

HPV Positivity and Risk of Cervical Cancer according to HIV-Infection: A Comparative Assessment in the Population of Cameroonian Women

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Abstract

Background

Cervical cancer, caused by the human papillomavirus (HPV), remains a global health challenge. In HIV highly-burdened settings, it would be relevant to understand the severity of cervical cancer in case of co-infection with HPV. We therefore sought to determine the effect of HPV on the occurrence of cervical lesions among women with versus without HIV-infection.

Methods

A cross-sectional analytical study was conducted throughout 2012 among 257 women living in Yaoundé, Cameroon. HIV serology, genotyping of high-risk oncogenic HPV and cervical vaginal smear (CVS) were performed for all participants; among those reported to be HIV seropositive, HIV plasma viral load and CD4 count were measured. Results of the CVS were interpreted following the Bethesda 2001 guidelines. Statistical analyses were performed using Graph Pad version 6.0; $p < 0.05$ was considered statistically significant.

Results

The mean age of our study participants was 37 ± 6.5 years. According to HIV serology, 184 (71.59%) were HIV-positive vs. 73 (28.40%) HIV-negative women, with a similar age distribution respectively (36 ± 2.80 years versus 42 ± 8.48 years). Among HIV-positive women, median CD4 was 438 [IQR: 317–597] cells/mm³ and median viremia < 40 [IQR: $<40 - 2318$] copies/mL. Following successful genotyping, the prevalence of high-risk oncogenic HPV was 36.32% (73/201), with a significantly higher proportion among those with HIV-infection (41.98% [55/131] vs. 25.71% [18/70]; $p = 0.02$; OR = 2.1). CVS revealed 31.74% (97) normal cervix; 38.91% (100) inflammation; 16.34% (42) low-grade squamous intra-epithelial lesion; 6.34% (18) high-grade squamous intra-epithelial lesion. Overall rate of cervical lesions was 23.34% (60/257), with a non-significantly higher proportion in HIV-infected participants (25.00% [46/184] versus 19.17% [14/73]; $p = 0.31$). Of relevance, the presence of high-risk oncogenic HPV was significantly associated with cervical lesions ($p < 0.0001$; OR = 5.07), with a higher risk of cervical lesion among HIV-positive ($p < 0.0001$ and OR = 5.67) versus HIV-negative ($p = 0.03$ and OR = 3.83).

Conclusion

Though oncogenic HPV appears as an independent factor of the occurrence of cervical lesions, the risk of cervical lesion is substantially higher among HIV/HPV co-infection compared to HPV-infection alone. Thus, prevention of cervical cancer should be prioritised for women living with HIV-infection in HPV-endemic settings.

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). Cervical cancer is caused primarily by so-called high-risk oncogenic HPV genotypes (HPV-HR) (4), with genotypes 16 and 18 being predominantly found in most cervical cancers occurring worldwide (5, 6). In 2018 the number of new cases was estimated at 570,000 globally, with approximately 90% of the cases occurring in developing countries (7, 8). 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. Faced with this threat, the world health organisation (WHO) launched on 17 November 2020 a strategy to eliminate cervical cancer, targeting 90% of vaccine coverage among girls by the age of 15; 70% coverage of CVS screening among women aged 35–45; and 90% treatment coverage for women suffering of cervical cancer (9). However, these considerations overlook vulnerable female populations, who might serve as priority targets in meeting the aforementioned goals. Of note, a recent study of HIV-infected pregnant women in Rio de Janeiro, Brazil, found an overall cervical HPV prevalence of 84%, among which 80% were due to HPV-HR (10). In sub-Saharan Africa, most cervical cancers are associated with persistent HPV-HR infection, with more than 75,000 new cases and nearly 50,000 deaths occurring each year(11), indicating higher burdens of HPV and cervical cancer in this part of the globe (98% related deaths occurring in developing countries) (12, 13).

Driven factors of cervical cancers are the aging of women (14), as well as HIV infection; the later leading to a decrease in the number and function of TCD4 + lymphocytes (15–17). 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(18, 19). 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 (20, 21). 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 (15), or the presence of other favouring conditions of co-infections or comorbidities (22, 23).

Given that cervical cancer is inevitably preceded by cervical lesions (21, 24), often driven by the presence of HPV, it would be of great importance to ascertain the effect HIV/HPV co-infection could have on the severity of cervical lesion in settings with high burden of these infectious diseases. We therefore sought to determine the effect of HPV on the occurrence of cervical lesions among women with versus without HIV-infection in Cameroon.

Methods

Study design and setting

A cross-sectional study was carried-out in 2012 among women attending the General Hospital or the Gyneco-obstetrical and Paediatric Hospital of Yaoundé, Cameroon. For each enrolled woman, blood and cervical samples were collected. HIV screening tests, CD4 lymphocyte counts, HIV viral load, HPV genotyping and cervical smear 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/). Briefly, CIRCB is a reference centre for HIV/AIDS, performing laboratory analysis with external quality controls and proficiency testing for HIV screening (CDC DTS), HIV early infant diagnosis (CDC PT program), CD4 and viral load (QASI, Canada).

Sampling strategy

Following a consecutive non-probabilistic sampling method, a minimum sample size of 245 women was required using the following statistical formula $N = p(1-p)(Z_{\alpha}^2/d^2)$; with N being the minimum number of participants; P being the prevalence of cervical cancer among women in Cameroon in 2016 ($P = 23.6\%$); Z_{α} at the interval confidence of 95% ($Z_{\alpha} = 1.96$), d being the error rate set at 6% ($d = 0.06$). Eligible women (sexually active, aged 18 years and above) who provided their informed consent were enrolled into the study. However, any eligible woman who was reported to be pregnant or those who had undergone a total hysterectomy were not considered for inclusion. After consenting, a standard questionnaire was administered to all participants, covering socio-demographic characteristics, gynaeco-obstetrical and reproductive history. Whole blood and cervical samples were then collected.

HIV screening tests

HIV screening was performed following a two-steps serial algorithm as per the national guidelines of Cameroon (25).

HIV viral load

Centrifugation of whole blood from EDTA tube for each patient was performed to obtain plasma, which was then separated in 700- μ L aliquot used for viral RNA extraction and amplification/detection for plasma viral load by Real-Time PCR on the abbot m2000RT platform as per the manufacturer's instructions. (www.abbotmolecular.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® (Becton Dickinson), as previously described (www.bdbiosciences.com/en-us/instruments/clinical-instruments/clinical-cell-analyzers).

HPV genotyping

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

viral DNA was extracted and amplified using the Abbott real-time polymerase chain reaction assay, with simultaneous detection and genotyping of HPV 16, HPV 18, and a pooled detection of 12 other HR-HPV genotypes (HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66 and HPV 68).

Cervical smear

Slides for the cervico-vaginal smear (CVS) slides were prepared using the standard *Papanicolaou* 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 (26). Furthermore, grading to CVS profile observed from each woman was classified into one of the four categories as follows: normal cervix (women without any apparent lesion); inflammation (women with mild cervical tissue alteration); low-grade squamous intraepithelial lesions – LSIL (women with minor squamous cell lesions); high-grade squamous intraepithelial lesions – HSIL (women with atypical and high-grade squamous cell lesions).

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. 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, with a similar distribution according to HIV status (36 ± 2.80 years for HIV-positive versus 42 ± 8.48 years for HIV-negative women). The most common age group was [30–39] years representing 44.30% of the study population. Based on HIV status, we had 71.59% (184/257) HIV-positive versus 28.40% (73/257) HIV-negative women. According to marital status, single women were the most represented with 52.14% (134/257), followed by the married women with 34.24% (88/257), the widowed with 10.11% (26/257) and finally the divorced with 3.50% (9/257).

Immune status and HIV viral load of HIV + participants

Out of the 184 HIV-positive women enrolled in this study, 64.67% (119) undergone CD4 lymphocytes count. 40.33% (48/119) were immune-competent ($CD4 \geq 500$) and 59.67% (71/119) immune-compromised ($CD4 < 500$). The median CD4 was 438 [IQR 317–597] cells/mm³. Regarding HIV viral load, 82.60% (152/184) had undergone viral load testing among whom 105/152 (69.08%) had a viral load < 1000 copies/mL and 30.92% (47/152) a viral load ≥ 1000 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 HPV-HR 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). Figure 1 gives a breakdown of the distribution of these genotypes among the study population. (Fig. 1).

Following socio-demographic characteristics, neither the age nor the marital status were found associated to HPV-HR positivity ($p = 0.11$ and $p = 0.14$, respectively). There was a significant association between HPV-HR 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/mm³) were 2.33 times more likely to be co-infected with HPV-HR than those with higher CD4 ($p = 0.04$). However, a slightly higher proportion of HPV-HR 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 1.(Table 1)

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 cervix; 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 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) versus 5.47% (4/73) among HIV-positive versus 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 2. (Table 2)

Association between HPV positivity, cervico-vaginal smear and HIV status

HPV-HR 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 HPV-HR, whereas HIV-negative had about 4 times more risk (OR = 5.67, $p < 0.0001$ versus OR = 3.83, $p = 0.03$; respectively). (Table 3)

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.

From the population of 257 study participants, the mean age of 37 years old clearly falls within the range of the most sexually active population and therefore having chronic exposure to sexually transmitted infections, including HPV. According to the marital status, single women were more represented than all the other groups (about half of the population), this defining the age-group with high vulnerability among women in similar sub-Saharan African countries. This age range also aligned with previous findings conducted by Mboumba Bouassa *et al.* in Chad, Sosso *et al.* in Cameroon, and Obiri-Yeboah *et al.* in Ghana (35, 37 and 44 years, respectively (15, 27, 28).

The overall HPV-HR 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 HPV-HR positivity, suggesting that risk of infection with HPV might not be driven by age or gender. Interestingly, HPV-HR positivity rate was 2 times significantly higher among HIV-positive versus HIV-negative women, thus inferring that HIV infection leads to a higher risk of HPV acquisition through immunodeficiency, irrespective of the plasma viremia (9, 32). 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 HPV-HR as compared to their HIV-negative peers (33–34).

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, (33) 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. Henceforth, risks of acquiring cervical cancer would be non-significant in case of co-infection with HIV. More so, regarding CD4 cell count and viral load, HIV-positive women have similar frequencies of cervical lesions. This suggests no direct Implication of HIV infection on the disease progression of HPV-related cervical cancer, likely due to differences in the cellular reservoir and physiopathology(19). However, this result could be mitigated by the fact that great majority of HIV-positive women in our study population mainly had a mild immunodepression (median CD4: 438 cells/mm³) and had a control of the viral replication (median viremia: <40 copies/mL) (34, 35).

Importantly, our findings showed that the general population of women infected with HPV-HR were about 5 times more likely to have cervical lesions than those with normal cervix. Interestingly, HIV-positive women co-infected with HPV-HR were about 6 times more likely to have cervical lesions while HIV-negative women infected with HPV-HR were about 4 times more likely to have cervical lesions. This is consistent with previous global reports (35–37), and henceforth underscores that the need to systematically screen for cervical cancer among HIV-infected women (every biannually) as compared to HIV-negative women in whom screening is recommended every three years (37).

As limitation, the reference molecular technique used for HPV genotyping does not allow to discriminate beyond HPV16 and HPV18. Given the high circulation of other HPV-HR within our context, a full characterization of these genotypes (through sequencing, etc) might be essential for appropriate selection of HPV vaccine candidate for the country. A cohort monitoring design would have depicted further the risk in the occurrence of cervical cancer, thus calling for further studies using such methodological approach.

Conclusion

Though oncogenic HPV appears as an independent factor of the occurrence of cervical lesions, the risk of cervical lesion is substantially higher among HIV/HPV co-infection compared to HPV-infection alone. The prevailing grade of cervical cancers are 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.

Abbreviations

- AIDS**
Acquired immunodeficiency syndrome;
- CD4**
Cluster of differentiation 4;
- CIRCB**
“Chantal BIYA” International Reference Centre for research on HIV/AIDS prevention and management;
- DNA**
deoxyribonucleic acid;
- HIV**
Human Immunodeficiency Virus;
- HPV**
human papilloma virus;
- HR-HPV**
high risk oncogenic Human Immunodeficiency Virus;
- LR-HPV**

low risk non-Human Immunodeficiency Virus;

PLHIV

People living with HIV;

RT-PCR

real-time polymerase chain reaction;

WHO

world health organization.

Declarations

Ethics approval and consent to participate

This study obtained ethical clearance from the CIRCB Ethics Committee on the Project N^o 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.

Consent for publication:

Not applicable.

Disclosure statement:

Authors declare that they have no financial, personal, or professional interests that could be construed to have influenced this manuscript.

Availability of data and materials:

The dataset is available from the corresponding author.

Competing interests:

The authors declared that, this study is without conflicts of interests.

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Authors' contributions:

All authors read and approved the final manuscript. SMS, MCTT, JF, RK, JT, AN, GN, and AN designed the study. MCTT, ADN, TV, CC, ENJS, AA, AK, and BY analysed and interpreted the data. SMS, JF, RK and

MCTT performed the HPV testing. VC and AN managed all aspects of the study in Yaoundé. SMS and JF supervised the performance of laboratory testing. MCTT, JF, and SMS drafted the manuscript.

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Tables

Due to technical limitations, table 1, 2, 3 is only available as a download in the Supplemental Files section.

Figures

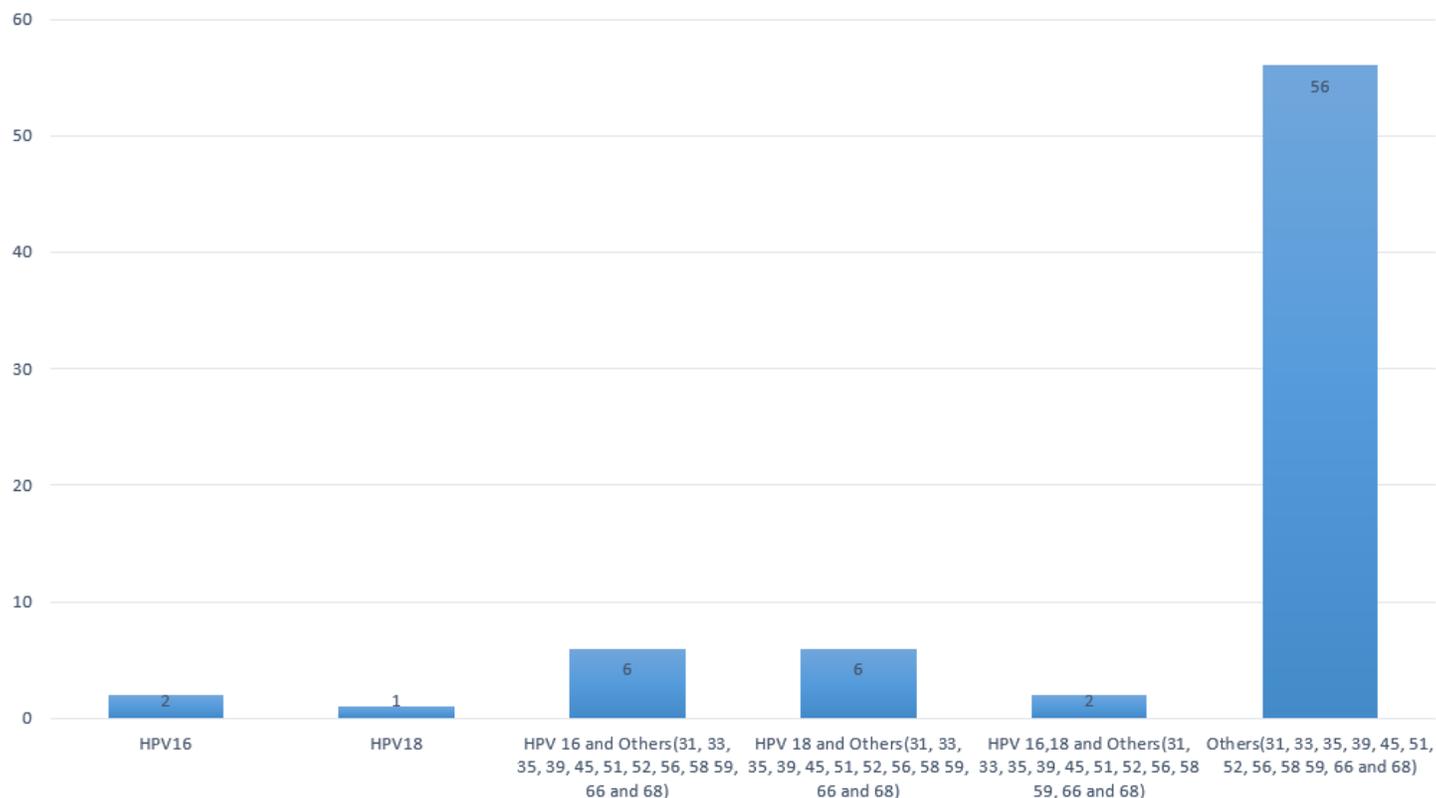


Figure 1

Genotypic diversity of HPV-HR Legend, HPV: human papillomavirus; others refer to oncogenic HPV other than the 16 and 18 genotypes identified by the molecular detection assay.

Supplementary Files

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- [Table2Distributionofcervicallesions.pptx](#)
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