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Type-specific HPV incidence and clinical spectrum of lesions induced by high-risk oncogenic HPV types among study participants in Eastern Uganda

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Abstract

Different studies show that high-risk HPV genotypes are the main etiological agents for cervical cancer development and cancer-related deaths in women worldwide. In Uganda, cervical malignancies due to human papillomavirus (HPV) are predominant among sexually active women. However, data on the incidence and clinical spectrum of lesions associated with high-risk HPV infection is inadequate. The current study was aimed to determine incidence and clinical spectrum of lesions induced by high-risk oncogenic HPV types among study participants in Eastern Uganda. We piloted a prospective follow-up study among 1,077 women aged 15-55 years to assess the incidence and clinical spectrum of lesions associated with human papillomavirus infections (HPV). HPV Real-Time PCR using HPV High-Risk Screen Real-TM Quant 2x kit (Sacace, Biotechnologies, Italy) was used for genotyping high-risk HPV types. Four hundred and sixteen (416) of 1,077 (38.6%) women were monitored for an average time of 18 months (inter-quartile range 9.6-26.6). Forty-three (43) women had incident HPV infections during 214 person-years of follow-up reflecting an incidence rate of 20.1 per 100 person-years. Incident HPV infections were marginally associated with HIV positivity (RR = 3.0, 95% CI: 0.8 - 8.2) and usage of oral contraceptives (RR=2.6, 95% CI: 1.4 - 2.8) but not with the age of study subjects, or number sexual partners. Clearance for high-risk HPV infections was frequently ranging between 37.5% and 100.0% for high-risk types. Only 41.3% of women cleared all their infections. Clearance was associated with HIV negativity (Adjusted clearance = 0.3, 95% CI: 0.2 - 0.8) but not with age at study entry or oral contraceptive usage. Incident HPV infections and clearance of HPV type-specific infections were common among study participants. We also found a high prevalence of high-risk HPV types in cervical lesions, which reveals an association between cervical lesions and high-risk HPV types.

Keywords: Human papillomavirus; Cancer of the cervix; Incidence; Multiple infections

1. Introduction

Clinical and epidemiological studies have established that high-risk HPV genotypes are the main etiological agents for cervical cancer development [1,2] and cancer-related deaths in women worldwide [3]. Studies conducted over the past decade have clearly shown that HPV infection precedes the development of cervical cancer and have confirmed that sexual transmission is the predominant mode of HPV acquisition.

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Globally, the estimated HPV prevalence among women is 11.7%, which shows some variation worldwide between 10 and 25%; the rates are higher for women in Africa, Eastern Europe, and Latin America[4,5]. Overall, approximately 70% of cervical cancers are associated with either HPV type 16 or 18. Other tumorigenic serotypes include HPV 52, 31, and 58 [6,7]. In Uganda, High-risk HPV types are particularly rampant among sexually active women infecting half of the women aged 12-24 years[8]. It has been estimated that, 33.6% of women in Uganda are infected with human papillomavirus, and that 47.5 per 100,000 women every year develop cervical cancer [7,9]. Most infections in young women with or without cervical abnormalities are described as being transient [10] as approximately 90% of women cleared a specific type of HPV within 24 months [8,11].

Presently, cervical cancer-related studies that were previously conducted involved selected groups, and small numbers[12], and they are not sufficient enough to provide data on the burden of type-specific HPV incidence, lesion clearance, and biomarkers of HPV to the general population in Uganda. Yet this information is crucial and important to support the implementation of HPV vaccination and cervical cancer screening programs among women in Uganda [13].

The current study was aimed to determine incidence and clinical spectrum of lesions induced by high-risk oncogenic HPV types among study participants in Eastern Uganda .The finding of the study will serve as a national baseline data to support the implementation of HPV vaccination and to help in planning for cervical cancer screening programs in Uganda by providing data on HPV incidence, lesion clearance, and biomarkers of HPV infections in a cohort of Ugandan women aged 15-55 years.

2. Material and methods

2.1 Study area

This study was conducted at selected regional referral hospitals in Eastern Uganda. These hospitals include; Tororo, Mbale, Butalejja, Kumi, and Soroti referral hospitals Fig.1.

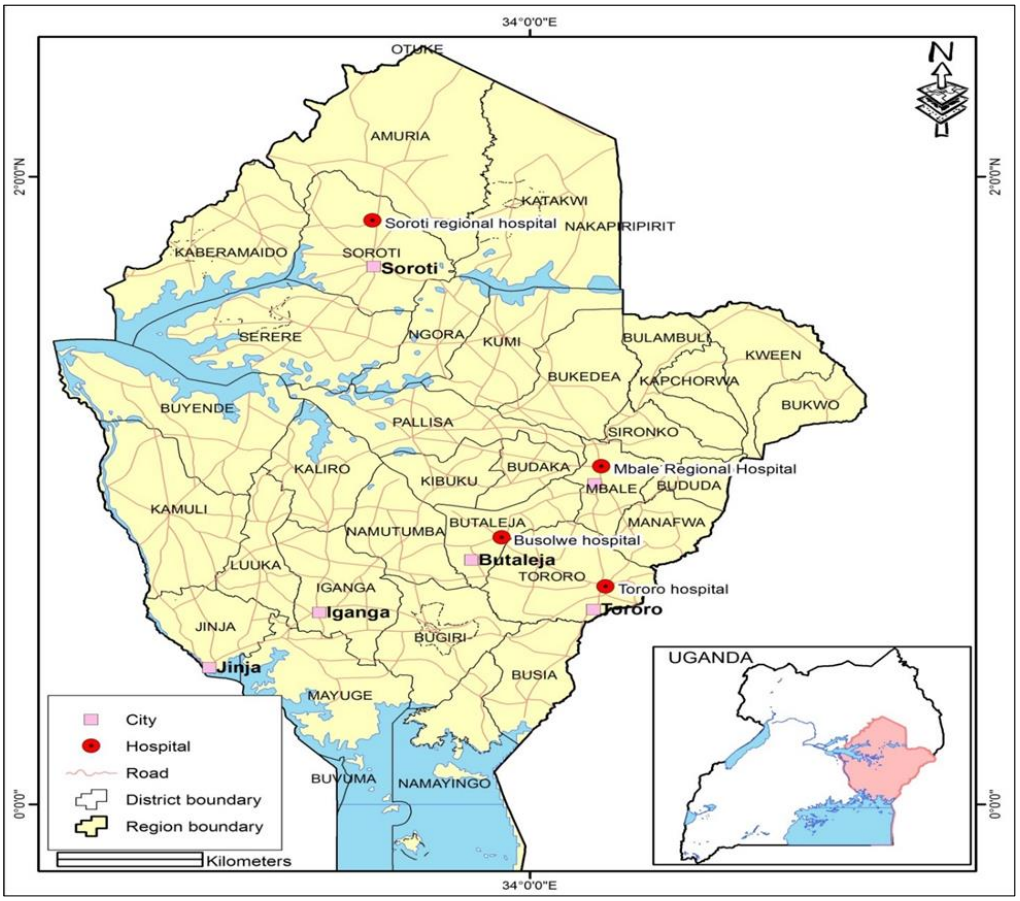

Figure 1 Map of Eastern Uganda indicating regional hospitals for this study: nationsonline.org(28)

2.2 Study population and follow-up visits

Women were recruited and followed up between September 2017 and March 2020 as was previously described by [8]. Participants aged 15-55 years and presenting themselves for health services at the regional hospitals of Mbale, Tororo, Butaleja, and Soroti were invited to take part in the study. Follow-up visits were scheduled between 6-12, 13-18, and 19-24 months from baseline.

2.3 Gynecological examination and collection of clinical materials

After meeting with the patients, written informed consent was obtained and a brief oral questionnaire was administered. Two nursing sisters, who had been trained in DVI of the cervix, and Papanicolaou (Pap) smear, performed a gynecologic examination onsite. In all visits after visual inspection of the vulva, a non-lubricated sterile speculum was inserted, and cervical exfoliated cells were collected. In this study, 183 cervical scrapes from women with cervical cancer were obtained by performing a 360º rotation of the transformation zone by using a sterile swab (Copan International) which was then placed in a labeled 15 mL holding tubes containing 5 mL of phosphate-buffered saline (PBS), pH 7.2; samples were kept temporarily at 4°C for an average of 6 hours and then transferred to a freezer for storage at -20°C until transportation to the laboratory for HPV analysis.

2.4 HPV-DNA extraction

The DNA-Sorb-A DNA isolation kit was used for DNA isolation (Sacace Biotechnologies). The extracts were therefore decanted and disposed of without affecting the pellets. For every vial, a different tip was used. Every vial was then aggressively vortexed, cleaned with 500 µl of wash buffer, and swirled for a half minute at 10,000 g. The extract was again decanted and segregated. After repeating the aforementioned steps, the extra wash buffer was dried from the opened capped vials by incubating them at 65°C for 5–10 minutes. After being homogenized in 100 l of DNA-eluent, the Genetic material particulate was maintained at 65°C for five minutes while being repeatedly vortexed. The vials were further agitated for one minute at 12000 g, and DNA was recovered within the extract. This was either utilized right away or pre-used after storage at -20 Celsius.

2.5 PCR amplification

Real-Time PCR was used quantitatively to detect the 12 pathogenic HPV types (serotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) in the samples provided. E1 and E2 sections were mostly the main areas of target by polymerase chain reaction. The PCR mix of 15ul was added to 10 µl of the isolated genetic material. Amplicons for the targeted high high-risk HPV-types were present the PCR-mix. Reagents were blended by striking the vials, and together with the prepared positive and negative controls by the kit manufacturer were loaded into the PCR (Rotor-Gene Q, Qiagen, German). The amplification conditions were set up in accordance with the directions provided by the kit's supplier . The specimen was regarded to be satisfactory when the fluorescence signal of (Ct≤33) was observed.

2.6 Ethics approval and consent to participate

Ethical approval for this sstudy was obtained from the Uganda National Council for Science and Technology (No. HS2246). The significance of this research was clearly explained to study participants, and written informed consent from each participants was obtained prio to the study.

2.7 Data management and statistical analyses

Stata version 11 for Windows was used to analyze the data. The Kaplan-Meier approach was used to estimate the prevalence of high-risk HPV types at enrolment as well as those who remained positive at various points after enrolment. Incidence and clearance was investigated in all study participants screened more than once. From the first time, a woman tested negative until a positive test or the last visit, the risk period for each HPV type or combination set of HPV types was assessed for incidence analysis. The incidence of the high-risk HPV types was computed for women who were free of all infections until at least one of the HPV types was detected. Similarly, clearance was estimated for all women who were infected with at least one HPV type until they were free of infection from all HPV types in the cohort. We utilized Poisson regression to calculate relative risk (RR) for HPV incidence and clearance by separating the follow-up time into 6-month intervals for risk period and occurrences.

3. Results

3.1 Characteristics of the Cohort

Table 1 shows the demographic and reproductive patterns of the study subjects in the respective study hospitals in Eastern Uganda. Of the 1,077 women recruited at the beginning of the study, only 416 (38.6%) women had at least one follow-up visit. The time between visits was highly variable. The median time of follow-up visit was 18 months, with an interquartile range of 7.5-25.5 months.

Table 2 shows the Prevalence of HPV infections at enrolment and the cumulative positivity for each HPV type among 416 women with up to 3 follow-up visits between September 2017 and March 2019. The overall prevalence of high-risk HPV types at enrolment was 21.2% (43 positive cases) with a cumulative positive rate of 30.3%. The point prevalence of HPV infection at each subsequent follow-up visit varied little: 20.2%, and 10.1% for visits 2–3, respectively. The most common high-risk types cumulatively detected in descending order were HPV 16 (n = 47, 11.3 %), HPV 18 (n = 31 ,7.5%), HPV 31 (n = 13 ,3.1%), HPV 33 (n=16,3.8%), HPV 52(n=12,2.9%), and HPV 45(n=6,1.4%. Cumulatively, (30.3%) high-risk HPV types were frequently detected. Single infections occurred more frequently (27.4%) than multiple infections (1.0 %).

3.2 Incidence of HPV Infections

Table 3 shows Type-specific HPV incidence, clearance, and rates per 100 person-years for groups according to oncogenicity followed up between September 2017 and March 2019. Forty-three women had an incident HPV infection during 214 person-years of observation, reflecting an incidence rate of 20.1 per 100 person-years. Type-specific incidence rates ranged between 0.4 and 3.2 per 100 person-years of observation for high-risk HPV types studied. Incident high-risk HPV types had a slightly lower rate of 20.1 per 100 person-years than were single incident HPV infection rates with 21.1 per 100 person-years, but multiple HPV infections had the lowest rate of 1.0 per 100 person-years of observation. Incident HPV infections were marginally associated with HIV positivity (RR= 3.0, 95% CI: 0.6 - 8.2) and usage of oral contraceptives (RR=2.6, 95% CI: 1.4 -- 2.8) but not with the age of study subjects, or number sexual partners, (Table 4).

3.3 Clearance of HPV Infections

Overall, 83 women with high-risk HPV infections cleared their infections during 201 person-years of observation reflecting complete clearance for all HPV types of 41.3% (Table 3). Clearance for HPV type-specific infections was frequent ranging between 37.5% and 100.0% for high-risk types. Women with single-type high-risk infections (43.5%) cleared their HPV infections as much as those with high-risk multiple infections (50.0%). Clearance was associated with HIV negativity (Adjusted clearance = 0.2, 95% CI: 0.1 - 0.8), but not with the age of study subjects, number of sexual partners, or use of oral contraceptives. Incident HPV infections were common in both HIV-positive (rates between 2.3 and 14.5 per 100 person-years) and HIV-negative women (rates between 0.9 and 4.3 per 100 person-years) [Data not shown]. The risk of high-risk HPV types (RR = 2.2, 95% CI: 1.1 - 5.3) was of statistical significance among HIV positive compared to HIV negative women. No difference was observed in risk for multiple infections (RR = 2.3, 95% CI: 0.8 - 7.8) compared to HIV-negative women.

3.4 Incidence of HSIL Infections

One hundred and forty-two (34.1%) of the 416 women with at least one or two follow-up periods were studied. Thirty--seven (37) of 142 (26.1%) developed HSILs between the study entry period and the first follow-up (Table 5). Incident HSILs infections were more predominant in women infected with HPV 16 and HPV 18 as opposed to women not infected with those types (RR = 3.4,95% CI: 1.0 - 10.4), and (RR = 2.2,95% CI: 0.3 - 12.2 respectively) even though the variation was slightly statistically insignificant.

Table 1 Socio-demographics of studied participants to their histological conditions

Histological diagnosis, N (1,077) women					
Characteristics	**Normal (n =661)**	**ASCUS (n =125)**	**LSIL (n =114)**	**HSIL (n =94)**	**INV.CANCER (n=83)**
Type of hospital					
Mbale hospital	165(25.0)	40(32.0)	34(29.8)	30(31.9)	28(33.7)
Butaleja hospital	119(18.0)	34(27.2)	30(26.4)	24(25.5)	13(15.7)
Tororo hospital	309(46.7)	36(28.8)	21(18.4)	18(19.2)	18(21.7)
Soroti hospital	68(10.3)	15(12.0)	29(25.4)	22(23.4)	24(28.9)
Age group (years)					
15-24	169(25.5)	18(14.4)	30(26.3)	6(6.4)	11(13.3)
25-34	210(31.8)	33(26.4)	34(29.8)	22(23.4)	18(21.7)
35-44	198(30.0)	40(32.0)	28(24.6)	32(34.0)	24(28.9)
45-55	84(12.7)	34(27.2)	22(19.3)	34(36.2)	30(36.1)
Education level					
None	144 (21.8)	33(26.4)	18(15.7)	15(16.0)	24(28.9)
Primary	261(39.5)	36(28.8)	32(28.1)	25(26.6)	28(33.7)
Secondary	180(27.2)	25(20.0)	36(31.6)	28(29.8)	18(21.7)
Graduate	76(11.5)	31(24.8)	28(24.6)	26(27.6)	13(15.7)
Marital status					
Single	214(32.4)	28(22.4)	28(124.6)	16(17.0)	16(19.3)
Married	115(17.4)	34(27.2)	34(29.8)	24(25.5)	28(33.7)
Widowed	271(41.0)	35(28.0)	34(29.8)	26(27.7)	27(32.5)
Divorced	61(9.2)	28(22.4)	18(15.8)	28(29.8)	12(14.5)

ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL high-grade squamous intraepithelial lesion/cancer

Table 2 Prevalence of human papillomavirus (HPV) genotypes at enrollment and Cumulative positivity of HPV types among 416 women with 3 follow-ups between September 2017 and March 2019 in Kampala, Uganda

High-risk HPV Types	**Prevalence at Entry (%)**	**Cumulative Positivity (%)**	**Positive Once (%)**	**Positive ≥ 2 Visits (%)**
HPV 16	36 (8.7)	47 (11.3)	39 (9.4)	8 (1.9)
HPV 18	24 (5.8)	31 (7.5)	25 (6.0)	6 (1.4)
HPV 31	7 (1.7)	13 (3.1)	10 (2.4)	3 (0.7)
HPV 33	10 (2.4)	16 (3.8)	12 (2.9)	4 (1.0)
HPV 45	3 (0.7)	6 (1.4)	4 (1.0)	2(0.4)
HPV 52	6 (1.4)	12 (2.9)	8 (1.9)	4 (1.0)
Type 16/18	1 (0.2)	2 (0.4)	2(0.4)	0 (0.0)
Type 18/33	1 (0.2)	1 (0.2)	1(0.2)	0 (0.0)

Number of women with:				
High-risk HPV types	88 (21.2)	126 (30.3)	84 (20.2)	42 (10.1)
Single HPV infections	86 (20.7)	114 (27.4)	74 (17.8)	40 (9.6)
Multiple infections	2 (0.4)	4 (1.0)	3 (0.7)	1 (0.2)

Table 3 Type-specific HPV incidence, clearance and rates per 100 person-years for groups by oncogenicity

	Incidence			**Clearance**		
HPV Types	**Incident Cases**	**Person Years**	**Incidence Rate per 100 p. yrs**	**No. Women Cleared**	**Person Years**	**Clearance Rate per 100 p.yrs**
High-risk HPV types						
HPV 16	14	438	3.2	41	58	70.7
HPV 18	8	400	2.0	45	58	77.6
HPV 31	5	217	2.3	7	9	77.8
HPV 33	8	307	2.6	8	8	100.0
HPV 45	2	333	0.6	3	8	37.5
HPV 52	4	400	1.0	5	16	31.3
Type 16/18	1	125	0.8	2	1	100.0
Type 18/33	1	250	0.4	1	1	100.0
Number of women with						
High-risk HPV types	43	214	20.1	83	201	41.3
Single infections	41	194	21.1	74	170	43.5
Multiple infections	1	214	0.5	2	4	50.0

Table 4 Risk factors for HPV incidence and clearance among the study participants between September 2017 to march 2019

Incidence					**Clearance**			
Baseline Characteri-stics	**No. Study participants (%)**	**Time at risk (PYS)**	**Rate per 100 p.yrs**	**RR (95%CI)a**	**No. Study participants (%)**	**Time at risk (PYS)**	**Rate per 100 p.yrs**	**RR (95%CI)a**
Age (yrs) at study entry								
≥35	84 (51.2)	124	24.6	1 (ref.)	122 (47.7)	74	9.5	1 (ref.)
25 -- 34	58 (35.4)	86	27.9	1.2 (0.6 -- 2.2)	106 (44.4)	62	8.1	1.2 (0.7 -- 2.0)
15 – 24	22 (13.4)	33	42.4	2.1 (1.1 -4.4)	28 (10.9)	14	0	2.2 (1.0 -4.5)
Have multiple sex partners								

One	52 (31.7)	76	31.6	1 (ref.)	62 (24.2)	34	8.8	1 (ref.)
Two	42 (25.6)	62	27.4	0.8 (0.5 -- 1.4)	76 (29.7)	42	11.9	0.8 (0.5-1.4)
Three	36 (22.0)	53	34.0	1.5 (0.7 -- 2.8)	58 (22.7)	43	2.3	0.8 (0.4-1.4)
Four or more	34 (20.7)	50	28.0	1.1 (0.6 -- 2.4)	60 (23.4)	32	9.4	1.0 (0.6-1.6)
HIV status								
Negative	136 (82.9)	201	25.9	1 (ref.)	238 (93.0)	133	8.3	1 (ref.)
Positive	18 (11.0)	27	44.4	3.0 (0.6 - 8.2)	14 (5.5)	0	0	0.2 (0.1-0.7)
Unknown	10 (6.1)	15	26.7	2.4 (1.3 -- 2.7)	4 (41.5)	6	0	-
Use of contraceptives								
Two Years	94(57.3)	139	34.5	1 (ref.)	32 (12.5)	12	16.7	1 (ref.)
Two years	46(28.1)	68	39.7	2.6 (1.4 -- 2.8)	94 (36.7)	52	5.8	0.4 (0.2-1.0)
Two or More years	24(14.6)	36	36.1	2.3 (1.3 -- 2.6)	130 (50.8)	368	7.9	0.5 (0.3-1.1)

Key: CI, Confidence Intervals; p. yrs, person-years

Table 5 HSIL incidences among women with abnormal cytology followed up between September 2017 and March 2020 in Kampala, Uganda

HPV type	**No. of women**	**Incident HSIL**	**Person years**	**Incidence rate per 100 p. yrs**	**Crude RR (95% CI)a Infected/noninfected**	**p-value**
HPV 16						
Non-infected	138	19	118	16.1	1	
Infected	4	1	10	10	3.4 (1.0 -- 10.4)	0.05
HPV 18						
Non-infected	136	16	103	15.5	1	
Infected	6	1	3	31.3	2.2 (0.3--12.2)	0.44

Abbreviations: CI, Confidence Intervals; P. Yrs, Person--Years

4. Discussion

This study was a hospital-based analysis of type-specific HPV infection with high-risk types among women aged 15 to 55 years in Eastern Uganda. The research identified type-specific HPV incidence, clearance, and clinical spectrum of cervical lesions associated with high-risk oncogenic HPV genotypes, their severity, and their relation to cervical neoplasia in patients receiving healthcare services at selected health facilities in Eastern Uganda.

Our study observed a high incidence of HPV infections of 20.1 per 100 person-years of follow-up. These observations were similar to findings previously described by [14,15] who reported an incidence rate of 18% in women with high-grade lesions, [14] and of 11.1% -25% [15] in genital specimens respectively. Higher incidence rates of 30.5 per 100 person-years than identified in our analysis [16] have been reported among young women in Uganda, whereas a lower incident rate of 4.2 [17] has also been recorded in Taiwan. The observed variation in high-risk HPV incidence could be attributable to differences in the diagnostic period, time of follow-up, and a group of study subjects investigated.As was observed in our study, incident HPV infections were highly dependent on the patient's HIV serostatus. This was in line with studies reported by [15,16] which showed that patients infected with HIV were twice more likely to have incident HPV infections than HIV-negative patients. Our present study also showed that there was a statistically significant association between incident HPV 16 and HPV18 infections among HIV-positive patients. A survey study conducted in a rural setting in Uganda, [18] reported the incidence of HPV 16 and HPV 18 to be three times in women infected with HIV than in seronegative HIV women. The sample demographic included in their survey comprised both teenage and elderly women aged 15 to 55 years, which may explain the disparity between our results and other studies.

Nevertheless, our current study's small sample size may have hampered our capacity to discern the difference. Even with the narrow age bracket of the study participants in our analysis, we noticed an elevated high-risk HPV incidence which was consistent with other experiments with a wider age range [19].

Furthermore, our study reported clearance for high-risk HPV infections ranging between 37.5% and 100.0% for high-risk types, somewhat lower than a clearance ranging between 42.3% and 100.0% for high-risk HPV infections observed in a cohort study [16] performed among young women in Uganda. In their study [16] HPV infection clearance of 31.2% was observed among the study participants as compared to a 41.3% clearance observed in our current analysis. The observed variation could be attributed to the differing HPV DNA identification techniques utilized in the previous analysis as opposed to that used in our study, as well as the age distribution of the women investigated. Clearance was highly linked to HIV seronegativity but not to the ages of study participants at study entrance, or other infections at the start of follow-up. Numerous variations in the clearance of HPV infections [20,21] have been observed across many studies. In some it has been observed that women with multiple sexual partners have much lower HPV infection clearance, which might be due to previous exposure or previous disease reactivation. This phenomenon was not observed in our present study possibly because of the age range of the study participants included in our study. In our study, HPV infection clearance of 41.3% was observed at the end of the study follow-up period of 18 months. Our time range was sufficient for a patient to completely recover/clear or get reinfected with either a new or similar HPV type. It could be that the observed clearance of study participants in our research was due to incident infections acquired after the baseline infection, and not due to persistent previous infections.

In our present study, LSIL, and HSIL were all commonly associated with the identification of type-specific high-risk HPV types, the strongest associations were noticed between HSIL/cancer and the diagnosis of high-risk HPV types, as has been reported in previous studies [22,23]**.** The high incidence of HPV infections in HSIL/cancer suggests that many older women already had their cellular alterations and could be harboring persistent HPV types. The decrease in the prevalence of HSIL/Cancer from 7.4% to 6.8% between the first and second visits in study subjects who contributed two or more acceptable specimens for cytologic examination highlights the persistent characteristics of infection with HPV- types in association with cervical lesions in older women. As a result of our findings, cytologic screening for cervical malignancies in women of average age is more likely to reveal high-grade cervical abnormalities as opposed to low-grade cervical lesions in young women [8]. Based on current knowledge of the typical progression of HPV infection and the lesions it causes in the cervical region, appropriate interventions such as follow-up accompanied by medical procedures may be recommended in older women with HSIL/Cancer. Subsequently, testing accompanied by HPV analysis should be strongly adhered in older women since many of them are HPV positive, as seen by the cumulative HPV results. Furthermore, we also observed that HPV16 and HPV18 were the two HPV types most closely linked with HSIL/cancer, as single or multiple HPV infections. Strangely, whereas HPV16 and HPV18, were predominantly detected in HSIL/cancer samples (31.6 percent, and 19.5%, respectively), more than half of study subjects with such pathology were also diagnosed positive for other HPV types. Our findings of a high risk of cervical abnormalities associated with HPV16, and HPV18 are consistent with those from a recent study in China which found that HPV16 and HPV18 were the most prevalent subtypes identified in patients with cervical intraepithelial neoplasia[24,25]. The prevalence of HPV 16 and HPV18 and their interaction with HSIL/cancer tend to vary among different study populations [2]. Different HPV types will likely predominate in a given population either because of the random incorporation of a particular HPV type into that population, or because of the specialized ability of such HPV types to support endemic infections in a specific geographical area. It is indeed also possible that regional-related sequence variations for a particular HPV type might modify its neoplastic ability, leading to different risk associations in diverse populations. It is also likely that HLA polymorphisms detectable in different populations might influence the likelihood of HPV persistence and cervical neoplasia progression by modifying the immune response to complex HPV-encoded epitopes[26,27].

Our study had several advantages. It utilized a very sensitive real-time PCR kit for high-risk HPV detection to unravel HPV infections among women in Eastern Uganda. Low HPV detection was well managed in our investigation due to the excellent sensitivity of the PCR kit. However, one limitation of our study was that our cohort had a narrow age range, consisting of only women aged 15 to 55. The incidence rates presented in this study are estimates that might be influenced by the HPV history of the cohort participant before enrolment since we did not include women who had never had sexual intercourse. We were unable to investigate the acquisition and clearance of diverse infections due to the small number of cohort participants.

5. Conclusion

There is a need for more statistics from cohort studies, especially studies that have a broad age group which includes women with the variable risk of cervical cancer since there are only a few articles that offer data on rates of acquisition

and clearance of HPV infections. More data is also needed to determine effective procedures for identifying women who clear infections, as well as the eligibility of women to be included in incidence estimates before enrolment. Furthermore, PCR primers and genotyping techniques with variable sensitivities for high-risk HPV detection are needed. Lastly, the natural history of HPV infection in males must be clarified to properly comprehend the dynamics of HPV infection in women. Because the high incidence of high-risk HPV and high-grade cervical dysplasia in women after one cycle of high-risk HPV-based screening and treatment raises concerns regarding the likelihood of progression from high-risk HPV infection to dysplasia, caution is advised when spacing cervical cancer screening intervals using high-risk HPV testing in women.

Compliance with ethical standards

Acknowledgments

The authors thank the medical staff of Mbale regional referral hospital, Butalejja-Busolwe hospital, Tororo hospital and Soroti regional hospital for their technical assistance during the screening period. We consequently thank the entire study participants who provided consent for this study. We also thank the village health officers who helped our study team during the follow up of the participants.

Disclosure of conflict of interest

The authors declare that they have no competing interest in this work.

Statement of ethical approval

The ethical approval was obtained from Kampala International University Western campus (KIU), and Mbarara University of Science and Technology (MUST) Institutional Research and Ethics Committee (IREC) on Human Research (Approval No. 06/01-17) and Uganda National Council for Science and Technology (Approval No. HS2246).

Statement of informed consent

A written consent to participate in the study was mandatory, and was obtained from all study participants aged (15-55) years before the screening exercise. Surprisingly, among the study participants who turned up for the study, there was no one below sixteen years of age (<16years). For this reason, the parental consent prepared for study participants below sixteen years of age was never used.

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