 0.35; 95% CI [0.15-0.83]. The prevalence of cervical premalignant lesions of 22% was higher compared to that reported in earlier studies. Tobacco smoking and prior history of screening were independent factors significantly associated with positivity for cervical premalignant lesions. Government and stakeholders should incorporate cessation of tobacco smoking campaigns into cervical cancer screening programs and prioritize the poor who cannot afford the Pap test.
Keywords: Cervical Premalignant Lesions, Grades, Prevalence, Risk Factor, Uganda.

INTRODUCTION

Worldwide, Human Papilloma Viruses 16 and 18 contribute up to 70% of all cervical cancer cases, with over 41% to 67% of high-grade cervical lesions and 16-32% of low-grade cervical lesions[1]. Despite though, only 5% of women in low income countries have ever been screened for cervical malignant lesions as opposed to 84% of their counterparts in high income countries[2]. In addition, women who are affected by cervical premalignant lesions and cervical cancer are generally younger in Africa compared to the rest of the world [3] yet late detection and missed diagnosis are still challenges in African developing countries[4].

There is an increasing burden of cervical premalignant lesions in Uganda[5],with some studies reporting as high as 26.5% for low grade squamous intraepithelial lesions and 43.9% for high grade cervical intraepithelial neoplasm [6]. Cervical premalignant lesions especially high grade cervical pre-cancer cells can gradually progress into invasive cancer in 20 to 25% of the cases [6] particularly for women residing in

low income countries with inadequate access and minimal uptake of screening services [7]. Whereas cervical cancer is the commonest malignancy amongst women aged 15 to 44 years in Uganda[8], there is still poor availability, accessibility and utilisation of cervical premalignant lesion screening services before progressing to invasive stage[7]. Despite dismal availability of screening strategies available in Uganda, cervical pre-malignant lesions are still responsible for full blown cervical cancer and mortality of 6.09 per 100,000 women [9], whereas the factors associated with positivity and different grades of cervical premalignant lesions remain poorly documented.

Since the known risk factors for cervical premalignant lesions are variant and late detection of high grade lesions yield poor prognosis [10], we designed a conceptual framework below with the aim to determine the prevalence and the independent risk factors associated for positivity of cervical premalignant lesions and for the different grades in our local context. In resource limited settings, sound knowledge of such risks is prerequisite to successful preventive interventions to guide prioritisation of most at risk during policy formulation.

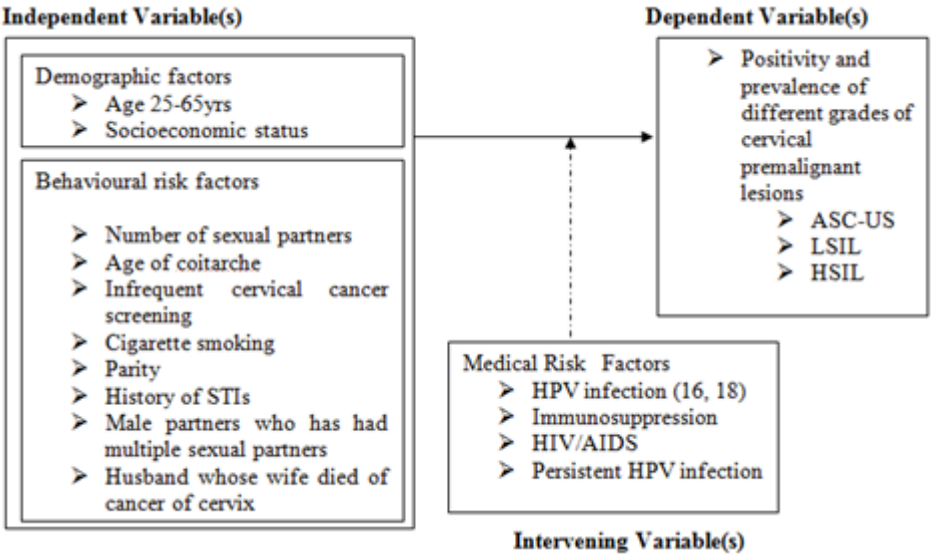

Fig-1: Conceptual framework showing interaction of variables

MATERIALS AND METHODS

Study design

We used a cross sectional descriptive and analytical study and collected data using investigator administered survey questionnaire that was designed based on parameters of interest. The cross sectional study was appropriate since prevalence of cervical premalignant lesions and associated factors were studied at the same time.

Study settings

We conducted the study at Kampala International University Teaching Hospital (KIU-TH) in the department of gynaecology out patients' clinic. This is a private 700 bed capacity tertiary hospital in Western Uganda, with obstetrics and gynaecology departments whose outpatients section offers cervical cancer screening, antenatal care, postnatal care, family planning, health education amongst others. The cervical cancer screening unit is run from Monday to Friday by at least one specialist, two senior residents, one intern doctor and one midwife, attending to approximately 480 patients per month.

Study population

We recruited women aged 25-65 attending the gynaecology clinic at KIU-TH.

Rationale for age group

According to the American Cancer Society [11],the need for cervical cancer screening vary depending on age and the method used, whether it's the index or follow up, degree of exposure to the risk factors, whether the woman is done with reproduction or still active and the type of hysterectomy if this was performed earlier. These factors affect the persistence of high risk type HPV. According to Centre for Disease Control (CDC) [12], the recommended age for screening for cervical premalignant lesions is 21 to 65 years, with 21years using Pap method while co-testing for 30 years depending on whether the woman is exposed to high risks for acquiring high risk HPV. It should also be noted that women aged more than 65 years have a small cervical transformation zone due to changes in oestrogen levels and this makes it less likely to be infected by the high risk type and persistence of HPV in that zone[11].

Sample size calculation

The first objective of the study intended to determine the prevalence of cervical premalignant lesions, and the second objective intended to look at the difference in proportions as the parameter of interest for factors significantly associated with positivity for cervical premalignant lesions and for the different grades, thus the sample size was calculated using Leslie Kish [39] formula as below.

$N=\frac{Z^2\ P\ x\ Q}{D^2}$; where

N=Desired sample size for population greater 10,000.

Z=Standard normal deviation, assuming a 95% confidence interval Z= 1.96.

P=Proportion of the population estimated to have cervical premalignant lesions. Based on the study done on the prevalence of cervical premalignant lesions in Kyadondo county, in Uganda[6], the prevalence of cervical premalignant lesions was reported to be 26.5% for low grade cervical intraepithelial neoplasm (LCIN1) and 43.9% for high grade cervical intraepithelial neoplasm (HCIN2), giving a total prevalence of 70.4%.

D=Degree of accuracy for 95% confidence interval (0.05).

Substituting for P=0.704 and Q= (1-P) =0.296.

$$N=\frac{(1.96)^2\times 0.704\times 0.296}{(0.05)^2}$$

$N=\frac{0.80209151}{0.0025}$=321 women

Sampling technique

Consecutive sampling method was used until desired sample size was realised. This was aimed at realizing the desired sample size in the stipulated time frame that was approved by the internal review committee.

Inclusion criteria

We included women aged 25 to 65 years, those who consented for the study and those who had completed their menstrual flow.

Exclusion criteria

We excluded pregnant women, those menstruating at the time of the study and those already diagnosed of invasive cervical cancer.

Flow of study participants

Participants were received, registered, health educated and eligible ones signed a consent form. We performed speculum vaginal examination and obtained Pap smear samples for cyto-pathological analysis as shown in fig.2.

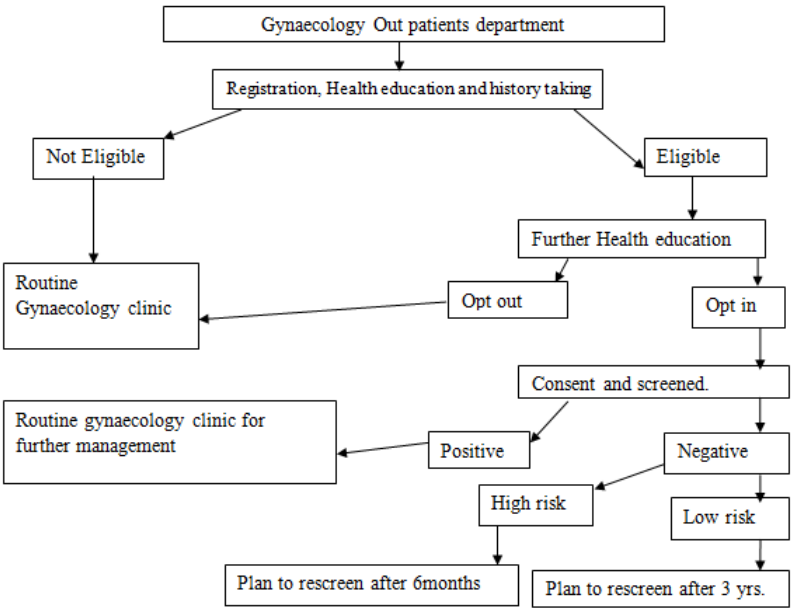

Fig-2: Flow Chart Showing Study Procedure and Flow of Participants

Data Collection

We collected data by use of an investigator-administered questionnaire which was purposively designed to meet study objectives. We translated the questionnaire into the local language (Runyankole) for the illiterate for better understanding of the question. We pre-tested the questionnaire at Ishaka Adventist hospital prior to data collection to ensure validity of the tool.

Sample Collection Methods and Cyto-Pathological Analysis

Two rooms with adequate source of light were secured in the gynaecology clinic for the purposes of the study, examination gloves, disposable Cusco's

speculums and Pap smear kits were provided by the investigators for the purpose of carrying out the study but not as a mode of attracting the participants. Following explanation of the procedure and obtaining informed consent from eligible study participants, we obtained samples using Pap smear kits (IMED, USA).

Each Pap smear slide was labelled with a unique number to avoid duplication. Research participants were positioned in lithotomy position in presence of a female chaperon, Cusco's speculum was introduced into the vagina and a spatula was oriented to best fit the cervical contour, then scraped the Squamo-columnar junction as well as the cervical surface completing at least one full rotation as described by Hoffman *et al*. [13]. The samples were placed in the specimen box and transported at every 4:00 pm of the day to cytopathology laboratory of Kampala International University Teaching Hospital for analysis by the investigators and cytopathologists, using the method of Hoffman *et al* [13].

The slides were examined under the microscope using 10x and 100x magnifications. We interpreted precancerous cells as cells with moderate increased nuclear cytoplasmic ratio with no loss of polarity and were hyper chromatic whereas normal cells were interpreted as cells that were monotonous, oriented and had normal shape, normal nuclear cytoplasmic ration and exhibited normochromatic staining picture. We used the Bethesda 2014 classification system [14] as a guide for interpretation of precancerous cervical smears stained by Papanicolaou method.

Quality Control

The data tool used in this study had a content validity index (CVI) of 0.76 after pretesting. We collected 30 Pap smear samples for quality control purposes. These were analysed at both Kampala International University Teaching Hospital Laboratory and Mbarara University of science and technology, cytopathology laboratory but results were found consistent.

DATA ANALYSIS

We entered data into Microsoft-Excel (version 2010) and exported it into STATA Version 14 (Statacorp, Texas, 2017). Being a cross-sectional and analytical study, we computed the percentages to estimate the prevalence and conducted bivariate and multivariate regression analysis to obtain crude and adjusted prevalence ratios respectively for factors significantly associated with positivity and for the different grades of cervical premalignant lesions. We considered the level of statistical significance of $\alpha \leq 0.05$ at 95% confidence interval.

Ethical Consideration

The study followed the National Institute of Health guidelines on research involving humans as research participants. We obtained ethical clearance from Mbarara University of Science and Technology Research and Ethics Committee (IRB N0. 09/10-16). All participants indicated their consent by endorsement of an informed consent form document with a signature or thumb prints. The consent form document was prepared in English and translated into the local language (Runyankole) to allow comprehension by the illiterate. The translated version was approved by internal review boards of Kampala International University and Mbarara University of Science and Technology before it was subjected to participants. We used unique dummy numbers on questionnaires to hide identity, and prevented access to data by non-investigators and those primarily not involved in the care of participants by use of passwords. We informed all participants of the potential risks that were involved in the process of sample collection such as pain, per vaginal bleeding which were managed by the investigators and that there was no intent of disclosure of participants' information to the public without their consent.

All participants got feedback of their results at least within 2- 4 weeks and depending on the findings, they were directed to respective levels of care accordingly. This was to allow the professor of pathology ample time to review the samples thoroughly as well as attending to other samples for the hospital since she was alone in the department at the time of data collection. Each participant provided us with her telephone contacts on the data collection tool and for those who had no phones; contacts for the nearest relatives were used to inform them when their results were ready. The study was more of benefit than a risk to participants since every participant received their results and was directed to the next level for further management depending on the results. Each research participant was handled as an individual, with uttermost respect for their participation and was free to withdraw from the study any time if theyso wished.

RESULTS

Socio-Demographic, Behavioural and Medical Characteristics of Study Participants:

The intended sample size for the study was 321 participants but only 315 were analysed due to the fact that 2.8% (n=9) had unsatisfactory result during sample examination. Since the proportion of participants with unsatisfactory results was less than 5% of intended sample size, it was presumed that this could not produce a very significant effect on the results. Of the 315 women whose results were satisfactory for analysis, majority 49.9% (n=154) were aged between 25 to 34 years. The majority were: Christians 90.8% (n=286), Banyankole by tribe 68.9% (n=217) and married 83.8% (n=264). Most of them 50.4% (n=159)

had attained primary level of education and were peasant farmers 58.7% (n=185) as shown in (Table 1).

Table-1: Socio-Demographic Characteristics of Study Participants

Characteristics	Number of participants(N=315)	Percentage (%)
Age group (years)		
25-34	154	49.9
35-44	93	29.5
45-54	45	14.3
55-64	13	4.1
≥65	10	3.2
Religion		
Christian	286	90.8
Muslim	29	9.2
Tribe		
Munyankole	217	68.9
Mukiga	56	17.8
Muganda	13	4.1
Others	29	9.2
Marital status		
Married	264	83.8
Widow	19	6.0
Single	18	5.7
Divorce/separated	14	4.4
Education status		
None	36	11.4
Primary	159	50.4
Secondary	64	20.3
Tertiary	34	10.8
University	22	7.0
Occupation		
Peasant farmer	185	58.7
Self-employed	55	17.5
Student	33	10.5
Civil servant	24	7.6
Others	18	5.7
Total	315	100

Behavioural Characteristics of Study Participants

The behavioural characteristics of women in this study showed that only 11.1% (n=35) of the women had ever screened for cervical premalignant lesions, of which majority had tested once 82.9% (n=29) and only 5.7% (n=2) earlier tested positive. Majority of the women 75.6% (n=238) first had unprotected sexual intercourse at the age younger than 19 years. Only 52% (n=164) had had unprotected sexual intercourse with a single partner.

The majority of the women 70.7% (n=218) had husbands with only one sexual partner known to the participant and 0.3% (n=1) of their husbands had lost a wife due to cervical cancer. Over 4% (n=13) of the women reported history of smoking tobacco of which majority 54.6% (n=8) had ceased smoking for the past 5 years. Over 19.7% (n=62) had ever been diagnosed and treated for STIs, mainly syphilis 51.6% (n=32). Up to 38.7% (n=122) carried 5-6 pregnancies to term (at least 37 weeks of gestation). Fewer women 18.0% (n=57) were reportedly able to pay for cervical cancer screening services in their nearest hospitals as shown in (Table 2).

Table-2: Behavioural Characteristics of Study Participants

Variable	Number of participants (N=315)	Percentage (%)
Ever taken a cervical cancer screening?		
No	280	88.9
Yes	35	11.1
Frequency of previous pap test	N=35	
Once	29	82.9
Twice	6	17.1
History of pap test		
Negative	33	94.3
Positive	2	5.7
Onset of first unprotected sexual intercourse (years)		
≤ 19	238	75.6
20-24	68	21.6
25-29	7	2.2
≥30	2	0.6
Number of sexual partners with unprotected sexual intercourse		
1	164	52.0
2-4	146	46.3
≥5	5	1.6
Number of partners husband has	N=308	
1	218	70.7
2-4	89	29.0
≥5	1	0.3
Husband lost a wife due to cervical cancer		
No	314	99.7
Yes	1	0.3
Smoke tobacco		
No	302	96
Yes	13	4
Cessation of smoking (years)		
<5	8	54.6
≥5	5	45.4
History of STI		
No	253	80.3
Yes	62	19.7
STI		
Chlamydia trachomatis	21	33.9
Herpes simplex type 2	1	1.6
Syphilis	32	51.6
C. trachomatis, Herpes, syphilis	1	1.6
C. trachomatis & Herpes	0	1.6
C. trachomatis and Syphilis	5	0.0
Number of pregnancies carried beyond 37 weeks		
None	8	2.5
1-2	102	32.4
3-4	71	22.5
5-6	122	38.7
Nulliparous	12	3.8
Pay for cervical premalignant lesions screening		
No	258	82.0
Yes	57	18.0

Medical Characteristics of Study Participants

The medical characteristics of the studied participants revealed that out of 0.6% (n=2) women who had ever tested for HPV, 0.3% (n=1) of them were positive. HIV/AIDS was amongst the commonest other diagnosed medical condition 64.3% (n=18) alongside cancer other than that of the cervix as shown in (Table 3).

Table-3: Medical Characteristics of Women Attending Gynaecology Clinic at KIU-TH

Variable	Number of participants (N=315)	Percentage (%)
Ever tested for HPV		
No	313	99.4
Yes	02	0.6
HPV status		
Negative	314	99.7
Positive	1	0.3
Other diseases diagnosed		
HIV/AIDS	18	64.3
Cancer	10	35.7
Received any organ transplant		
No	315	100
Yes	0	000

Prevalence of Cervical Premalignant Lesions

Of the 315 participants, 21.9% (n=69) were positive for cervical premalignant lesions of which, majority 79.7% (n=55) had LSIL as shown in (Table 4).

Factors Associated with Positivity for Cervical Premalignant Lesions

None of the socio-demographic variables was independently associated with positivity for cervical premalignant lesions at bivariate analysis (Table 5).

Table-4: Showing Prevalence of Different Grades of Cervical Premalignant Lesions

Grade of premalignant lesions	Number of positive pap smears (n=69)	Frequency (%)	95% CI
ASC-US	5	7.3	3.0-16.6
LSIL	55	79.7	68.3-87.8
HSIL	9	13.0	6.8-23.5

Table-5: Bivariate analysis for socio-demographic factors associated with positivity of cervical premalignant lesions

	Cervical Premalignant lesions				
Variable	Negative (n=246)	Positive (n=69)	cPR	95%CI	p-value
Age in years n (%)					
25-34	117 (76.0)	37 (24.0)	1.00		
35-44	77 (82.8)	16(17.2)	0.75	0.42-1.21	0.22
45-54	36 (80.0)	9 (20.0)	0.83	0.43-1.59	0.58
55-64	8 (61.5)	5(38.5)	1.60	0.76-3.37	0.22
>65	8 (80.0)	2 (20.0)	0.83	0.23-2.98	0.78
Occupation n (%)					
peasant	145 (78.4)	40 (21.6)	1.00		
self-employed	42 (76.4)	13 (23.6)	1.09	0.63-1.89	0.75
student	26 (78.8)	7 (21.2)	0.98	0.48-2.00	0.96
civil servant	21 (87.5)	3 (12.5)	0.58	0.19-1.73	0.33
Others	12	6	1.54	0.76-3.13	0.23
Tribe n (%)					
Munyankole	168 (77.4)	49 (22.6)	1.00		
Mukiga	39 (69.4)	17 (30.6)	1.34	0.84-2.15	0.22
Mufumbira	11 (84.6)	2 (15.4)	0.68	0.19-2.50	0.56
others	28 (96.5)	1 (3.5)	0.15	0.02-1.07	0.06
Education n (%)					
None	27 (71.1)	9 (28.9)	1.00		
Primary	125 (78.6)	34 (21.4)	0.86	0.45-1.62	0.63
Secondary	50 (84.3)	14 (15.6)	0.88	0.42-1.82	0.72
Tertiary	28 (82.4)	6 (17.6)	0.71	0.28-1.77	0.46
University	16 (72.7)	6 (27.3)	1.10	0.45-2.65	0.85
Marital status n (%)					
married	205 (77.7)	59 (22.3)	1.00		
widow	14 (73.7)	5(26.3)	1.18	0.54-2.59	0.68
single	14 (77.8)	4 (22.2)	0.99	0.41-2.43	0.99
divorced	13 (92.9)	1(7.1)	0.32	0.05-2.15	0.24

However on bivariate analysis of behavioral factors, those who had ever been screened before were more likely to be positive for cervical premalignant lesions during the current screening (cPR 1.67; 95% CI [1.01-2.82], P=0.047) whereas presumed ability to pay for the screening services was associated with a lower odds for cervical premalignant lesions (cPR 0.35; 95% CI [0.15-0.84], p=0.019) as shown in (Table 6).

Table-6: Showing bivariate analysis for behavioural factors associated with positivity forcervical premalignant lesions: (cPR=Crude Prevalence Ratio; *P<0.05)

Pap screening Result n (%)	Negative N=246	Positive N=69	cPR	95% CI	P-value
Ever taken a Pap test?					
no	223 (79.3)	57(20.4)	1.00		
yes	23 (65.7)	12(34.3)	1.68	1.01-2.82	0.047*
1st age of unprotected sex (years)					
≤19	183 (76.9)	55(23.1)	1.00		
20-24	54 (79.4)	14(20.6)	0.89	0.53-1.50	0.66
≥25	9 (100.0)	0 (0.0)	-		
Number of partners with unprotected sex					
1	130 (79.3)	34 (20.7)	1.00		
2-4	112 (76.7)	34 (23.3)	1.12	0.74-1.71	0.59
≥ 5	4 (80.0)	1 (20.0)	0.96	0.16-7.73	0.97
Number of partners to your husband					
1	166 (76.1)	52(23.9)	1.00		
2-4	73(82.0)	16 (18.0)	0.76	0.46-1.25	0.27
≥ 5	1 (100.0)	0(0.0)	-	-	
Smoked Tobacco					
No	232 (78.4)	64 (21.6)	1.00		
Yes	8 (61.5)	5(38.5)	1.81	0.88-3.74	0.11
History of STI & HPV					
No	199 (78.7)	54(21.3)	1.00		
Yes	47(75.8)	15(24.2)	1.13	0.69-1.87	0.62
No. pregnancies >37weeks					
None	86 (75.4)	28 (24.6)	1.00		
1-2	55(77.5)	16(22.5)	0.92	0.54-1.57	0.75
3-4	100 (82.0)	22 (18.0)	0.73	0.45-1.21	0.22
5-6	5 (62.5)	3 (37.5)	1.53	0.59-3.96	0.38
Pay for premalignant lesion screening					
No	194 (75.2)	64 (24.8)	1.00		
Yes	52 (91.2)	5 (8.8)	0.35	0.15-0.84	0.019*

We conducted multivariate analysis for all potential behavioural factors with plausibility for being associated with cervical premalignant lesions, that is to say those that demonstrated a p-value of ≤ 0.2 on bivariate model. The reduced model had variable including history of tobacco smoking, presumed ability to pay for a Pap test and history of ever been screened for cervical premalignant lesions. The analysis showed that participants who had ability to pay for the screening services were less likely to test positive during the current study compared to those who had no ability to pay for the screening service. This association was statistically significant (aPR= 0.35, 95% CI[0.15-0.83] P=0.017). Those who smoked tobacco were twice more likely to test positive for cervical premalignant lesions compared to their counterparts who never smoked and this was statistically significant (aPR=2.12, 95% CI [1.03-4.39] P=0.042).Participants who had earlier on screened for cervical premalignant lesions were more likely to screen positive in the current study compared with those who had not screened before and this was statistically significant (aP=1.71, 95% CI[1.01-2.91] P=0.045) (Table 7).

Table-7: Multivariate analysis for factors associated with positivity for cervical premalignant lesions amongst women aged 25-65 years attending gynaecology clinic of KIU-TH: (†aPR=Adjusted Prevalence Ratio; *p<0.05)

Variable	aPR†	95%CI	p-value
Pay for cervical premalignant cancer screening			
No	1.00		
Yes	0.35	0.15-0.83	0.017*
Smoke Tobacco			
No	1.00		
Yes	2.12	1.03-4.39	0.042*
Pap screening			
no	1.00		
yes	1.71	1.01-2.91	0.045*

Factors Associated With the Different Grades of Cervical Premalignant Lesions

We used the ordinal logistic regression model at bivariate level to establish the socio-demographic and behavioural distribution of different grades of cervical premalignant lesions. Results showed that being a widow was associated with lower odds of positivity for the different grades of cervical premalignant lesions (cPR 0.07; 95% CI [0.01-0.54]; P=0.01) and this was statistically significant (Table 8).The behavioural (Table 9) and other socio-demographic variables did not demonstrate significant relationship with the different grades of cervical premalignant lesions; however, the factors with p-value of ≤ 0.2 were considered for inclusion in multivariate analysis (Table 10) after controlling for confounders.

Table-8: Bivariate ordinal logistic regression analysis of socio-demographic distribution of different grades of cervical premalignant lesions (*P<0.05)

	Prevalence of different grades of cervical premalignant lesions					
Characteristic	ASC-US (n=5)	LSIL (n=55)	HSIL (n=9)	OR	95% CI	P-value
Age group (years) n (%)						
25-34	0	33(89.2)	4(10.8)	1.00		
35-44	1(6.3)	13(81.3)	2(12.5)	0.77	0.16-3.67	0.74
45-54	2(22.2)	5(54.6)	2(22.2)	0.49	0.06-4.33	0.52
55-64	0 (0.0)	4(80.0)	1(20.0)	1.68	0.19-14.83	0.64
≥65	2 (100)	0 (0.0)	0(0.0)	-	-	-
Religion						
Christian	5(7.7)	51(78.5)	9(13.8)	1.00		
Muslim	0(0.0)	4(100)	0(0.0)	0.71	0.06-7.92	0.78
Tribe						
Munyankole	4(8.8)	39(78.7)	6(12.5)	1.00		
Mukiga	1(5.9)	13(76.5)	3(17.6)	1.53	0.40-5.90	0.54
Mufumbira	0 (0.0)	2(100)	0(0.0)	0.79	0.03-23.62	0.89
Others	0 (0.0)	1(100)	0(0.0)	0.79	0.01-91.44	0.92
Marital status						
Married	3(5.1)	47(79.7)	9(15.3)	1.00		
Widow	2(40.0)	3(60.0)	0(0.0)	0.07	0.01-0.54	0.01*
Single	0(0.0)	4(100.0)	0(0.0)	0.51	0.04-7.31	0.62
Divorce/separated	0(0.0)	1(100.0)	0(0.0)	0.51	0.003-88.84	0.80
Education status						
None	2(22.2)	6(66.7)	1(11.1)	1.00		
Primary	1(2.9)	29(85.5)	4(11.8)	3.52	0.49-25.16	0.21
Secondary	2(14.3)	10(71.4)	2(14.3)	2.06	0.22-18.99	0.52
Tertiary	0(0.0)	4(66.7)	2(33.3)	11.48	0.93-141.11	0.06
University	0(0.0)	6(100.0)	0(0.0)	2.06	0.15-28.85	0.59
Occupation						
Peasant farmer	4(10.0)	31(77.5)	5(12.5)	1.00		
Self-employed	1(7.7)	11(84.6)	1(7.7)	0.85	0.17-4.35	0.85

Table-9: Bivariate ordinal logistic regression analysis of behavioural distribution of different grades of cervical premalignant lesions

	Grades of cervical premalignant lesions					
Variable	ASC-US (n=5)	LSIL (n=55)	HSIL (n=9)	OR	95% CI	P-value
History of cervical cancer screening n (%)						
No	3(5.3)	48(84.2)	6(10.5)	1.00		
Yes	2(16.7)	7(58.3)	3(25.0)	1.26	0.26-6.20	0.77
Age of first coitus in Yrs. n(%)						
≤ 19	3(5.5)	44(80.0)	8(14.5)	1.00		
20-24	2(14.3)	11(78.6)	1(7.1)	0.39	0.08-1.18	0.23
Number of sexual partners with unprotected sexual intercourse, n (%)						
1	3(8.8)	25(73.5)	6(17.6)	1.00		
2-4	2(5.9)	29(85.3)	3(8.8)	0.71	0.22-2.32	0.57
≥5	0 (0.0)	1(100)	0 (0.0)	0.60	0.01-70.8	0.83
Number of partners husband has, n (%)						
1	2(3.8)	42(80.8)	8(15.4)	1.00		
2-4	3(18.8)	12(75.0)	1(6.3)	0.23	0.05-1.10	0.07
Smoked tobacco n (%)						
No	4(6.3)	51(79.7)	9(14.1)	1.00		
Yes	1(20.0)	4(80.0)	0 (0.0)	0.22	0.03-1.87	0.16
History of STI n (%)						
No	5(9.3)	42(77.8)	7(13.0)	1.00		
Yes	0(0.0)	13(86.7)	2(13.3)	1.62	0.42-1.37	0.49
Carried pregnancy > 37 weeks n(%)						
None	2(7.1)	23(82.1)	3 (10.7)	1.00		
1-2	1(6.3)	14(87.5)	1(6.3)	0.81	0.17-3.81	0.79
3-4	2(9.1)	15(68.2)	5(22.7)	1.81	0.45-7.31	0.41
5-6	0(0.0)	3(100)	0(0.0)	0.81	0.04-14.72	0.89
Pay for cervical premalignant lesions screening, n(%)						
No	4(6.3)	51(79.7)	9(14.1)	1.00		
Yes	1(20.0)	4(80.0)	0(0.0)	0.22	0.03-1.87	0.16

We conducted a multivariable ordinal logistic regression analysis on potential risk factors to obtain adjusted odds ratios controlled for multiple confounders and other covariates. The women whose husbands had 2-4 other sexual partners were controversially less likely to test positive for high grade squamous intraepithelial lesions compared to those whose husbands had only one other known sexual partner. This association was statistically significant (aOR=0.05 95%CI [0.00-0.60], P=0.02).

Additionally, those who had ability to pay for cervical premalignant lesions screening services in their hospitals were less likely to test positive for high grade squamous intraepithelial lesions compared to those who were not able to pay for the services. This association was also statistically significant (aOR=0.03; 95%CI; [0.01-0.78]; p=0.04) as shown in (Table 10).

Table-10: Multivariate analysis of socio-demographic and behavioural factors associated with high grade squamous intraepithelial lesion (HSIL) (*P<0.05)

Variable	Adjusted (aOR)	95% CI	P-value
Number of partners husband has			
1	1.00		
2-4	0.05	0.01-0.60	0.02*
Smoke tobacco			
No	1.00		
Yes	0.25	0.02-3.20	0.29
Pay for cervical premalignant lesions screening			
No	1.00		
Yes	0.03	0.01-0.78	0.04*

DISCUSSION

Prevalence of Cervical Premalignant Lesions

The present study aimed at determining the prevalence and risk factors to cervical premalignant lesions, the prevalence of cervical premalignant was found to be 21.9% (n=69). This prevalence is much higher than the 6.4% reported in Western Uganda Okwi *et al*. [15], and higher than the overall country prevalence of 11.2%[15]. Lower prevalence compared to this study has been reported in Ethiopia[16], Nigeria [17,18], Rwanda [19], Egypt [20] and Thailand [21]. The difference between the current and earlier studies is not only attributable to the differences in reliability of the screening methods used in these studies [15], but also inconsistent screening programs in Uganda due to lack of financial commitment which translates into low screening uptake of about 4.8% in rural Uganda [22]. Moreover, programs such as Reproductive Health Uganda, Marie stopes Uganda and others have not been well coordinated by the ministry of health for the purposes of harmonising screening for cervical premalignant lesions [23]**.** The difference in reliability of screening methods has been reported by Hassan *et al*. [20]where the Pap smear method had a higher sensitivity (83.3%) compared to visual inspection under acetic acid which had a sensitivity of**(**66.7%), explaining a higher prevalence in the present Pap smear based study.

Factors Associated With Positivity for Cervical Premalignant Lesions

The study aimed at establishing factors associated with positivity for cervical premalignant lesions. We found that none of the socio-demographic or medical factors were significantly associated with positivity of cervical premalignant lesions at multivariate level in the present study. However with regards to behaviour factors, those with positive history of smoking were twice more likely to be screened positive for cervical premalignant lesions (aPR 2.12; 95% CI [1.03-4.39]; P=0.042) whereas those who had ever been screened before were 1.7 times more likely to turn out positive for cervical premalignant lesions during the current screening (aPR 1.71; 95%CI [1.01-2.91]; P=0.045). However, ability to pay for a pap test was associated with lower odds of positivity for cervical premalignant lesions (aPR 0.35; 95% CI [0.15-0.83]; P=0.017). The number of full term pregnancies did not reach statistical significance for positivity of cervical premalignant lesions.

The present study showed that smoking tobacco significantly exposed women to development of premalignant cervical lesions compared to those who didn't. This was consistent with a similar study [17]. According to Centre for Disease Control [24], tobacco smoking is not only known to play a significant role in cervical cancer but also in progression of cervical premalignant lesions [25]. According to Castle [26], the BaP carcinogen in tobacco causes amplification of HPV replication in cervical cells as well as E6 and E7 HPV Oncogenes, all of which are necessary for progression of cervical premalignant lesions[26]. These tobacco carcinogens negatively affect the body's immunity against HPV infection as well as promoting integration of HPV genome into human cervical cells [27], encouraging persistency and progression of the cervical premalignant lesions. Other studies [28] have found a two fold increase of progression of cervical carcinoma in situ to invasive cervical cancer amongst smokers compared to non-smokers and the likelihood of progression increased with the intensity of smoking. The risk of persistence of HPV infection is also higher amongst smokers particularly those who started smoking at an early age, including childhood exposure to passive smoking [29]. Thus one strategy on cervical cancer control is policy formulation and awareness on smoking cessation [28].

The present study demonstrates that women who had ever been screened before were more likely to be positive during the current screening for cervical premalignant lesions. It is thus likely that such women could have been exposed to risks of acquiring HPV and this could have been one of the primary driving forces to undertake a screening test. Also, such participants could have had suspicious lesions for which they were counselled on the need for follow-up, increasing the likelihood of a positive test in the present study. Although it takes up to 10 years for premalignant lesions to progress to advanced cervical cancer, poor health seeking behaviour and stock outs of screening kits contribute to late diagnosis in African countries [30]. Cervical cancer screening guidelines give appropriate timing of screening intervals and co-testing depending on the woman's level of risk [11]. Therefore, there should be proper follow up of women with early cervical premalignant lesions to avert the mortalities attributable to late detection [16]. According to Nakisige *et al*. [22], the baseline life time screening rate in Uganda for cervical cancer was low at 4.8% to 30% compared to that in developed countries which stands at 85%. Thus, its suggested that increasing accessibility of services to those previously unscreened women should be of priority [22].

This study showed that participants with ability to pay for cervical premalignant lesions screening services at their nearest hospitals were significantly less likely to be tested positive compared to those who were not able to pay for such services. This could probably be attributed to low socio-economic status of women unable to afford cervical cancer screening services. It has been shown that HPV testing is not cost effective especially in developing countries [31]and that majority of the women fail to afford the cost of the Pap test [17]. Still, the low socio-economic status places most women at the community

disadvantaged financially and geographically at accessing and utilizing the screening services in time, hence presenting when it is in advanced stages [32]. This is consistent with the literature that cervical premalignant lesions is very prevalent among women living in low resource setting [16]. It is important that the government of Uganda provides free screening services even in private sectors under public-private partnership to improve on the accessibility of such services to the poor.

Factors Associated With High Grade Squamous Intraepithelial Cervical Lesions

The findings of this study reported various grades of cervical premalignant lesions with high prevalence of low grade squamous intraepithelial lesions (LSIL). However, a study conducted in Kyadondo county in Uganda showed a higher prevalence of 43.9% for high grade squamous intraepithelial lesions (HSIL) and 26.5% for LSIL, which was not in agreement with findings of the present study [6]. Furthermore, other similar studies reported higher prevalence (79%) for HSIL in Lusaka, Zambia [33]. A study done in Kenya[8] showed LSIL to be 21.4% which was lower than that for the current study and 45% for HSIL which was higher compared to the current study and this could be attributable to the fact that they were looking specifically at HPV types compared to the current study.

The Atypical Squamous Cells of Undetermined Significance (ASC-US) findings of the present study were consistent with related studies done by Thomas *et al*. [34] in Ibadan, Nigeria who reported 1.99%. However, the same study[34] reported lower rates of (3.89%) LSIL and (1.54%) HSIL. In addition, Durowade *et al*. [17] also reported lower rates of HSIL (0.5%) and LSIL (4.5%) compared to the findings of this study. Another study by Omar *et al*. [35] in Soweto, reported a prevalence of 2.4% for LSIL and 1.8% for HSIL, quite lower than that reported in the present study and other recent studies [20].

Compared to the present study, the World Health Organization stated that the likely pattern of cervical lesions expected in women aged 25-65 years were: LSIL (3-10%) and HSIL (1-5%) [17], which were consistently lower than the present study.This is mainly attributable to the screening methods used in low resource countries – VIA compared to Pap smear method which has a higher sensitivity hence the high overall prevalence in the current study. The above grades are asymptomatic, thus carefully planned community-based screening programme is one strategy to help solve the problem since by the time cervical cancer is clinically obvious, all therapeutic interventions will only produce slight improvement in the prognosis [17].

On bivariate analysis, being widowed was the only significant factor associated with lower odds for HSIL (OR 0.07; 95%CI [0.01-0.54]; P=0.01). This could be attributable to reduced rate of exposure to recurrent infection with the high risk type of HPV as well other STIs all of which are potential factors for progression of the premalignant lesions. Similarly, other studies have showed marital status of women as a predisposing risk factor for cervical premalignant lesions with higher prevalence among the currently married 6.7%[20]compared to the widowed, which was comparable to results of this study. Unlike the widowed, the divorced women are at higher risk of getting premalignant lesions and their progression to cervical cancer [33]. However, Makuza *et al*. [19] reported high prevalence in women who lived alone (single, divorced/separated) which was not in agreement with the present study. The study by Okwi *et al*. [15] reported lower rates among those married once compared to those who were engaged in more than one relationship/marriage. This was inconsistent with the findings of the present study in which this association was not statistically significant. Further studies are required to determine factors that might drive the influential effects of marital status on progression of cervical premalignant lesions.

On multivariate analysis, ability to pay for cervical cancer screening services (aPR 0.03; 95%CI [0.00-0.78], P=0.04) was significantly associated with lower odds for progression to higher grades. This could be due to better health seeking behaviour and accessibility to these screening services even if they were mainly situated in urban health facilities unlike those unable to facilitate the screening service on their own. This is in-line with similar study by Sornam *et al*. [36]where prevalence and progression of cervical premalignant lesions to invasive stage was found among women of low socioeconomic status and education level, all compounding the problem.

Having a husband with multiple partners (aPR 0.05; 95% CI [0.00-0.60], P=0.02) were significantly associated with lower risks for higher grades of cervical premalignant lesions. This needs further investigation, although existing studies demonstrate that not only having a husband with multiple sexual partners is an independent risk to progression of cervical malignant lesions but also the husband's life styles such as circumcision status, HIV status, co-infection with other STDs and condom use might be significant determinants of progression to higher grades of cervical premalignant lesions [37, 33]. The nature of high-risk HPV types the woman's husband is harbouring may also be a significant determinant of progression to high-grade premalignant cervical lesions rather than the number partners the woman's husband has [38].

CONCLUSIONS

The current prevalence of 21.9% for cervical premalignant lesions is much higher than what is earlier reported in Western Uganda and National average. The significant risk factors for cervical premalignant lesions in the present study were the positive history of tobacco smoking and history of ever been screened before. Being widowed, having a husband with multiple sexual partners and ability to pay for the Pap screening test were protective factors for high grade squamous intraepithelial cervical premalignant lesions.

RECOMMENDATIONS

The government should provide free screening for cervical premalignant lesions in collaboration with private sectors through public-private partnerships for early detection and management of the premalignant lesions to help in lowering this prevalence amongst the poor. Comprehensive community awareness campaigns and screening programmes for cervical premalignant lesions should incorporate tobacco smoking cessation campaigns among other risk factors since they are major driving forces for acquisition, persistence and progression of cervical premalignant lesions. Prospective cohort studies are required to investigate how the woman's husband having multiple sexual partners is protective factor from progression to higher grades of cervical premalignant lesions

LIMITATIONS AND DELIMITATIONS

We did not perform colposcopy for better visualization and biopsy of cervical lesions; however a pap smear gave a fairly good representation of the results. There were no HPV-DNA screening kits at the facility where we conducted the study, which would help to correlate positive results with HPV infection, since HPV is one of the major risk factors associated with cervical premalignant lesions; however all positive cases were linked to higher facilities for further management to mitigate this problem. Disclosure of some information like how many sexual partners have you ever had, HIV sero–status and other STIs were prone to recall and social desirability bias. We however conducted a comprehensive health education and counseling to participants to open up and give real information was ensured including thorough explanation with regards to the benefits of participation and the potential benefit of study findings in the future when recommendations are implemented.

AUTHOR CONTRIBUTION

R.M conceded the study and collected the data, C.A performed the statistical analysis, A.A.D performed the cyto-pathological analysis, and H.L designed the study and drafted the final manuscript, while IB supervised the study. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

We declare no conflict of interest. The content of this paper is solely the responsibility of the authors and does not reflect any official vies of their institutional affiliations.

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APPENDIX 1

Operational definitions

Throughout this study, the following key terms are used in the context described as below:

Atypical Squamous Cells cannot Exclude HSIL

Refers to cellular changes which do not meet criteria for HSIL cytology, yet high-grade lesion cannot be dismissed.

Atypical Squamous Cells of Undetermined Significance (ASC-US)

These cells seemingly appear but do not meet the criteria for SIL CIN 2 or 3. They are associated with 5% risk of progression to SIL CIN 2 or 3.

Carcinoma in Situ (CIS)

Full-thickness involvement of cervical squamous epithelium

Cervical Cytology

A diagnostic technique that involves microscopic examination of individual cells or cell clusters scraped, brushed, or washed from the surface of the cervix and stained with Papanicolaou's stain.

Cervical Intraepithelial Neoplasia (CIN) or Premalignant Lesions

These are cervical epithelial lesions that are considered to be cancer precursors, however lack invasive cancer features.

Ectocervix

The visible surface of the cervix during cuscos vaginal examination

Endocervix

Refers to the glandular epithelised canal of the cervix

High-grade Squamous Intraepithelial lesion and Glandular Abnormalities

These include characteristics of CIN 2 and CIN 3 with high histological likelihood of these lesions

High-Grade squamous intraepithelial lesions (HSIL)

Squamous cell lesions synonymous with CIN 2 and 3

Low-grade Squamous Intraepithelial Lesions (LSILS)

Squamous histological changes related to human papillomavirus infection and Cervical Intraepithelial Neoplasm (CIN) 1.

Mild Dysplasia or CIN 1

Abnormal cells limited to the lower one third of the squamous epithelium.

Moderate Dysplasia or CIN 2

Abnormal cells extending into the middle one third of squamous epithelium

Non-neoplastic Findings

These include findings in keeping with, but not truly diagnostic of organisms like, Trichomonas vaginalis, Antinomies species, Candida species, herpes simplex virus, nor flora suggestive of bacterial vaginosis.

Severe Dysplasia (CIN 3)

Abnormal squamous cells extend into the upper third of cervical squamous epithelium

Transformation Zone

A colposcopic term for the area of cellular change that is observed adjacent to the Squamocolumnar junction

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