

Prevalence of cervical intraepithelial lesions and associated factors among women attending a cervical cancer clinic in Western Uganda; results based on Pap smear cytology

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Abstract

Introduction: There are high incidence and mortality rates of cervical cancer among females in East Africa. This is exacerbated by limited up-to-date data on premalignant lesions and associated factors in this setting. In this study, we determined the prevalence of cervical intraepithelial lesions and associated factors among women attending the Mbarara Regional Referral Hospital cervical cancer clinic in Southwestern Uganda.

Methods: In this cross-sectional study, 364 participants were recruited from among women attending the Mbarara Regional Referral Hospital cervical cancer clinic from 1 April to 30 June 2023. On consent, the study nurse collected demographic data and Pap smears, which were microscopically examined and reported by a laboratory scientist and a pathologist following the Bethesda grading system (2014). Statistical analyses were done in STATA version 17, using proportions, Chi-square, bivariate, and multivariate logistic regression analysis to determine associated factors at ≤ 0.05 significance level.

Results: The mean age of participants was 41.9 years. A third of all study participants (37.6%, 132/351) were contraceptive users, mostly hormonal contraceptives (87.1%, 115/132). Almost 88% (307/351) had an unknown Human Papilloma Virus status. The prevalence of cervical intraepithelial lesions among our study participants was 6.6% (23/351), of which 73.9% (17/23) were low-grade squamous intraepithelial lesions. More than half (9/17, 52.9%) of low-grade squamous intraepithelial lesions were active hormonal contraceptive users. Use of hormonal contraceptives (OR: 3.032, p : 0.0253), use of intrauterine devices (OR: 6.284, p : 0.039), and any family history of cervical cancer (OR: 4.144, p : 0.049) were significantly associated with cervical intraepithelial lesions.

Conclusion: The prevalence of cervical intraepithelial lesions was 6.6%, lower than global estimates. Use of hormonal and intrauterine device contraceptives, as well as family history of cervical cancer, were significantly associated with cervical intraepithelial lesions among our study population. Prospective studies are recommended to further understand associations between different types of intrauterine devices and hormonal contraceptives, and cervical lesions.

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Keywords

Cervical intraepithelial neoplasia, risk factors, cervical cancer, LSIL, HSIL, ASCUS, Uganda

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Introduction

Globally, cervical cancer is number four among the most common malignancies affecting women.¹ About a million incident cervical cancer cases and 307,000 mortalities were reported in Sub-Saharan Africa in 2020,² with low and middle-income countries recording increasing incidence and mortality rates.^{3,4} Incidence and mortality rates stand at 40.1/100,000 and 28.6/100,000, respectively among females in East Africa.² Cervical cancer is, however, ranked as the commonest cancer among women, responsible for death of more women than any other cancer in Sub-Saharan Africa, Asia (including India), as well as some countries in Central and South America.⁵ On a similar note, 569,847 incident cases of cervical cancer were reported worldwide in 2018 by Bray et al.,⁶ with an age-standardised incident rate in East Africa being 40.1 per 100,000. South Africa had the highest age-standardised incidence rate of 43.1 per 100,000. Majority of African countries, including Uganda, have been reported to have an age-standardised incidence rate of at least 40 per 100,000.¹ In 2019, it was reported that 2784.9 million women worldwide aged 15 years and older were at risk of developing cancer of the cervix.⁷ The prevalence of cervical precancerous lesions around Africa has been reported to be in the range between 3.7% and 22.6%.^{8–16} From the Ugandan perspective, Eilu et al.¹⁷ showed that the prevalence of cervical intraepithelial neoplasia stands at 38.6%.

Human papillomavirus (HPV) is a well-established necessary but not sufficient cause of cervical lesions.^{18,19} Development of cervical cancer occurs through several stages, starting with chronic infection with high-risk HPV (HrHPV) genotypes, through premalignant stages (cervical intraepithelial neoplasia (CIN)), and finally culminates into invasive cervical cancer (ICC).^{20,21} HPV16 and HPV18 have been implicated to be HrHPV subtypes highly associated with around 70% of all cervical cancers.²² After a persistent infection with HrHPV genotypes, epithelial cells undergo a series of changes, typically epithelial-mesenchymal transition,²³ turning epithelial cells into mesenchymal cells which can metastasise; a property that is thought to contribute to the metastatic nature of human cancer cells.²⁴ During the productive stage of infection, the viral genome is relatively maintained at a low number of copies in the basal cells.^{25–28} The viral episomes remain maintained in basal cells by being replicated alongside the host cell chromosomes.^{29–31} Thereafter, the viral life cycle goes on along with the differentiation program in keratinocytes and it is dependent on several cellular and viral factors and proteins.²⁹ Interactions of various viral and cellular pathways involving mainly proteins and other biomolecules like micro RNAs, E6 and E7,

contribute towards progression of cervical epithelial cells to a cancerous state. Outgrowth of dysplastic lesions is said to be facilitated by increasing expression of viral oncogenes, E6 and E7, which themselves interact with various proteins that regulate the cell cycle.³¹

A number of factors, including HIV infection, age at sexual debut, Chlamydia trachomatis infection, oral contraceptives, smoking, gravidity, use of multiple sexual partners, and other forms of immunosuppression, are associated with cervical cancer.^{21,32–36} There is limited information regarding the current magnitude of cervical cancer or its premalignant lesions and associated factors in resource-limited settings, which is normally attributed to poor data collection and reporting systems.^{37,38} Available information³⁹ is too old to be relied on for decision making. Uganda is experiencing a very low cervical cancer screening rate,^{40–42} and this might increase the burden due to cervical cancer or its premalignant lesions as a result of late detection and treatment.⁴³ The low screening rate for cervical cancer is said to be driven by scarcity of knowledge on cervical cancer and its screening services, religious barriers, community misconceptions, fear of embarrassment during screening procedures, fear of screening outcomes, and long distances travelled to reach screening centers among others.^{44,45} There is still a lot of unknown information regarding prevalence and factors associated with cervical intraepithelial lesions, as well as barriers to screening. This study, therefore, aimed at determining the prevalence of cervical intraepithelial lesions and associated factors among women attending the Mbarara Regional Referral Hospital (MRRH) cervical cancer clinic in South Western Uganda.

Materials and methods

Study design

A cross-sectional study was conducted, including all women who presented at the MRRH cervical cancer clinic from 1 April to 30 June 2023, seeking cervical cancer screening, testing, and treatment services. Results of this study have been reported following the STROBE guidelines for cross-sectional studies.

Study setting

We conducted this study at the MRRH cervical cancer clinic from 1 April to 30 June 2023. MRRH is a public and free access tertiary health facility and is the primary teaching hospital for the medical school of Mbarara University of Science and Technology (MUST); and serves the entire

Southwestern Uganda. The distance between MRRH and Kampala, the Ugandan capital, is about 260km. At this clinic, an average of 15 women are screened for cervical lesions per day, and the clinic runs 5 days a week. Being the only cervical cancer screening and treatment center in the region of Southwestern Uganda, it receives women from all districts of Southwestern Uganda plus the neighbouring countries, including Tanzania, Rwanda, Burundi, and the Democratic Republic of Congo. Staff at the clinic include nurses, midwives, medical officers, and residents, and all are supervised by a gynecologic oncologist. Screening for cervical cancer is voluntary and free of charge, although some women get referred to the clinic by lower health facilities. There is no role played in cervical cancer screening by any insurance service provider. Primary screening tests at the clinic are visual inspection with acetic acid (VIA) and Pap smear cytology, while diagnostic tests include colposcopy and histology. Patients who get diagnosed with cervical lesions either get treatment onsite or get referred to radiotherapy or chemotherapy at the Uganda Cancer Institute. At the clinic, cervical cancer screening services are available to all women aged 21 years and above, following national guidelines. Conventional Pap smear cytology and general histology are performed at the histopathology laboratory in the pathology department of MUST. This laboratory is the regional histopathology laboratory for the Ministry of Health, and it is run by qualified and certified histotechnologists together with pathologists and participates in external quality assurance.

Variables

The main outcome of this study was the prevalence of cervical lesions. The independent variables for this study included age, district, and village of residency, history of blood pressure, diabetes history, marital status, the highest educational level attained, HIV status, smoking status, contraceptive use, type of contraceptive being used, family history of cervical cancer, age at first sexual encounter, total number of lifetime partners, and number of full-term births. For those who reported to be HIV positive, we captured HIV viral load and CD4 count.

Sampling procedure

We used simple random sampling to recruit study participants among all women who sought cervical cancer screening and testing services at the cervical cancer clinic of MRRH. This was adopted to avoid selection bias.

Sample size determination

For this cross-sectional study, the sample size of 364 participants was estimated using the formula by Kish Leslie 1965. For this calculation, we considered $d=0.05$, the level of

precision which is assumed to be ± 0.05 , $Z_{(1-\alpha)} = 1.96$ (Score of normal standard variance curve corresponding to 95% level of confidence) for a two-sided test (1.96); and a prevalence of CIN of 38.6%.¹⁷ Thirteen participants were excluded from data analysis because their Pap smears were non-diagnostic on examination.

Data collection

Upon arrival at the clinic, participants were assessed for eligibility to participate in the study and then after, written informed consent was sought. After the provision of written informed consent, participants were taken through a description of the study and its objectives. Pap smears were then collected, and VIA and other tests were performed thereafter.

Demographic data collection

The midwives from the cervical cancer clinic served as study assistants and administered a pretested questionnaire to gather demographic data. This questionnaire had been used previously^{35,46} and was pretested at the Uganda Cancer Institute among women seeking cervical cancer care. After the provision of written informed consent, participants were assisted in filling out the questionnaire to capture their demographic data, including age, district, and village of residency, history of blood pressure, diabetes history, marital status, the highest educational level attained, HIV status, smoking status, contraceptive use, type of contraceptive being used, family history of cervical cancer, age at first sexual encounter, total number of lifetime partners, and number of full-term births. For those who were reported to be HIV positive, we captured HIV viral load and CD4 count results from clinic files.

Cytological evaluation

Pap smear collection was performed by midwives at the clinic following a routine standard procedure. The patient was placed on an examination table, and the midwife used a cytobrush or spatula to delicately remove cells from the surface of the cervix while a speculum was gently pushed into the vagina to allow a clear view of the cervix. Smears were created on glass slides, promptly fixed with 95% alcohol, and then stained using the Pap staining technique in accordance with standard operating procedures in laboratories. Smears were examined microscopically by the principal investigator, together with a qualified and certified pathologist. All the examinations and grading followed the Bethesda grading system (2014).⁴⁷ The results were categorised as follows: squamous cell carcinoma (SCC), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells of undetermined significance (ASCUS), and negative for intraepithelial lesion or malignancy (NILM).

Statistical analysis

Data was collected by the principal investigator with the help of research assistants. It was then entered into an Excel spreadsheet (Microsoft Office Professional Plus 2013, version 15.0.4675.1003, Microsoft Inc, USA) and then imported into STATA 17 (Stata Corp LLC, College Station, TX, USA) software. Descriptive statistics were employed to describe the population using frequencies, means \pm standard deviations (SDs), and median values for continuous variables. We also employed Chi-square tests, frequencies, and proportions to describe categorical variables. The prevalence of cervical intraepithelial lesions was presented as proportions. We used bivariate and multivariate logistic regression analysis to arrive at factors associated with cervical lesions. Bivariate analysis was done first, and we purposively selected variables ($p < 0.2$) for multivariate analysis. We considered a p -value of < 0.05 as being significant.

Ethical considerations

Prior to participating in the trial, each subject gave their written informed consent. On all instruments used for gathering data and on laboratory specimens, we used study numbers rather than names. During data analysis, we disconnected all participants' personal information. All interactions between research assistants and participants happened in a quiet, cosy side room of the clinic that was only available to one person at a time. This study received ethical approval from the Mbarara University of Science and Technology Research Ethics Committee (MUST-REC) (MUST-2022-612) as well as the Uganda National Council for Science and Technology (UNCST) (HS2722ES). We also sought administrative clearance from the MRRH Director before commencing the study. All women whose results indicated a diagnosis of cervical intraepithelial lesions received the standard package of care available at the cervical cancer clinic, and all participants received their Pap smear results.

Eligibility criteria

This study included all women of 21 years and above who reported to the MRRH cervical cancer clinic during the time of the study and provided written informed consent to participate. All women were recruited regardless of their family or personal history of cervical cancer. We excluded all those women who were too ill, as well as those who were undergoing treatment for cervical lesions.

Results

The response rate for this study was 100%, and recruited a total of 364 participants following our inclusion criteria. Thirteen participants were excluded from analysis because they had nonsatisfactory Pap smears, and hence, they were

considered to have missing information. We eventually included 351 in the analysis. The mean age of study participants was 41.9 (± 12.2). The majority of our participants (63.8%, 224/351) were residing in districts other than Mbarara city, were married (65.2%, 229/351), and were non-smokers (98.3%, 345/351). More than half (58.1%, 204/351) of the study participants were HIV positive, and their mean CD4 count as well as viral load were 493.392 cells per μl and 4719.833 copies per μl , respectively, as shown in Table 1.

We assessed our study participants for other reproductive characteristics. The most common gynaecological complaint was vaginal discharge, with a prevalence of 12.8% (45/351). More than a third (37.6%, 132/351) were contraceptive users, specifically hormonal contraceptives (87.1%, 115/132). A big proportion (80.3%, 282/351) of our participants reported to have had their sexual debut at an age between 12 and 20 years. Almost 88% (307/351) had an unknown HPV status, while 69.1% (242/351) reported to have had multiple sexual partners, as shown in Table 2.

Prevalence of cervical lesions

We observed a total number of 23 participants with positive cytology results out of 351 participants. These participants were LSIL+,²⁴ and one participant who was ASCUS but got treatment following an earlier positive VIA test. This makes a prevalence of 6.6%. More than half (73.9%, 17/23) of all positive cases were LSILs. All participants (23/23) with positive Pap smears reported no history of high blood pressure. A good number of participants (19/23) with cervical lesions were married: 100% for ASCUS, 80% for HSIL, and 82.4% for LSIL. More than half (52.9%, 9/17) of participants with LSIL had attained a maximum of primary school education. The same proportion of participants (52.9%, 9/17) were HIV positive and had suppressed viral load, as shown in Table 3.

Of all participants who had LSIL, 82.4% (14/17) reported to have had their sexual debut at 31 years and above. Still, for those with LSIL, more than half (58.8%, 10/17) were active contraceptive users, especially hormonal contraceptives (52.9%, 9/17). Additionally, whereas 60% (3/5) of people with HSIL reported having two or more lifetime sexual partners, more than half (70.69%, 12/17) of participants with LSIL did the same. A big proportion of participants (80%, 4/5) with HSIL reported to have had 4 or more full-term births, as shown in Table 4.

Factors associated with cervical lesions

Several variables were considered for multivariate analysis after their bivariate analysis revealed p values of less than 0.2, as well as being biologically plausible in cervical cancer. These variables included the number of full-term births, lifetime sexual partners, age at sexual debut, HIV status, type of contraceptive used, family history of cervical cancer, and highest educational level. After adjusting for number of

Table 1. Socio-demographic characteristics of study participants at Mbarara Regional Referral Hospital, 1 April to 30 June 2023.

Variables	Category	n/351	Percentage
Age		41.9 (12.2)	
Age group	21–29	59	16.8
	30–39	99	28.2
	40–49	92	26.2
	50 and above	101	28.8
Region of residence	Central Uganda	2	0.6
	Other parts of Western Uganda	224	63.8
	Mbarara city	125	35.6
History of high BP	No	312	88.9
	Yes	39	11.1
Diabetes history	No	333	94.9
	Yes	18	5.1
Marital status	Divorced	47	13.4
	Married	229	65.2
	Single	70	19.9
	Widowed	5	1.4
Highest educational level	Never studied	45	12.8
	Pre-primary	30	8.5
	Primary school	138	39.3
	Secondary school	87	24.8
	Tertiary institution	35	10
	University	16	4.6
HIV status	Unknown	1	0.3
	Negative	146	41.6
	Positive	204	58.1
HIV viral load category	N/A	146	41.6
	Not suppressed	18	5.1
	Suppressed	187	53.3
HIV viral load copies per µl		4719.8 (16606.9)	
CD4 count		493.4 (234.5)	
Smoking	No	345	98.3
	Yes	6	1.7

Continuous variables, age, HIV viral load, and CD4 count are presented as mean (standard deviation).

full-term births, type of contraceptive used, HIV status, age at sexual debut, CD4 counts, HIV viral load, highest educational level, and number of life-time sexual partners, the results of the multivariate analysis showed that the likelihood of cervical lesions was three times higher in those who reported using hormonal contraceptives than in those who had not used any form of birth control. This difference was statistically significant (OR: 3.032, p -value=0.025, 95% CI: 1.150–7.989). Also, participants who reported to have used IUDs as contraceptives were six times more likely to develop cervical lesions compared to those who had not used any contraceptive, and this observation was also statistically significant (OR: 6.284, p -value=0.039, 95% CI: 1.094–36.095). Participants who reported a family history of cervical cancer were also four times more likely to have cervical lesions than those who reported not to have such a family history of cervical cancer. This observation was statistically significant (OR: 4.144, p -value=0.049, 95% CI: 1.004–17.101), as shown in Table 5.

Discussion

In this study, we found that 6.6% of all participants recruited were positive for cervical lesions. This prevalence was lower than is reported in most studies. Studies in other low-resource African countries have reported higher prevalence rates, such as 26.7–37% in Kenya.⁴⁸ There was a reported prevalence of 18.2% in Bangladesh⁴⁹ and 22.1% in Ethiopia.⁵⁰ Previous studies that have been conducted among HIV-positive and negative populations have reported prevalence rates of 22.9% and 5.79%, respectively, in Swaziland.⁵¹ This difference could be attributed to the fact that most of these studies were conducted among HIV-positive people, bearing in mind that HIV is a risk factor for cervical lesions.^{52–54} However, other studies in Cameroon have reported lower prevalence rates of 3.33%.⁵⁵ A case-control study in Nigeria documented a slightly higher but comparable prevalence of abnormal Pap cytology results (8.0%).⁵⁶ This observation could be attributed to the comparability of study populations

Table 2. Reproductive characteristics of study participants at Mbarara Regional Referral Hospital, 1 April to 30 June 2023.

Variables	Category	n/351	Percentage
Other gynaecological conditions	None	264	75.21
	Cervicitis	35	9.97
	Vaginal discharge	45	12.82
	Warts	1	0.28
	Candidiasis	2	0.57
	Trichomoniasis	2	0.57
	Syphilis	2	0.57
Contraceptive use	No	219	62.4
	Yes	132	37.6
Contraceptive type (N= 132)	BTL	2	1.5
	Condom	2	01.5
	Hormonal	115	87.1
	IUD	13	9.9
Cervical cancer family history	No	331	94.6
	Yes	19	5.4
Age at sexual debut	31 and above	2	0.57
	21–30	67	19.09
	12–20	282	80.34
Lifetime sexual partners (number)	0–1	108	30.86
	2 and above	242	69.14
Full-term births (number)	0	12	3.42
	1–3	163	46.44
	4 and above	176	50.14
VIA test results	Negative	312	88.9
	Positive	37	10.5
	Suspicious for cancer	2	0.6
HPV status (16 and 18)	Negative	14	4
	Positive	30	8.5
	Unknown	307	87.5

All data was categorical, and the total number of participants was 351, except for type of contraceptive (N= 132).

in terms of socioeconomic status and sexual behaviour. Increased prevalence of cervical neoplasia in our study was found among participants who were married and less educated (primary education). This pattern of prevalence was earlier reported in similar studies by Bayo et al.⁵⁷ in Mali and Palacio-Mejía et al.⁵⁸ in Mexico. These women may have developed cervical neoplasia as a result of their early sexual experience and multiple sexual partners, both of which are significant risk factors for HPV infection.

We found that all participants (23/23) with positive Pap smears reported no history of high blood pressure. This is in agreement with other studies, which have shown that cervical lesions are significantly associated with other metabolic syndrome components except high blood pressure.^{59–64} It would be imperative to think of an indirect link between high blood pressure and cervical lesions. For instance, from our recent studies in Ugandan populations, we also observed significant associations between other metabolic syndrome components with cervical lesions.^{36,46} Besides, high blood pressure being associated with inflammation likely impairs one's immune system,⁶⁵ which would

eventually predispose one to reduced ability to clear infections, including HPV.

This study presents a higher prevalence of cervical lesions among married women. This contradicts the commonly perceived notion about marriage as a protective factor against cervical lesions⁶⁶ and that single women are at increased risk of cervical cancer.⁶⁷ This indicates that married women in this study population are likely exposed to HPV or other risk factors for cervical cancer. In fact, population dynamics and trends indicate that 8.3% of all women in Uganda are married or cohabiting in polygamous relationships.⁶⁸ Such observations in this population could explain the increased prevalence of sexually transmitted infections, including Chlamydia Trachomatis and HPV, which are associated with cervical lesions.³⁵ However, an equally high prevalence of cervical lesions among married women was reported in a hospital population in Cameroon.⁶⁹

We found out that usage of IUDs and hormonal contraceptives, as well as having a family history of cervical cancer, were significantly associated with cervical lesions in this study population. Although it deviates from many of the risk

Table 3. Prevalence of cervical lesions across selected socio-demographic characteristics of study participants at Mbarara Regional Referral Hospital, 1 April to 30 June 2023.

Variable	ASCUS N= 1	HSIL N= 5	LSIL N= 17	NILM N= 328	Test	p-Value
Age group						
21–29	0 (0.0%)	1 (20.0%)	3 (17.6%)	55 (16.8%)	Fisher's exact	0.79
30–39	0 (0.0%)	2 (40.0%)	6 (35.3%)	91 (27.7%)		
40–49	1 (100.0%)	0 (0.0%)	5 (29.4%)	86 (26.2%)		
50 and above	0 (0.0%)	2 (40.0%)	3 (17.6%)	96 (29.3%)		
Region of residence						
Central Uganda	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	Fisher's exact	0.71
Other parts of Western Uganda	1 (100.0%)	4 (80.0%)	9 (52.9%)	210 (64.0%)		
Mbarara city	0 (0.0%)	1 (20.0%)	8 (47.1%)	116 (35.4%)		
History of high BP						
No	1 (100.0%)	5 (100.0%)	17 (100.0%)	289 (88.1%)	Fisher's exact	0.44
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	39 (11.9%)		
History of diabetes						
No	1 (100.0%)	5 (100.0%)	16 (94.1%)	311 (94.8%)	Fisher's exact	0.71
Yes	0 (0.0%)	0 (0.0%)	1 (5.9%)	17 (5.2%)		
Marital status						
Divorced	0 (0.0%)	1 (20.0%)	2 (11.8%)	44 (13.4%)	Fisher's exact	0.70
Married	1 (100.0%)	4 (80.0%)	14 (82.4%)	210 (64.0%)		
Single	0 (0.0%)	0 (0.0%)	1 (5.9%)	69 (21.0%)		
Widowed	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1.5%)		
Highest educational level						
Never studied	0 (0.0%)	2 (40.0%)	2 (11.8%)	41 (12.5%)	Fisher's exact	0.97
Pre-primary	0 (0.0%)	0 (0.0%)	1 (5.9%)	29 (8.8%)		
Primary school	1 (100.0%)	2 (40.0%)	9 (52.9%)	126 (38.4%)		
Secondary school	0 (0.0%)	1 (20.0%)	4 (23.5%)	82 (25.0%)		
Tertiary institution	0 (0%)	0 (0.0%)	1 (5.9%)	34 (10.4%)		
University	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (4.9%)		
HIV status						
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	Fisher's exact	0.70
Negative	0 (0.0%)	1 (20.0%)	8 (47.1%)	137 (41.8%)		
Positive	1 (100.0%)	4 (80.0%)	9 (52.9%)	190 (57.9%)		
Smoking						
No	1 (100.0%)	5 (100.0%)	17 (100.0%)	322 (98.2%)	Fisher's exact	1.00
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (1.8%)		
HIV viral load category						
N/A	0 (0.0%)	1 (20.0%)	8 (47.1%)	137 (41.8%)	Fisher's exact	0.52
Not suppressed	0 (0.0%)	1 (20.0%)	0 (0.0%)	17 (5.2%)		
Suppressed	1 (100.0%)	3 (60.0%)	9 (52.9%)	174 (53.0%)		
CD4 count						
200≤	0 (0.0%)	2 (11.8%)	0 (0.0%)	49 (14.9%)	Fisher's exact	0.54
<200	0 (0.0%)	1 (5.9%)	0 (0.0%)	4 (1.2%)		
Not indicated	5 (100.0%)	14 (82.4%)	1 (100.0%)	275 (83.8%)		

Data for categorical variables were presented as frequency (proportion).

factors that have been widely accepted, this provides new information regarding risk factors for cervical intraepithelial lesions. For instance, many authors from previous studies reported smoking, HIV positivity, contraceptive use, and a family history of cervical cancer as possible risk factors for cervical cancer.^{7,52,53,70–78} Furthermore, in a study on the risk

factors for cervical neoplasia, Kjellberg et al.⁴¹ discovered a substantial correlation between higher grades of CIN and HPV, smoking, and prolonged contraceptive usage. In addition, our previous study showed that obesity is significantly associated with cervical intraepithelial lesions.⁷⁹ For family history of cervical cancer, it is crucial to acknowledge the

Table 4. Prevalence of cervical lesions across reproductive characteristics of study participants at Mbarara Regional Referral Hospital, 1 April to 30 June 2023.

Variable	ASCUS N=1	HSIL N=5	LSIL N=17	NILM N=328	Test	p-Value
Age at sexual debut						
31 and above	1 (100.0%)	5 (100.0%)	14 (82.4%)	262 (79.9%)	Fisher's exact	0.87
21–30	0 (0.0%)	0 (0.0%)	3 (17.6%)	64 (19.5%)		
12–20	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)		
Contraceptive use						
No	0 (0.0%)	3 (60.0%)	7 (41.2%)	209 (63.7%)	Fisher's exact	0.11
Yes	1 (100.0%)	2 (40.0%)	10 (58.8%)	119 (36.3%)		
Type of contraceptive						
BTL	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	Fisher's exact	0.18
Condom	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)		
Hormonal	1 (100.0%)	1 (20.0%)	9 (52.9%)	105 (32.0%)		
IUD	0 (0.0%)	1 (20.0%)	1 (5.9%)	11 (3.4%)		
None	0 (0.0%)	3 (60.0%)	7 (41.2%)	208 (63.4%)		
Family history of cervical cancer						
No	1 (100.0%)	4 (100.0%)	14 (82.4%)	312 (95.1%)	Fisher's exact	0.15
Yes	0 (0.0%)	0 (0.0%)	3 (17.6%)	16 (4.9%)		
Number of lifetime sexual partners						
1	1 (100.0%)	2 (40.0%)	5 (29.4%)	100 (30.6%)	Fisher's exact	0.57
2 and above	0 (0.0%)	3 (60.0%)	12 (70.6%)	227 (69.4%)		
Number of full-term births						
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (3.7%)	Fisher's exact	0.60
1–3	0 (0.0%)	1 (20.0%)	10 (58.8%)	152 (46.3%)		
4 and above	1 (100.0%)	4 (80.0%)	7 (41.2%)	164 (50.0%)		
Other gynaecological conditions						
None	1 (100.0%)	4 (80.0%)	14 (82.4%)	245 (74.7%)	Fisher's exact	0.62
Cervicitis	0 (0.0%)	1 (20.0%)	3 (17.6%)	31 (9.5%)		
Vaginal discharge	0 (0.0%)	0 (0.0%)	0 (0.0%)	45 (13.7%)		
Warts	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)		
Candidiasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)		
Trichomoniasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)		
Syphilis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)		

Data for categorical variables were presented as frequency (proportion).

role of genetic and epigenetic factors in cervical carcinogenesis. For instance, the apolipoprotein B mRNA editing enzyme catalytic polypeptide like DNA-editing protein is said to play an important role in molecular pathogenesis of cervical cancer as well as other cancers.^{80–82}

We observed no association between smoking and cervical lesions. This could be explained by the fact that there were very few cases of smokers in the study population. In fact, smoking has been found not to be associated with any grade of cervical lesions, as evidenced in previous studies by Castellsagué et al.⁸³ However, smoking has been shown to be associated with cervical precancerous lesions,^{69,84} and other malignancies.^{85–87} In our population, age was not associated with cervical lesions, though it was earlier proposed by Bhatla et al.⁸⁸ that the age group of 21–40 years could be a risk factor based on the high prevalence of HPV and other factors in the same age group.

We found that usage of IUDs is significantly associated with cervical lesions among the study population. Previous studies have reported contradicting results in regard to IUDs and cervical lesions.^{89–92} A systematic review by Cortessis et al.⁹³ reported that cervical cancer is less frequent in women who have used IUDs, and hence, IUDs may be apparently protective against cervical lesions. This protective nature of IUDs against cervical lesions is based on observations that IUDs reduce HPV infection risk and also trigger immune system responses that tend to fight viral infections, including HPV.⁹⁴ From the case-control study, nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) Study, non-significantly decreased risk of both CIN3/CIS and ICC was observed among IUD users.⁷³

However, in agreement with our findings, recent evidence from a case-control study by Averbach et al.⁹⁵ showed that IUD usage is associated with CIN2+ but not with CIN3+ In

Table 5. Logistic regression analysis showing association between cervical lesions and selected variables of study participants at Mbarara Regional Referral Hospital, 1 April to 30 June 2023.

Variables	Category	COR	p-Value	95% CI	AOR	p-Value	95% CI
Number of full-term births	0	1			1		
	1–3	0.989	0.98	0.424–2.308	1.337	0.564	0.4982–3.591
	4 and above	1			1		
Number of life-time sexual partners	0–1	1			1		
	2 and above	0.826	0.674	0.339–2.011	0.849	0.748	0.312–2.313
Age at sexual debut	31 and above	1			1		
	21–30	0.614	0.442	0.177–2.130	0.980	0.976	0.257–3.731
	12–20	1			1		
HIV status	Negative	1			1		
	Positive	1.122	0.795	0.472–2.666	0.887	0.804	0.344–2.284
	Unknown	1			1		
Type of contraceptive	None	1			1		
	Hormonal	2.179	0.086	0.897–5.295	3.032	0.025*	1.150–7.989
	IUD	3.782	0.111	0.737–19.395	6.284	0.039*	1.094–36.095
	BTL	1			1		
Family history of cervical cancer	Condom	1			1		
	No	1			1		
CD4 count	Yes	3.079	0.094	0.823–11.494	4.144	0.049*	1.004–17.101
	200≤	1			1		
Highest educational level	<200	6.125	0.173	0.451–83.116	5.053	0.234	0.351–72.672
	None	1			1		
	Pre-primary	0.353	0.363	0.038–3.328	0.272	0.269	0.027–2.738
	Primary school	0.976	0.968	0.299–3.193	0.811	0.743	0.231–2.841
	Secondary school	0.625	0.5	0.159–2.453	0.493	0.36	0.108–2.244
	Tertiary institution	0.302	0.294	0.032–2.826	0.191	0.172	0.018–2.055
	University	1			1		

Data were adjusted for number of full-term births, type of contraceptive used, HIV status, age at sexual debut, CD4 counts, HIV viral load, educational level, and number of life-time sexual partners.

COR: crude odds ratio; AOR: adjusted odds ratio; 95% CI: 95% confidence interval.

*Statistically significant ($p \leq 0.05$).

some populations, including those in less developed countries, usage of IUDs is thought to increase the risk of sexually transmitted infections (STIs), including HPV, whose association with cancer of the cervix is well known.⁹⁶ A study among Kenyan sex workers found that usage of IUDs was significantly associated with increased incident *C. trachomatis* infection.⁹⁷ This is in agreement with our earlier study, which demonstrated that a co-infection of *C. trachomatis* and HPV is associated with cervical lesions.³⁵ Certain types of IUDs, including LNG-IUS, which may not be popular in our study population, have been shown to increase HPV acquisition and persistence.⁹⁸ Lekovich et al.'s⁹⁹ comparative study, which examined the differences in cervical cytology and high-risk human papillomavirus (HPV) infection clearance between levonorgestrel- and copper-containing IUD users, also supported the findings of our study by showing that levonorgestrel-containing IUDs may be linked to higher risk of high-risk HPV infection acquisition and lower clearance when compared to copper-containing IUDs.

We found a significant association between cervical lesions and usage of hormonal contraceptives. This is in

agreement with results from a systematic review by Deese et al.,¹⁰⁰ who provided evidence that is supportive of an increased risk of many other STIs, including HSV-2 infection among users of other contraceptive methods, depot medroxyprogesterone acetate (DMPA). Iversen et al.'s¹⁰¹ reported observations have also demonstrated that the risk of cervical cancer remains strongly correlated with the use of currently available contraceptives, particularly for women who have not received the HPV vaccine. We note that HPV vaccination among our study participants has a very low coverage.^{102,103} Moreover, with a low cervical cancer screening uptake.^{41,42} The usage duration of hormonal contraceptives could also have a significant correlation with cervical lesions. To further understand the potential impact of the usage duration of hormonal contraceptives on cervical lesions, a case-control study by Kusmiyati et al.¹⁰⁴ revealed that exposure to hormonal contraceptives for more than 5 years can increase one's risk of cervical cancer by 4.2 times.

It is well known that hormonal contraceptives change the way cells metabolise their substances, which can lead to long-term HPV infections and the eventual development of

cervical cancer. The expression of the oncogenes E6 and E7 of HrHPV genotypes may be encouraged by oestrogen and progestin. This process triggers the destruction of the p53 tumour suppressor gene and the incorporation of viral DNA, resulting in cellular transformation and the development of cancer.^{105–107} Hormonal contraceptives are also known to bind to certain HPV-DNA sequences within transcriptional regulatory areas, which may control cellular death and promote HPV-DNA integration into the host cell genome.^{108–114} With increased availability and usage of hormonal contraceptives in our population, there is an increased risk of cervical cancer as a result of hormonal contraception in a predominantly unvaccinated population.^{102,103} This is based on recent observations that hormonal contraceptive use is also associated with a number of STIs, including HIV, HPV, and *Chlamydia Trachomatis*,¹¹⁵ which are known risk factors for cervical lesions.

Recent evidence from a review by Anastasiou et al.¹¹⁶ showed no evidence of an association between hormonal contraceptive use and cervical lesions. However, this study was limited by sample size that is, very few included studies. Additionally, case-control research conducted in Nigeria by Ajah et al.⁵⁶ had previously found no link between cervical neoplasia and hormonal contraception. This study did not reveal any significant association between oral contraceptive use and cervical cancer or any grade of cervical lesion. On the contrary, a recent systematic review has shown that longer duration of oral contraceptive pills use has an associated risk for developing cervical cancer, especially for Adenocarcinoma.¹¹⁷

Our study is limited by the inherent weaknesses of a cross-sectional study. This design is non-ideal for studying associations between population variables. Therefore, associations presented here may not be easily extrapolated to the wider population. We also acknowledge that classic Pap smear testing could have lowered the diagnostic power compared to liquid cytology. Another limitation of this study is that we only included women who visited the cervical cancer clinic. This could have caused a selection bias. However, the major strength of this study is its statistical power, which we considered while calculating the sample size. We also employed standard methods during collection, processing, examining, and reporting methods for Pap smear specimens. The results of our study could be generalised to the entire Ugandan population as well as other populations in resource-limited countries. This is so, considering the fact that screening uptake rates are said to be between 30.3%⁴¹ and 44%,⁴² with a low HPV vaccine completion rate of 43.3%.¹⁰²

Conclusion

Based on Pap smear cytology, the prevalence of cervical intraepithelial lesions was 6.6%, which was lower than global estimates. Use of hormonal and IUD contraceptives, as well as family history of cervical cancer, showed significant

associations with cervical intraepithelial lesions among our study population. Prospective studies are recommended to further understand associations between different types of IUDs, hormonal contraceptives, and cervical lesions.

Policy implications

The current burden of cervical lesions indicates the need to develop and maintain a national cervical cancer program and to put in place efforts that increase cervical cancer screening towards the World Health Organization targets.

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Author contribution

The corresponding author, FS, conceived the idea and developed the first draft of the manuscript. Co-authors TCR, DT, NN, and JN supervised the whole project, from data collection to analysis, and reviewed the manuscript. HL and CMC reviewed and provided overall guidance in the entire write-up and approved the final version prior to submission. JNN, RA, and AB participated in data analysis. All authors reviewed and approved the final version of the manuscript. All authors are accountable for all aspects of this manuscript.

Availability of data and materials

All the data from which this article was generated is available from the corresponding author upon meaningful request.

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Ethics approval

Ethical approval for this study was obtained from Mbarara University of Science and Technology Research Ethics Committee (MUST-2022-612) and Uganda National Council for Science and Technology (HS2722ES). We also sought administrative clearance from the Hospital Director, Mbarara Regional Referral Hospital, before commencement of the study.

Informed consent

Written informed consent was obtained from all subjects before the study.


Consent for publication

Not applicable.

Trial registration

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

References

- Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Global Health* 2020; 8(2): e191–e203.
- Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Cancer J Clin* 2021; 71(3): 209–249.
- Buskwofie A, David-West G and Clare CA. A review of cervical cancer: incidence and disparities. *J Natl Med Assoc* 2020; 112(2): 229–232.
- Akinyemiju TF. Socio-economic and health access determinants of breast and cervical cancer screening in low-income countries: analysis of the World Health Survey. *PLoS One* 2012; 7(11): e48834.
- WHO. *Prevention and control of noncommunicable diseases: Guidelines for primary health care in low resource settings*. Geneva: World Health Organization, 2012.
- Bray F, Ferlay J, Soerjomataram I, et al. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 2018; 68: 394–424.
- Bruni L, Diaz M, Castellsagué M, et al. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis* 2010; 202(12): 1789–1799.
- Donkoh ET, Agyemang-Yeboah F, Asmah RH, et al. Prevalence of cervical cancer and pre-cancerous lesions among unscreened Women in Kumasi, Ghana. *Medicine* 2019; 98(13): e14600.
- Thomas J, Ojemakinde K, Ajayi I, et al. Population-based prevalence of abnormal cervical cytology findings and local risk factors in Ibadan, Nigeria: implications for cervical cancer control programs and human papilloma virus immunization. *Acta Cytol* 2012; 56(3): 251–258.
- Handlogten KS, Molitor RJ, Roeker LE, et al. Cervical cancer screening in Ghana, west Africa: prevalence of abnormal cytology and challenges for expanding screening. *Int J Gynecol Pathol* 2014; 33(2): 197–202.
- Ajah LO, Ezeonu PO, Ozonu NC, et al. A five year review of cervical cytology in Abakaliki, Nigeria. *Am J Cancer Prev* 2015; 3(2): 23–26.
- Duru C, Oluoha R, Uwakwe K, et al. Pattern of PAP smear test results among Nigerian women attending clinics in a teaching hospital. *Int J Curr Microbiol App Sci* 2015; 4(4): 986–998.
- Durowade K, Osagbemi G, Salaudeen A, et al. Prevalence and risk factors of cervical cancer among women in an urban community of Kwara State, north central Nigeria. *J Prev Med Hyg* 2012; 53(4): 213–219.
- Wanyoike-Gichuhi J, Kayumba P and Khisa W. Prevalence of cervical cytology abnormalities among HIV infected women at Rwanda Military Hospital. *East Afr Med J* 2014; 91(10): 333–340.
- Kayumba P. *Prevalence of cervical cytology abnormalities among HIV infected women at Rwanda military hospital: a cross-sectional descriptive study*. Kenya: University of Nairobi, 2013.
- Zoa Assoumou S, Ndjoyi Mbiguino A, Mabika Mabika B, et al. Human papillomavirus genotypes distribution among Gabonese women with normal cytology and cervical abnormalities. *Infect Agents Cancer* 2016; 11(1): 1–8.
- Eilu E, Aliero AA, Odoki M, et al. Prevalence of cervical intraepithelial neoplasia and its associated factors among women attending healthcare services in Eastern Uganda. *J Cancer Res Exp Oncol* 2020; 12(1): 1–12.
- Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; 189(1): 12–19.
- Crosbie EJ, Einstein MH, Franceschi S, et al. Human papillomavirus and cervical cancer. *Lancet* 2013; 382(9895): 889–899.
- Woodman CB, Collins SI and Young LS. The natural history of cervical HPV infection: unresolved issues. *Nat Rev Cancer* 2007; 7(1): 11–22.
- Small W Jr, Bacon MA, Bajaj A, et al. Cervical cancer: a global health crisis. *Cancer* 2017; 123(13): 2404–2412.
- Sankaranarayanan R, Qiao Y-L and Keita N. The next steps in cervical screening. *Womens Health* 2015; 11(2): 201–212.
- Geiger T, Sabanay H, Kravchenko-Balasha N, et al. Anomalous features of EMT during keratinocyte transformation. *PLoS One* 2008; 3(2): e1574.
- Thiery JP. Epithelial–mesenchymal transitions in tumour progression. *Nat Rev Cancer* 2002; 2(6): 442–454.
- Pyeon D, Pearce SM, Lank SM, et al. Establishment of human papillomavirus infection requires cell cycle progression. *PLoS Pathog* 2009; 5(2): e1000318.
- Parish JL, Bean AM, Park RB, et al. ChIR1 is required for loading papillomavirus E2 onto mitotic chromosomes and viral genome maintenance. *Mol Cell* 2006; 24(6): 867–876.
- McBride AA. Replication and partitioning of papillomavirus genomes. *Adv Virus Res* 2008; 72: 155–205.
- Maglennon GA, McIntosh P and Doorbar J. Persistence of viral DNA in the epithelial basal layer suggests a model for papillomavirus latency following immune regression. *Virology* 2011; 414(2): 153–163.
- Baker T, Newcomb W, Olson N, et al. Structures of bovine and human papillomaviruses. Analysis by cryoelectron microscopy and three-dimensional image reconstruction. *Biophys J* 1991; 60(6): 1445–1456.
- Doorbar J. Molecular biology of human papillomavirus infection and cervical cancer. *Clin Sci* 2006; 110(5): 525–541.
- Doorbar J, Quint W, Banks L, et al. The biology and life-cycle of human papillomaviruses. *Vaccine* 2012; 30: F55–F70.
- Schottenfeld D and Fraumeni JF Jr. *Cancer epidemiology and prevention*. Oxford, UK: Oxford University Press, 2006.
- Thun M, Linet MS, Cerhan JR, et al. *Cancer epidemiology and prevention*. Oxford, UK: Oxford University Press, 2017.

34. Cohen PA, Jhingran A, Oaknin A, et al. Cervical cancer. *Lancet* 2019; 393(10167): 169–182.
35. Ssedyabane F, Amnia DA, Mayanja R, et al. HPV-chlamydial coinfection, prevalence, and association with cervical intraepithelial lesions: a pilot study at Mbarara regional referral hospital. *J Cancer Epidemiol* 2019; 2019: 9092565.
36. Mwangi GF, Niyonzima N, Atwine R, et al. Dyslipidemia: prevalence and association with precancerous and cancerous lesions of the cervix; a pilot study. *Lipids Health Dis* 2024; 23(1): 3.
37. Shimakawa Y, Bah E, Wild CP, et al. Evaluation of data quality at the Gambia national cancer registry. *Int J Cancer* 2013; 132(3): 658–665.
38. Joko-Fru WY, Jedy-Agba E, Korir A, et al. The evolving epidemic of breast cancer in sub-Saharan Africa: results from the African Cancer Registry Network. *Int J Cancer* 2020; 147(8): 2131–2141.
39. Mayanja R. Cervical Cancer at Mbarara Regional Referral Hospital: magnitude, trends, stages at presentation, impact of acetic acid screening and the need for radiotherapy services. *J Health Med Nurs* 2016; 27: e0002848.
40. Bruni L, Serrano B, Roura E, et al. Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis. *Lancet Global Health* 2022; 10(8): e1115–e1127.
41. Wanyenze RK, Bwanika JB, Beyeza-Kashesya J, et al. Uptake and correlates of cervical cancer screening among HIV-infected women attending HIV care in Uganda. *Global Health Action* 2017; 10(1): 1380361.
42. Sarah Maria N, Olwit C, Kaggwa MM, et al. Cervical cancer screening among HIV-positive women in urban Uganda: a cross sectional study. *BMC Womens Health* 2022; 22(1): 1–9.
43. Chongsuwat T, Ibrahim AO, Evensen AE, et al. Health facility assessments of cervical cancer prevention, early diagnosis, and treatment services in Gulu, Uganda. *PLoS Global Public Health* 2023; 3(2): e0000785.
44. Petersen Z, Jaca A, Ginindza T, et al. Barriers to uptake of cervical cancer screening services in low-and-middle-income countries: a systematic review. *BMC Womens Health* 2022; 22(1): 1–20.
45. Black E, Hyslop F and Richmond R. Barriers and facilitators to uptake of cervical cancer screening among women in Uganda: a systematic review. *BMC Womens Health* 2019; 19(1): 1–12.
46. Ssedyabane F, Ngonzi J, Kajabwangu R, et al. Association between obesity and cervical intraepithelial neoplasia: results from a case control study in south western Uganda. *BMC Womens Health* 2023; 23(1): 1–8.
47. Nayar R and Wilbur DC. The Bethesda system for reporting cervical cytology: a historical perspective. *Acta Cytol* 2017; 61(4–5): 359–372.
48. Njagi SK, Ngure K, Mwaniki L, et al. Prevalence and correlates of cervical squamous intraepithelial lesions among HIV-infected and uninfected women in Central Kenya. *Pan Afr Med J* 2021; 39(1): 44.
49. Bradford L, Dey B, Md Akram Hussain S, et al. Development of a cervical cancer screening program in a slum setting using visual inspection with acetic acid: analysis of feasibility and cost. *J Obstetr Gynecol* 2012; 2(02): 140–146.
50. Gedefaw A, Astatkie A and Tessema GA. The prevalence of precancerous cervical cancer lesion among HIV-infected women in southern Ethiopia: a cross-sectional study. *PLoS One* 2013; 8(12): e84519.
51. Jolly PE, Mthethwa-Hleta S, Padilla LA, et al. Screening, prevalence, and risk factors for cervical lesions among HIV positive and HIV negative women in Swaziland. *BMC Public Health* 2017; 17(1): 1–8.
52. Stelzle D, Tanaka LF, Lee KK, et al. Estimates of the global burden of cervical cancer associated with HIV. *Lancet Global Health* 2021; 9(2): e161–e169.
53. Yuan Y, Cai X, Shen F, et al. HPV post-infection microenvironment and cervical cancer. *Cancer Lett* 2021; 497: 243–254.
54. Adler DH, Wallace M, Bennie T, et al. Cervical dysplasia and high-risk human papillomavirus infections among HIV-infected and HIV-uninfected adolescent females in South Africa. *Infect Dis Obstetr Gynecol* 2014; 2014: 498048.
53. Nkfusai NC, Mubah TM, Yankam BM, et al. Prevalence of precancerous cervical lesions in women attending Mezam Polyclinic Bamenda, Cameroon. *Pan Afr Med J* 2019; 32(1): 174.
56. Ajah LO, Chigbu CO, Ozumba BC, et al. Is there any association between hormonal contraceptives and cervical neoplasia in a poor Nigerian setting? *Oncotargets Ther* 2015; 8: 1887–1892.
57. Bayo S, Bosch FX, de Sanjosé S, et al. Risk factors of invasive cervical cancer in Mali. *Int J Epidemiol* 2002; 31(1): 202–209.
58. Palacio-Mejía LS, Rangel-Gómez G, Hernández-Avila M, et al. Cervical cancer, a disease of poverty: mortality differences between urban and rural areas in Mexico. *Salud Pùbl México* 2003; 45: 315–325.
59. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 2007; 335(7630): 1134.
60. Frumovitz M, Jhingran A, Soliman PT, et al. Morbid obesity as an independent risk factor for disease-specific mortality in women with cervical cancer. *Obstetr Gynecol* 2014; 124(6): 1098.
61. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med* 2003; 348(17): 1625–1638.
62. Bhaskaran K, Douglas I, Forbes H, et al. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet* 2014; 384(9945): 755–765.
63. Song Y-M, Sung J and Ha M. Obesity and risk of cancer in postmenopausal Korean women. *J Clin Oncol* 2008; 26(20): 3395–3402.
64. Poorolajal J and Jenabi E. The association between BMI and cervical cancer risk: a meta-analysis. *Eur J Cancer Prevent* 2016; 25(3): 232–238.
65. Agita A and Alsagaff MT. Inflammation, immunity, and hypertension. *Acta Med Indon* 2017; 49(2): 158.
66. Machida H, Eckhardt SE, Castaneda AV, et al. Single marital status and infectious mortality in women with cervical cancer in the United States. *Int J Gynecol Cancer* 2017; 27(8): 1737.
67. Zena D, Elfu B and Mulatu K. Prevalence and associated factors of precancerous cervical lesions among women in Ethiopia: a systematic review and meta-analysis. *Ethiop J Health Sci* 2021; 31(1): 189–200.
68. Statistics UBO. *The national population and housing census 2014-main report*. Kampala: Uganda Bureau of Statistics, 2016.

69. Wabo B, Nsagha DS, Nana TN, et al. Prevalence and risk factors associated with precancerous cervical lesions among women in two cities in Cameroon. *Pan Afr Med J* 2022; 41(1): 276.
70. Zheng M, Hou L, Ma Y, et al. Exosomal let-7d-3p and miR-30d-5p as diagnostic biomarkers for non-invasive screening of cervical cancer and its precursors. *Mol Cancer* 2019; 18(1): 1–8.
71. Xin F, Liu P and Ma C. A circulating serum miRNA panel as early detection biomarkers of cervical intraepithelial neoplasia. *Eur Rev Med Pharmacol Sci* 2016; 20(23): 4846–4851.
72. Ghebre RG, Grover S, Xu MJ, et al. Cervical cancer control in HIV-infected women: past, present and future. *Gynecol Oncol Rep* 2017; 21: 101–108.
73. Roura E, Travier N, Waterboer T, et al. The influence of hormonal factors on the risk of developing cervical cancer and pre-cancer: results from the EPIC cohort. *PLoS One* 2016; 11(1): e0147029.
74. Cooper D, Hoffman M, Carrara H, et al. Determinants of sexual activity and its relation to cervical cancer risk among South African women. *BMC Public Health* 2007; 7(1): 1–8.
75. Louie K, De Sanjose S, Diaz M, et al. Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. *Br J Cancer* 2009; 100(7): 1191–1197.
76. Liu Z-C, Liu W-D, Liu Y-H, et al. Multiple sexual partners as a potential independent risk factor for cervical cancer: a meta-analysis of epidemiological studies. *Asian Pac J Cancer Prevent* 2015; 16(9): 3893–3900.
77. Fonseca-Moutinho JA. Smoking and cervical cancer. *Int Scholar Res Not* 2011; 2011: 847684.
78. Cancer ICoESoC. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet* 2007; 370(9599): 1609–1621.
79. Anufrieva V, Lebedenko EY, Gaida O, et al. Manageable risk factors for progression of HPV-associated cervical intraepithelial neoplasia. *Med Herald South Russia* 2022; 13(2): 34–43.
80. Revathidevi S, Murugan AK, Nakaoka H, et al. APOBEC: a molecular driver in cervical cancer pathogenesis. *Cancer Lett* 2021; 496: 104–116.
81. Starrett GJ, Luengas EM, McCann JL, et al. The DNA cytosine deaminase APOBEC3H haplotype I likely contributes to breast and lung cancer mutagenesis. *Nat Commun* 2016; 7(1): 12918.
82. Vartanian J-P, Guétard D, Henry M, et al. Evidence for editing of human papillomavirus DNA by APOBEC3 in benign and precancerous lesions. *Science* 2008; 320(5873): 230–233.
83. Castellsague X, Pawlita M, Roura E, et al. Prospective seroepidemiologic study on the role of Human Papillomavirus and other infections in cervical carcinogenesis: evidence from the EPIC cohort. *Int J Cancer* 2014; 135(2): 440–452.
84. Kjellberg L, Hallmans G, Åhren A, et al. Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection. *Br J Cancer* 2000; 82(7): 1332–1338.
85. Scherübl H. Smoking tobacco and cancer risk. *Dtsch Med Wochenschr* 2021; 146(6): 412–417.
86. Scherübl H. Tabakrauchen und Krebsrisiko. *Pneumologie* 2023; 77(01): 27–32.
87. Macacu A, Autier P, Boniol M, et al. Active and passive smoking and risk of breast cancer: a meta-analysis. *Breast Cancer Res Treat* 2015; 154: 213–224.
88. Bhatla N, Puri K, Joseph E, et al. Association of Chlamydia trachomatis infection with human papillomavirus (HPV) and cervical intraepithelial neoplasia—a pilot study. *Indian J Med Res* 2013; 137(3): 533.
89. Jensen K, Schmiedel S, Norrild B, et al. Parity as a cofactor for high-grade cervical disease among women with persistent human papillomavirus infection: a 13-year follow-up. *Br J Cancer* 2013; 108(1): 234–239.
90. Shields TS, Brinton LA, Burk RD, et al. A case-control study of risk factors for invasive cervical cancer among US women exposed to oncogenic types of human papillomavirus. *Cancer Epidemiol Biomark Prevent* 2004; 13(10): 1574–1582.
91. Zondervan K, Carpenter L, Painter R, et al. Oral contraceptives and cervical cancer—further findings from the Oxford Family Planning Association contraceptive study. *Br J Cancer* 1996; 73(10): 1291–1297.
92. Castellsagué X, Díaz M, Vaccarella S, et al. Intrauterine device use, cervical infection with human papillomavirus, and risk of cervical cancer: a pooled analysis of 26 epidemiological studies. *Lancet Oncol* 2011; 12(11): 1023–1031.
93. Cortessis VK, Barrett M, Wade NB, et al. Intrauterine device use and cervical cancer risk: a systematic review and meta-analysis. *Obstet Gynecol* 2017; 130(6): 1226–1236.
94. Hermans U and Heafez E. IUD use and carcinoma of the cervix. *Contracept Deliv Syst* 1981; 2(1): 109–118.
95. Averbach S, Silverberg MJ, Leyden W, et al. Recent intrauterine device use and the risk of precancerous cervical lesions and cervical cancer. *Contraception* 2018; 98(2): 130–134.
96. Kiweewa FM, Brown E, Mishra A, et al. Acquisition of sexually transmitted infections among women using a variety of contraceptive options: a prospective study among high-risk African women. *J Int AIDS Soc* 2019; 22(2): e25257.
97. Masese L, Baeten JM, Richardson BA, et al. Incidence and correlates of Chlamydia trachomatis infection in a high risk cohort of Kenyan women. *Sex Transm Dis* 2013; 40(3): 221–225.
98. Stensen S, Kjaer SK, Jensen SM, et al. Factors associated with type-specific persistence of high-risk human papillomavirus infection: a population-based study. *Int J Cancer* 2016; 138(2): 361–368.
99. Lekovich JP, Amrane S, Pangasa M, et al. Comparison of human papillomavirus infection and cervical cytology in women using copper-containing and levonorgestrel-containing intrauterine devices. *Obstet Gynecol* 2015; 125(5): 1101–1105.
100. Deese J, Pradhan S, Goetz H, et al. Contraceptive use and the risk of sexually transmitted infection: systematic review and current perspectives. *Open Access J Contracept* 2018; 9: 91–112.
101. Iversen L, Fielding S, Lidegaard Ø, et al. Contemporary hormonal contraception and cervical cancer in women of reproductive age. *Int J Cancer* 2021; 149(4): 769–777.
102. Patrick L, Bakeera-Kitaka S, Rujumba J, et al. Encouraging improvement in HPV vaccination coverage among adolescent girls in Kampala, Uganda. *PLoS One* 2022; 17(6): e0269655.
103. Malande OO, Munube D, Afaayo RN, et al. Barriers to effective uptake and provision of immunization in a rural district in Uganda. *PLoS One* 2019; 14(2): e0212270.

104. Kusmiyati Y, Prasistyami A, Wahyuningsih HP, et al. Duration of hormonal contraception and risk of cervical cancer. *Natl Public Health J* 2019; 14(1): 9–13.
105. Comar M, De Seta F, Zanotta N, et al. New diagnostic approaches. In: Cristaudo A and Giuliani M (eds.) *Sexually transmitted infections: Advances in understanding and management*. Cham: Springer International Publishing, 2020, p. 107.
106. Bosch FX, Lorincz A, Muñoz N, et al. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002; 55(4): 244–265.
107. Sasieni P. Cervical cancer prevention and hormonal contraception. *Lancet* 2007; 370(9599): 1591–1592.
108. Gadducci A, Cosio S and Fruzzetti F. Estro-progestin contraceptives and risk of cervical cancer: a debated issue. *Anticancer Res* 2020; 40(11): 5995–6002.
109. Castellsagué X and Muñoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis—role of parity, oral contraceptives, and tobacco smoking. *JNCI Monogr* 2003; 2003(31): 20–28.
110. Moodley M, Moodley J, Chetty R, et al. The role of steroid contraceptive hormones in the pathogenesis of invasive cervical cancer: a review. *Int J Gynecol Cancer* 2003; 13(2): 103–110.
111. Gadducci A, Barsotti C, Cosio S, et al. Smoking habit, immune suppression, oral contraceptive use, and hormone replacement therapy use and cervical carcinogenesis: a review of the literature. *Gynecol Endocrinol* 2011; 27(8): 597–604.
112. Marks M, Gravitt PE, Gupta SB, et al. The association of hormonal contraceptive use and HPV prevalence. *Int J Cancer* 2011; 128(12): 2962–2970.
113. Webster K, Taylor A and Gaston K. Oestrogen and progesterone increase the levels of apoptosis induced by the human papillomavirus type 16 E2 and E7 proteins. *J General Virol* 2001; 82(1): 201–213.
114. de Villiers EM. Relationship between steroid hormone contraceptives and HPV, cervical intraepithelial neoplasia and cervical carcinoma. *Int J Cancer* 2003; 103(6): 705–708.
115. Akter T, Festin M and Dawson A. Hormonal contraceptive use and the risk of sexually transmitted infections: a systematic review and meta-analysis. *Scient Rep* 2022; 12(1): 20325.
116. Anastasiou E, McCarthy KJ, Gollub EL, et al. The relationship between hormonal contraception and cervical dysplasia/cancer controlling for human papillomavirus infection: a systematic review. *Contraception* 2022; 107: 1–9.
117. Asthana S, Busa V and Labani S. Oral contraceptives use and risk of cervical cancer—a systematic review and meta-analysis. *Eur J Obstetr Gynecol Reprod Biol* 2020; 247: 163–175.