ORIGINAL ARTICLE

Human papillomavirus positivity and cervical lesions in relation to HIV infection: a comparative assessment in the Cameroonian female population

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DOI: 10.4081/jphia.2023.2334

Abstract. Cervical lesions, induced by high-risk oncogenic human papillomavirus (HR-HPV), in the context of HIV remains a global health challenge. We determined the effect of HR-HPV on the development of cervical lesions in women with and without HIV infection. A cross-sectional analytical study was conducted among 257 women living in Cameroon. HIV serology, HR-HPV genotyping and cervico-vaginal smear (CVS) were performed for all participants; among those declared HIV positive, plasma HIV viral load and CD4 count were measured. Statistical analyses were performed using Graph Pad version 6.0; P<0.05 was considered statistically significant. The mean age of the participants in our study was 37±6.5 years. According to HIV serology, 184 (71.59%) were HIV-positive vs. 73 (28.40%) HIV-negative. Among the HIV-positive women, the median CD4 count was 438 [IQR: 317-597] cells/mm3 and the median viremia was <40 [IQR: <40-2318] copies/ml. After successful genotyping, the prevalence of HR-HPV was 36.32% (73/201), with a significantly higher proportion in HIV-infected individuals (41.98% (55/131) vs. 25.71% (18/70); P=0.02; OR=2.1). The overall rate of cervical lesions was 23.34% (60/257), with a non-significantly higher proportion in HIV-infected participants (25.00% (46/184) vs. 19.17% (14/73); P=0.31). Relevantly, the presence of HR-HPV was significantly associated with cervical lesions (P<0.0001; OR=5.07), with a higher odds of cervical lesion in HIV-positive individuals (P<0.0001 and OR=5.67) compared to HIV-negative individuals (P=0.03 and OR=3.83). Although oncogenic HPV appears to be an independent factor in the development of cervical lesions, this study reveals higher odds of cervical lesions among HIV/HPV co-infection than in HPV infection alone.

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Key words: CVS, HR-HPV, HIV, Cameroon

Background

The burden of disease in sub-Saharan Africa is still driven by infectious pathogens, with a gradual increase of non-communicable diseases (NCDs) (1) largely dominated by interaction between communicable and NCDs (2). One of such common disease is cervical cancer, a NCD caused by human papillomavirus (HPV). The prevalence of cervical cancer varies depending on the geographic location; with poor countries always bearing the highest burden (3,4). Cervical cancer is caused primarily by so-called high-risk oncogenic HPV genotypes (HR-HPV) (5), with genotypes 16 and 18 being predominantly found in most cervical cancers occurring worldwide (6,7). In 2018 the number of new cases was estimated at 570,000 globally, with approximately 90% of the cases occurring in developing countries (8,9). Thus, if no further

action is taken, the annual number of new cases of cervical cancer is expected to increase to 700,000 between 2018 and 2030, while the annual number of related deaths is expected to rise from 311,000 to 400,000 (10,11). In sub-Saharan Africa, most cervical cancers are associated with persistent HR-HPV infection, with more than 75,000 new cases and nearly 50,000 deaths occurring each year (12), indicating higher burdens of HPV and cervical cancer in this part of the globe (13,14).

Driven factors of cervical cancers are the aging of women (15), as well as HIV infection; the later leading to a decrease in the number and function of TCD4+ lymphocytes (16-18). Because failure in the immune system gives room to the occurrence of infections, HIV-infected women have a significantly higher risk of developing invasive cervical cancer (19,20). Of note, HPV infections are more likely to persist in HIV-positive women, thereby contributing substantially to a higher risk of HPV infection and a higher risk of squamous intraepithelial lesions among women (21,22). This is particularly true in case of co-infection with HIV as the latter may serve as a cofactor in the carcinogenesis associated with HPV-HR infections, characterised by an estimated 8-fold risk in HIV-infected women (16,23), or the presence of other favouring conditions of co-infections or comorbidities (24,25).

According to previous authors, cervical cancer is inevitably preceded by cervical lesions (22,26), often driven by the presence of HPV and worsen by HIV/HPV co-infection especially in settings with high burden of these infectious diseases (27-29). We therefore sought to determine the effect of HPV on the occurrence of cervical lesions among women living with HIV (WLHIV) compare to their HIV-negative peers in Cameroon.

Materials and methods

Study design and setting. A cross-sectional study was carried-out in 2016 among women attending the General Hospital or the Gyneco-obstetrical and Paediatric Hospital of Yaoundé, Cameroon. The exams were performed at the Chantal BIYA International Reference Centre for research on HIV/AIDS prevention and management (CIRCB) in Yaoundé, Cameroon (http://circb.cm/btc_circb/web/).

Sampling strategy. Following a convenience sampling method, a total of 257 women were enrolled. Eligible women (sexually active, aged 18 years and older) who provided informed consent were enrolled in the study. However, any eligible women who were found to be pregnant or who had undergone total hysterectomy were not included in the study. After giving consent, a standard questionnaire was administered to all participants, covering socio-demographic characteristics, gynaeco-obstetric and reproductive history. Whole blood and cervical samples were then collected (30).

HIV screening tests. HIV screening was performed following a two-steps serial algorithm as per the national guidelines of Cameroon (31).

HIV viral load. Whole blood for each patient was performed to obtain plasma, which was used for viral RNA extraction and amplification/detection for plasma viral load by Real-Time PCR on the abbott m2000RT platform as per the manufacturer's instructions. (www.abbottmolecular.com/products/infectious-diseases/realtime-pcr/hiv-1-assay).

CD4 lymphocyte counts. Whole blood from EDTA tubes for each participant was used to perform the enumeration of CD4 T lymphocyte count using flow cytometry on the FACSCalibur®, as previously described (www.bdbiosciences.com/en-us/instruments/clinical-instruments/clinical-cell-analyzers).

HPV genotyping. For HPV genotyping, the Abbott Real Time HR-HPV test was used according to the manufacturer's instructions (www.molecular.abbott/int/en/products/infectious-disease/realtime-high-risk-hpv).

Cervical smear. Slides for the cervico-vaginal smear (CVS) slides were prepared using the standard *Papanicolau* staining protocol (http://www.ihcworld.com/_protocols/special_stains/papanicolaou_stain.htm). Interpretation of slides was done by specialised pathologists, as per the Bethesda 2001 guidelines (32).

Statistical analysis. Data were collected using Excel 2016, and analyses were performed using Epi-info version 7 and Graph pad prism version 6. Odd ratio (OR) was calculated to determine the odd of cervical cancer according to the presence or absence of HPV. The confidence interval (CI) for the statistical tests was set at 95%, and Chi square or Fisher-Exact tests were used whenever appropriate, with a significant threshold set at 5%.

Ethics considerations. Ethical clearance was obtained from the CIRCB Ethics Committee (ref N°1810), and administrative authorization was provided by health facilities where the study was conducted. All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was provided by each participant, and results were delivered free of charge to participants for their clinical benefits.

Results

Socio-demographic and basic characteristics of the study population. A total of 257 women participated in this study. The mean age of our study population was 37±6.5 years (36±2.80 years for WLHIV vs. 42±8.48 years for HIV-negative women). The most frequent age group was [30-39] years representing 44.30% of the study population. According to serological status, 71.59% (184/257) of the women were seropositive compared to 28.40% (73/257) of seronegative women. According to marital status, single women were the most represented with 52.14% (134/257), followed by married women with 34.24% (88/257), widows with 10.11% (26/257) and finally divorced women with 3.50% (9/257).

Immune status and HIV viral load of WLHIV. Out of the 184 WLHIV recruited in this study, 64.67% (119) had a CD4 count. 40.33% (48/119) were immunocompetent (CD4 ≥500) and 59.67% (71/119) immunocompromised (CD4 <500). The median CD4 count was 438 [IQR: 317-597] cells/mm3.

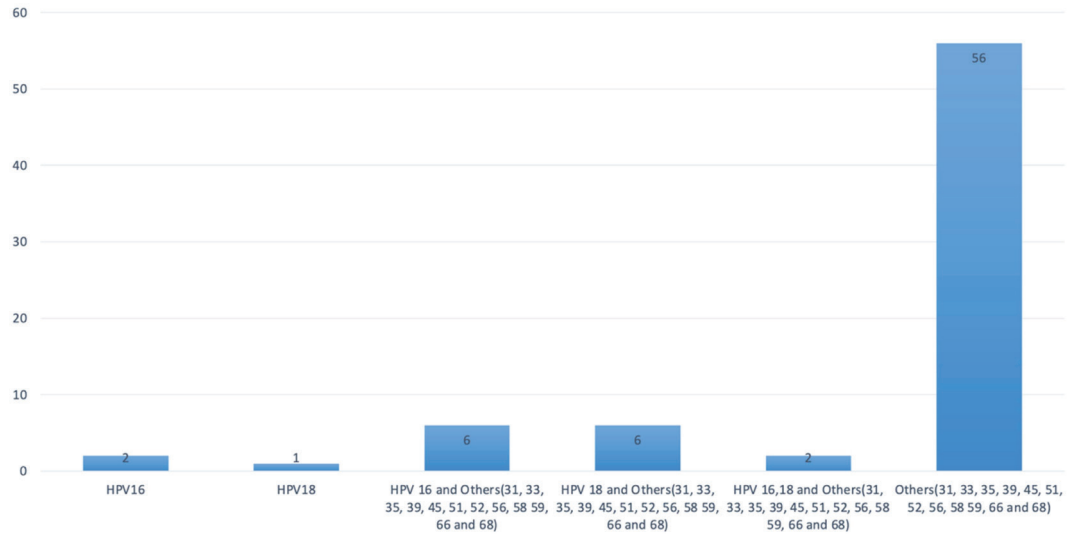

Figure 1. Genotypic diversity of HPV-HR.

Regarding HIV viral load, 82.60% (152/184) had undergone viral load testing of which 105/152 (69.08%) had a viral load <1,000 copies/ml and 30.92% (47/152) a viral load ≥1,000 copies/ml. The median viremia was <40 [IQR: <40-2318] copies/ml.

Distribution of high-risk oncogenic HPV in the study population. Overall, 78.21% (201/257) of CVS samples were successfully HPV-genotyping. Out of these 201 samples, 36.32% (73/201) were found with HR-HPV genotypes, among which HPV16 and HPV18 could be discriminated and the 12 other genotypes were detected but not discriminated (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). Fig. 1 gives a breakdown of the distribution of these genotypes among the study population.

Following socio-demographic characteristics, neither the age nor the marital status were found associated to HR-HPV positivity (P=0.11 and P=0.14, respectively). There was a significant association between HR-HPV and HIV-status (41.98% vs. 25.71% among HIV-positive and HIV-negative women respectively; P=0.02). Moreover, HIV-positive participants with low CD4 count (<500 cells/mm^3) were 2.33 times more likely to be co-infected with HR-HPV than those with higher CD4 (P=0.04). However, a slightly higher proportion of HR-HPV was found among women with a high HIV plasma viral load (67.6%) as compared to those with low viral load (49.2%), though not statistically significant (P=0.07). details are reported in Table I.

Distribution of cervical lesions in the study population. According to the profile of CVS from our study population, the overall prevalence of cervical lesions was 23.3% (60/257), distributed by grade as follows: 31.74% (97) had a normal cytology result; 38.91% (100) were reported with inflammation; 16.34% (42) had low-grade squamous intra-epithelial lesion (LSIL); and 6.34% (18) had high-grade squamous intra-epithelial lesion (HSIL).

Following HIV status, 80.8% (59/73) HIV-negative participants did not have any cervical lesions and 19.2% (14/73) had lesions among which 2 HSIL; meanwhile in WLHIV 75.0% (138/184) participants did not have any lesions against 25% (46/184) with cervical lesions among which 8 HSIL (P=0.31); as shown in Table II.

Following socio-demographic characteristics, age and marital status were not found to be associated with the presence of cervical lesions (P=0.93 and P=0.15, respectively). Specifically, the presence of HSIL according to HIV-status showed a similar distribution: 7.61% (14/184) vs. 5.47% (4/73) among HIV-positive vs. HIV-negative, respectively (P=0.54). Within the population of HIV-positive women in particular, variations in CD4-cell counts or in plasma viral load were not found to be associated to cervical lesions (P=0.35 and P=0.91, respectively); as shown in Table II.

Association between HPV positivity, cervico-vaginal smear and HIV status. HR-HPV positivity was significantly associated with the presence of cervical lesions (P<0.0001; OR=5.07). Furthermore, HIV-positive women were about 6 times more at risk to be found with cervical lesions when co-infected with HR-HPV, whereas HIV-negative had about 4 times more risk (OR=5.67, P<0.0001 vs. OR=3.83, P=0.03; respectively) (Table III).

Discussion

In a context of high burdens of poverty-related diseases such as HIV and HPV, it would be of great importance to understand the potential interaction between HIV and risk of cervical cancer in the frame of this co-infection. This co-infection might lead to increased risk of cervical cancer in settings like sub-Saharan Africa.

Of 257 study participants, single women were the most represented (about half of the population), followed by married women. The mean age was 37 years old, and this goes in line with the range of the most sexually active female population locally (33); which explain their chronic exposure to sexually transmitted infections, including HPV. This age-group also outlines women's vulnerability towards HPV-infection as

Table I. Distribution of HPV-HR positivity in the study population.

	HPV Genotype			
	Presence of HPV-HR	Absence of HPV-HR	P-value (OR; 95% CI)	Total
Age	n (%)	n (%)		
<37 years	49 (41.0)	71 (59.0)		120
>37 years	24 (29.6)	57 (70.4)	0.11	81
Total	73 (36.3)	128 (63.7)	(1.63; 0.89-2.98)	201
Civil status				
Single women	42 (41.2)	60 (58.8)		102
Others	31 (31.3)	68 (68.7)	0.14	99
Total	73 (36.3)	128 (63.7)	(1.53; 0.86-2.74)	201
HIV-status				
hiv (+)	55 (42.0)	76 (58.0)		131
hiv (-)	18 (25.7)	52 (74.3)	0.02	70
Total	73 (36.3)	128 (63.7)	(2.09; 1.10-3.96)	201
CD4 count among HIV(+)				
<500	39 (62.9)	23 (37.1)		62
>500	16 (42.1)	22 (57.9)	0.04	38
Total	55 (55.0)	45 (45.0)	(2.33; 1.02-5.32)	100
Viral load among HIV(+)				
>1,000	23 (67.6)	11 (32.4)		34
<1,000	32 (49.2)	35 (53.8)	0.07	65
Total	55 (55.6)	44 (44.4)	(2.28; 0.96-5.42)	99

Table II. Distribution of cervical lesions in the study population.

	CVS profile			
	Presence of cervical lesions	Absence of cervical lesions	P-value (OR; 95% CI)	Total
Age	n (%)	n (%)		
<37 years	36 (23.5)	117 (76.5)		153
>37 years	24 (23.1)	80 (76.9)	0.93	104
Total	60 (23.3)	197 (76.7)	(1.02; 0.56-1.85)	257
Civil status				
Single women	35 (26.1)	99 (73.9)		134
Others	25 (20.3)	98 (79.7)	0.15	123
Total	60 (23.3)	197 (76.7)	(1.39; 0.77-2.48)	257
HIV-status				
hiv (+)	46 (25.0)	138 (75.0)		184
hiv (-)	14 (19.2)	59 (80.8)	0.3 1	73
Total	60 (23.3)	197 (76.7)	(1.40; 0.71-2.75)	257
CD4 count among HDV(+)				
<500	25 (35.2)	46 (64.8)		71
>500	21 (43.7)	27 (56.3)	0.35	48
Total	46 (38.7)	73 (61.3)	(0.69; 0.33-1.47)	119
Viral load among HIV(+)				
>1,000	13 (27.7)	34 (72.3)		47
<1,000	30 (28.6)	75 (71.4)	0.91	105
Total	43 (28.3)	109 (71.7)	(0.95; 0.44-2.05)	152

Table III. HPV positivity and cervico vaginal smear according to HIV status.

		CVS profile			
		Presence of cervical lesions	Absence of cervical lesions	P-value (OR; 95% CI)	Total
Overall		n (%)	n (%)		
HPV Genotype	HPV+	28 (38.3)	45 (61.6)	O.0001	73
	HPV-	14 (10.9)	114 (89.1)	(5.07; 2.44-10.50)	128
	Total	42 (20.9)	159 (79.1)		201
HIV(+)					
HPV Genotype	HPV+	22 (40.0)	33 (60.0)	O.0001	55
	HPV-	08 (10.5)	68 (89.5)	(5.67; 2.28-14.08)	76
	Total	30 (22.9)	101 (77.1)		131
HIV(-)					
HPV Genotype	HPV+	6 (33.3)	12 (66.7)	0.03	18
	HPV-	6 (11.5)	46 (88.5)	(3.83; 1.05-14.04)	52
	Total	12 (17.1)	58 (82.9)		70

described by Mboumba Bouassa *et al* in Chad, Sosso *et al* in Cameroon, and Obiri-Yeboah *et al* in Ghana who reported respectively 35, 37 and 44 years as mean ages where women were co-infected with HIV/HPV (16,34,35).

The overall HR-HPV positivity rate indicated that one out of three women are carriers of HPV infection within our communities. No association was found between socio-demographic parameters and HR-HPV positivity, suggesting that HR-HPV infection might not be driven by age or marital status. Interestingly, HR-HPV positivity rate was 2 times significantly higher among HIV-positive vs. HIV-negative women, thus inferring that HIV infection leads to a higher risk of HPV acquisition through immunodeficiency, irrespective of plasma viremia (9,36-40). This result is also consistent with previous studies conducted in South Africa wherein HIV-positive women were nearly 5-8 times more likely to have HR-HPV as compared to their HIV-negative peers (32,33).

More than half of study participants were found to have cervical lesions, though at varying grades. Similar to findings of Moodley *et al* in South Africa (41) no substantial association was observed between socio-demographic parameters and cervical lesions. On the same line, cervical lesions were similarly distributed between HIV-positive and HIV-negative women. Moreover, regarding CD4 cell count, WLHIV have similar frequencies of cervical lesions than their negative peers. Henceforth, the risk of acquiring cervical cancer among participants in this study was not significant in case of HIV co-infection. Our findings were dissimilar with Massad *et al* and Denslow *et al* who agreed on the fact that combination of HIV/HPV co-infection favors the predominance of cervical lesions in settings where the burden of these infectious diseases is high (20,42). These discrepancies could be first explained by our very small sample size in comparison to these previous studies. Secondly, our results could be mitigated by the fact that great majority of WLHIV in the present study had a mild immunodepression (median CD4: 438 cells/mm3) and had a control of the viral replication (median viremia: <40 copies/ml) (42,43).

Importantly, our results showed that the general population of HR-HPV-infected women were about 5 times more likely to have cervical lesions than those with normal cytology results. Interestingly, HR-HPV-co-infected WLHIV were about 6 times more likely to have cervical lesions, whereas HR-HPV-infected HIV-negative women were about 4 times more likely to have cervical lesions. These results show that there is no difference between these odds ratios, which is inconsistent with previous global reports (43-45), which have emphasized the need for routine cervical cancer screening in WLHIV (every two years) compared with HIV-negative women in whom screening is recommended every three years. WLHIV with well-controlled HIV may not necessarily be needing more screening than their HIV-negative peers (37). On the other hand, the results seem to suggest that the presence of several HPV types may behave differently in HIV-positive individuals and that this in turn may influence their role in the aetiology of cervical cancer, thus suggesting that progression to HSIL of HPV infection with normal cytology.

As limitation, the molecular technique used for HPV genotyping can only distinguish between HPV 16 and 18. Given the high circulation of other HR HPVs in our setting, a full characterisation of these genotypes (by sequencing, etc.) could be essential for the appropriate selection of an HPV vaccine candidate for the country. A cohort follow-up design would have allowed a better description of cervical cancer risk, which calls for further studies using this methodological approach.

Conclusions

Although oncogenic HPV appears to be an independent factor in the development of cervical lesions, our findings highlight on the fact that the risk of cervical lesions is significantly higher in HIV/HPV co-infection women in Cameroon. Prevailing grade of cervical cancers found were LSIL and HSIL, suggesting a substantial burden of precancerous conditions in the female population of Cameroon. Considering the generalised burden of HIV in such countries, prevention of cervical cancer should

be systematically implemented for women, given priority to those living with HIV-infection.

Acknowledgments

Some of these data were selected for a poster presentation at the 13th international Conference on HIV treatment pathogenesis (INTEREST 2019), Accra, Ghana (Reference number Poster 092). We would like to thank the CIRCB for giving us the opportunity to initiate this first stage of this major project.

Funding

The financial and material resources such as reagents, laboratory consumables and access to the various platforms for carrying out the biological analyzes of the samples was provides by CIRCB where analysis of samples and data has been heavily involved.

Availability of data and materials

The dataset is available from the corresponding author.

Contributions

SMS, MCTT, JF, RKS, ENJS, ZS, JT, AT, EEL, GA, AN, ADN, VT, CC, AA, ACK, NF, MKNZ, BY, SCB, VC, ANd, designed the study; MCTT, JF, ADN, VT, CC, ENJS, BY, analysed and interpreted the data; SMS, JF, RKS, MCTT, performed the HPV testing; VC, ANd managed all aspects of the study in Yaoundé; SMS, JF, supervised the performance of laboratory testing; JF, MCTT, SMS, drafted the manuscript. All the authors approved the final version to be published.

Ethics approval and consent to participate

This study obtained ethical clearance from the CIRCB Ethics Committee on the Project N^0 1810 and also authorization from CIRCB where the study was conducted. The participants freely signed informed consent forms, which were written in French and English (with respect to the first language of the participant), while the minor participants provided their assent.

Informed consent

Not applicable.

Conflict of interest

The authors declare no potential conflict of interest.

Accepted: 16, December 2022; submitted: 26, September 2022.

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