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Prevalence of high-risk human papillomavirus genotypes and viral load correlated with squamous cell inflammation among women in Gabon

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Abstract

Background High-risk genotypes of Human Papillomavirus are responsible for 90% of cases of cervical cancer worldwide. Inflammation of squamous cells is mainly linked to HPV. In Gabon, HPV is endemic and circulates among the female population. The study aimed to determine the prevalence of HR-HPV genotypes and to investigate the correlation between squamous cell inflammation and HPV viral load in infected women in Gabon.

Methods The cross-sectional study was conducted at Libreville University Hospital Center (UHC) and National Public Health Laboratory from March to May 2024 among 399 women. Two cervical smears were taken. Genotype detection was carried out by multiplex fluorescence real-time PCR in the NPHL virology unit. Cytology was carried out in UHC's anatomic-pathology laboratory. Data were analyzed by SPSS software. Graphs were plotted using Microsoft Excel 2016.

Results The prevalence of Human Papillomavirus was 26.1% (95% CI: 22-30.6). The prevalence of HR-HPV genotypes was 24.8%. The most common HR-HPV genotypes were HPV-16/52/18/35/56/58/53/68. The rate of multiple HPV infections was 29.8% and 95.2% for the HR-HPV infection rate. Viral load was significantly correlated with squamous cell inflammation ($r=0.977$ and $P=0.001$).

Conclusion HR-HPV infection remains a concern in women, however early screening is necessary for optimal monitoring and management. HR-HPV viral load is a predictive marker of squamous cell inflammation.

Keywords Prevalence, HR-HPV, Viral load, Correlation, Squamous cell inflammation, Women of Gabon

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Introduction

Human papillomavirus (HPV) is a global health problem that infects the squamous epithelia of women (or men). HPV continues to plague the world. According to the World Health Organization (WHO), HPV is responsible for cervical cancer. Cervical cancer is the fourth most common cancer affecting women worldwide. In 2020, the number of new cases was estimated at nearly 604,000 cases and nearly 342,000 deaths. However, almost 90% of new cases and deaths worldwide in 2020 came from resource-limited countries [1–3].

Several studies in some African countries have shown that HPV is more prevalent and Africa has one of the highest HPV prevalences in the world. Studies carried out in particular in Ghana estimated an HPV prevalence of 89.8%, in South Africa with a prevalence of 32%, and in Nigeria with a prevalence of 35.7% among women. Similarly, in Cameroon, HPV circulates in the female population with a prevalence of 38.7% [4–7].

The HPV genotypes circulating in the world population are made up of nearly 200 strains identified to date, but 18 strains are at high risk and are likely to cause cervical cancer. HPV-16 is by far the most common since it is responsible for 53% of cervical cancers. It is followed by HPV-18, which is responsible for 17% of cases. HPV-16 and HPV-18 represent nearly 70% of cases of cervical cancer. But low-risk strains of HPV are mainly responsible for condyloma (genital warts) on the lips of the vulva, vagina or cervix. These warts are sexually transmitted but benign and do not develop into cervical cancer. These warts are 90% caused by the HPV-6 and HPV-11 genotypes [8–11].

HPV infection is the main cause of squamous cell inflammation in both women and men. Note also that inflammation of squamous cells often reflects the evolution and appearance of precancerous or cancerous lesions in people infected with high-risk HPV genotypes. The association between HPV viral load and inflammation of squamous cells could shed more light on the diagnosis and management of infected people. In addition, quantification of HPV DNA correlated with inflammation of squamous cells could predict the risk of developing cervical cancer at a stage of infection. HPV infection remains a real burden for global health, which negatively impacts the quality of life and social and economic development of people affected by cervical cancer caused by HPV. Complications are significant (mortality and morbidity) when screening is carried out late, that is to say, at an advanced stage of the cancer [12–15].

In Gabon, HPV circulates in the population and is responsible for cervical cancer. Mass HPV screening is only carried out during the international period (Pink October) of the fight against cervical cancer. Current HPV screening based solely on histopathological

examination for observation and identification of abnormal and normal cells is limited, especially in the detection of high-risk or low-risk genotypes. Molecular detection is not yet fully integrated into the screening of high-risk genotypes in the country's medical structures. The initiation of real-time PCR during a gynecological assessment will make it possible to identify the HPV genotypes, especially the high-risk genotypes involved in the inflammation of squamous cells and the appearance of neoplastic lesions. Systematic and voluntary screening at any time of the year is not yet a reality in the country. However, systematic and voluntary screening based on the detection of HPV DNA at any time of the year would make it possible to optimize surveillance, prevention and care of infected people in the country. Several studies carried out in the country have shown that cervical cancer caused by HPV is generally diagnosed at an advanced clinical stage where radio-surgical indication is required with all the psychological and economic consequences that ensue [16, 17]. It is necessary to screen this population early by looking for the presence of HPV DNA to determine the genotype in question, especially at high risk, which would reduce the mortality and morbidity rate in the female population of Gabon. This study aims to determine the prevalence of high-risk genotypes and to investigate the correlation between squamous cell inflammation and HPV viral load in infected women in Gabon.

Methods

Study design and setting

A cross-sectional study was conducted at the University Hospital Center (UHC) of Libreville and the National Public Health Laboratory (NPHL) of Libreville from March to May 2024 among 399 women coming to the UHC for HPV screening. A purposive sampling method was used. Two cervical smear samples (CSS) were taken. Viral load and genotype detection were carried out in the virology unit of NPHL. Cytology was carried out in UHC's anatomic-pathology laboratory. All participants aged 18 years or older and sexually active were included in the study. However, pregnant participants and participants during menstruation were excluded from the study.

Definitions

ASCUS (Atypical Squamous Cells of Undetermined Significance) is a term used to report a category of cervical epithelial cell abnormalities described by the Bethesda System for Reporting Cervical Cytology. ASCUS is the most common abnormal finding in a Pap test. Also called ASC-US and atypical squamous cells of undetermined significance [18]. Viral load (VL) was divided into three measurements namely: low VL (1–99.9 copies/ml); moderate VL (100–999 copies/ml), and high VL (≥ 1000 copies/ml).

Cervical sample collection

Sample collection was carried out by experienced medical personnel. The speculum was used to expose the cervix, and then the excess secretions were wiped away with a cotton swab. The cervical brush was rotated slowly 6 to 7 times in one direction to obtain sufficient cervical epithelial cells. Two cervical brushes were used for sampling. One of the cytological brushes was used to search for human papillomavirus DNA, and the other brush was placed in a preservation solution for cytology (Pap Staining). All samples were stored at 4°C and tested within 48 h.

Extraction, amplification of HPV DNA and genotyping

DNA extraction was conducted using the HPV DNA/RNA viral extraction kit (BioPerfectus Technologies Co. Ltd, Jiangsu, China). The extract (DNA) was treated the same day and then stored at 20 °C for 48 h following the manufacturer's protocol for amplification. The extract (5 µl) was added to 20 µl of the master mix. During amplification, a positive control, a negative control, a blank control, and the enzyme mix were included. Then, the plate was sealed with adhesive film and centrifuged for 30 s at revolution per minute (RPM). DNA quantification was conducted on the thermal cycler (QuantStudio5) following the manufacturer's protocol. Genotyping was conducted using the HPV genotyping Real-Time PCR kit (BioPerfectus Technologies Co. Ltd, Jiangsu, China). The detection of HPV DNA fragments was carried out in the FAM/VIC(HEX)/ROX fluorescence channels of seven reaction tubes including A(HPV16/18/31), B(HPV59/66/53), C(HPV33/58/45), D(HPV56/52/35), E(HPV68/51/39), F(HPV82/26/73) and G(HPV6/11/81). There are 47 cycles (UNG treatment, pre-denaturation, denaturation, annealing, extension, and fluorescent

signal) that were performed for 15 min and 50 s. A negative control was used. An internal control with a constitutive gene was established in the reaction tube H (FAM channel) to identify possible inhibition of PCR and to confirm the reliability of the kit reagents. Genotypes were identified taking into account the cycle threshold value (Ct), the specific probe (FAM, VIC, ROX), and the corresponding group (A, B, C, D, E, F, G, H) each consisting of three HPV types following the protocol of the manufacturer Bioperfectus.

Smear cytology

Papanicolaou staining was used to differentiate and distinguish specific cell types. The smear taken using the second swab was fixed in 95% ethanol for 15 min followed by tap water. Next, Harris Hematoxylin dye was incorporated for 1 to 3 min followed by rinsing with Scott's tap water. The smear was soaked in orange G-6 dye for 5 min, then in 95% ethanol for 10 dips then include eosin dye (EA-50 or modified EA-50 and EA-65 dye) for 2 min. The 100% ethanol was added over 1 min. Then, the smear was cleared in two stages using xylene for 2 min at each stage. After drying the smear reading under an optical microscope using a 100x objective.

Statistical analysis

Data analysis was done using SPSS software. The correlation test (r) was used. $P \leq 0.05$ was considered statistically significant. The correlation test made it possible to investigate the correlation between HPV viral load and squamous cell inflammation in infected women. Descriptive data were presented as frequencies and percentages.

Results

Distribution of sociodemographic data

The study consisted of 399 women only. The most representative age groups were between [18–34], [35–49], and [50–65], with 35.3%, 37.8%, and 24.1% respectively. The least representative was those ≥ 66 years old, or 2.8%. Participants with primary and university education were the most representative with 31.8% and 50.6% respectively. Likewise for the profession, the unemployed and working women were more represented, with 33.1% and 51.9% respectively. And for marital status, single and married women were more representative, respectively 47.8% and 48.2% (Table 1).

HPV prevalence in women

The study consisted of 399 outpatient women who agreed to participate. Among the 399 women in the study, 104 women were positive for one or more HPV genotypes. The overall HPV prevalence among study women was 26.1% (104/399) with 95% CI: 22.04–30.6 (Fig. 1).

Table 1 Sociodemographic data of the women in the study

Variables	N	%
Age		
18–34	141	35.3
35–49	151	37.8
50–65*	96	24.1
≥ 66	11	2.8
Education		
Primary	127	31.8
Secondary	70	17.6
University*	202	50.6
Occupation		
Student	60	15
Worker*	207	51.9
Unworker	132	33.1
Marital status		
Single	191	47.9
Married	192	48.1
Widow*	16	4

*Reference group; N: Number; %: Percentage

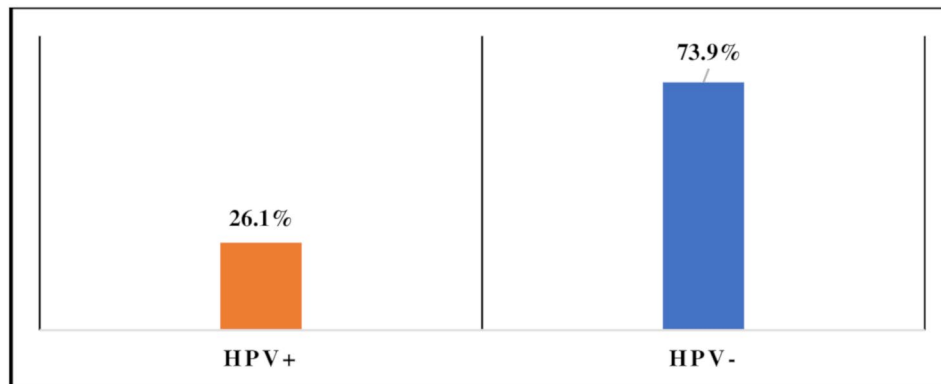


Fig. 1 Prevalence of HPV among women of Gabon

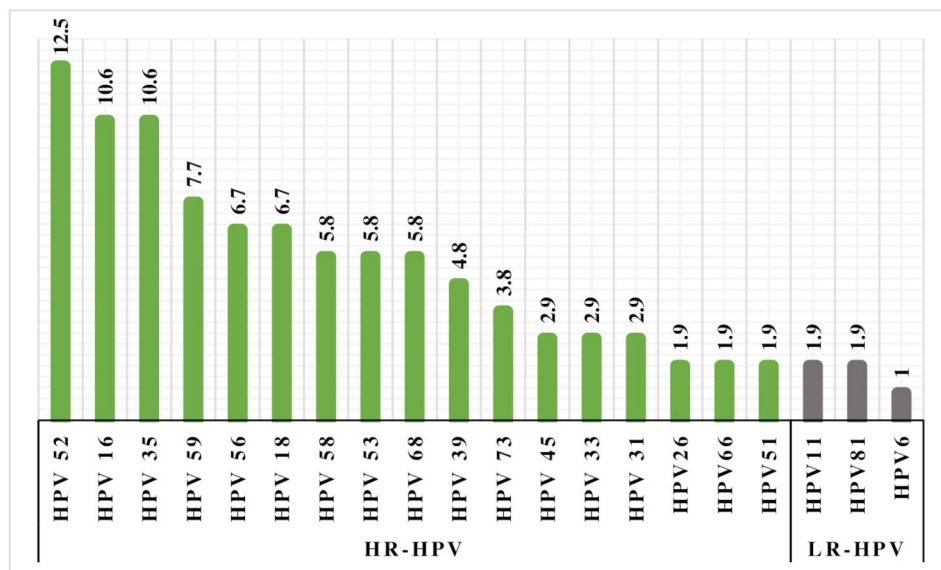


Fig. 2 Frequency of HR-HPV and LR-HPV genotypes, (%)
HR-HPV: High-risk Human Papillomavirus; LR-HPV: Low-risk Human Papillomavirus

Distribution of high-risk HPV genotypes circulating in women

The prevalence of high-risk HPV genotypes (HR-HPV) was 24.8% (99/399) with 95% CI: 19–27, and the prevalence of low-risk genotypes (LR-HPV) was 1.3% (5 /399) with 95% CI: 2–10. Commonly encountered HR-HPV genotypes were HPV-16, HPV-18, HPV-52, HPV-51, HPV-45, HPV-39, HPV-35, HPV-33, HPV-56, HPV-58, HPV- 31, HPV-73, HPV-68, HPV-66, HPV-26, HPV-53, and HPV-59. Commonly encountered LR-HPV genotypes were HPV-6, HPV-11, and HPV-81. The frequency of the most observed HR-HPV genotypes in infected women was 12.5% (HPV-52), 10.6% (HPV-16), 10.6% (HPV-35), 7.7% (HPV-59), 6.7% (HPV-18), 6.7% (HPV-56) 5.8% (HPV-58), 5.8% (HPV-53) and 5.8% (HPV-68 (Fig. 2).

Rate of multiple HPV infections

The rate of multiple HPV infections among positive women was 29.8% (31/104). HPV-16/HPV-35 (6.5%), HPV-52/HPV-58 (6.5%) and HPV-35/HPV-59 (6.5%) co-infections predominated. The infection rate of HR-HPV was 95.2% (99/104) and 4.8% (5/104) for the infection rate of LR-HPV (Fig. 3).

Histopathological observation

Cytology of cervicovaginal smears from the 104 positive women made it possible to identify normal and abnormal cells. Among the abnormal cells, 71.1% (74/104) showed abnormal cells with inflammation, 1% (1/104) of abnormal cells showed ASCUS, and no grade of cervical neoplasia was identified. Normal cytology was 27.9% (29/104) (Fig. 4).

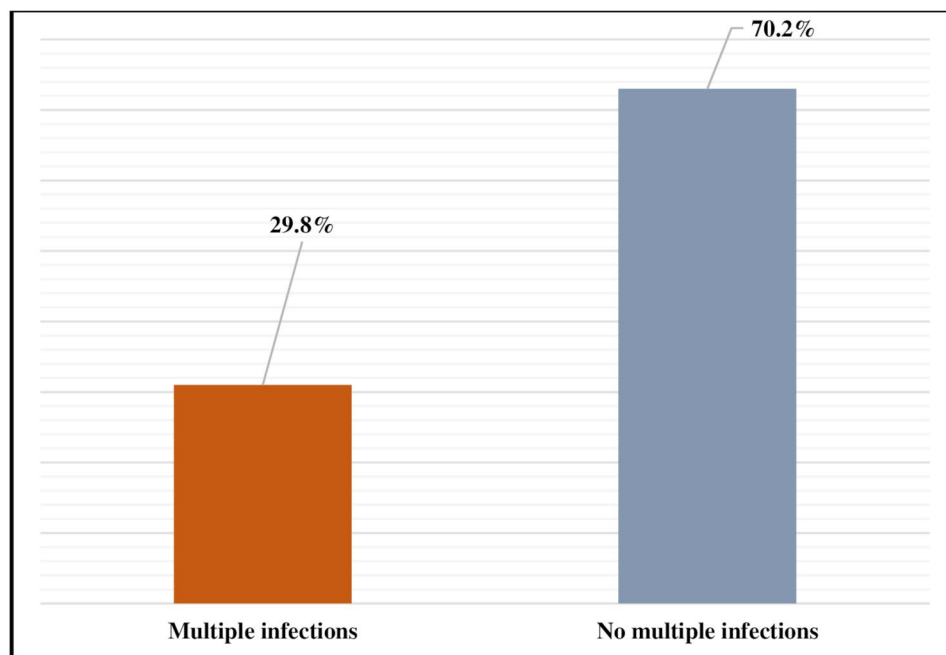


Fig. 3 Rate of multiple infections

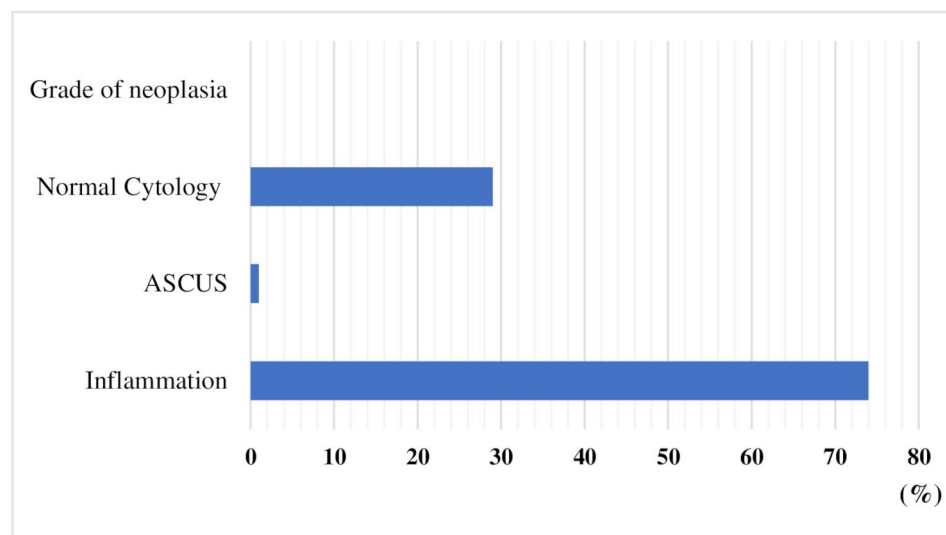


Fig. 4 Results of cervicovaginal smear cytology

Risk factors associated with squamous cell inflammation

Logistic regression of sociodemographic variables was used to identify risk factors associated with squamous cell inflammation in HPV-infected women. Moderate viral load (VL) (100–999 copies/ml) was considered a risk factor significantly associated with squamous cell inflammation (aOR=3.4, 95% CI: 1.3–8.4 $P=0.014$). High VL (≥ 1000 copies/ml) was also a risk factor significantly associated with squamous cell inflammation (aOR=3.6 95% CI: 1.5–8.9 $P=0.001$). Age, occupation, marital status, and education were not associated with squamous cell inflammation (Table 2).

Correlation between viral load and squamous cell inflammation

The SPSS software allowed us to make the variables “HPV viral load, inflammation of squamous cells, and ASCUS” act together to show the existence of a correlation between these variables. The Pearson correlation statistical test revealed a significant correlation between HPV viral load and squamous cell inflammation ($r=0.977$, $P=0.001$). No significant correlation was observed between HPV viral load and ASCUS ($r=0.061$, $P=0.537$) (Table 3).

Table 2 Risk factors associated with squamous cell inflammation

Variables	Inflammation			
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	aOR (95% CI)	P-value
Age				
18–34	1.0 (0.4–2.5)	0.56	1.1 (0.5–2.7)	0.42
35–49	1.0.1 (0.4–2.4)	0.57	1.1 (0.47–2.5)	0.55
50–65	-	-	-	-
≥ 66	-	-	-	-
Education				
Primary	1.4 (0.5–3.4)	0.328	1.5 (0.6–3.7)	0.328
Secondary	-	-	-	-
University	1.5 (0.6–3.5)	0.262	1.6 (0.7–3.8)	0.64
Occupation				
Student	-	-	-	-
Worker	0.8 (0.3–1.9)	0.378	0.9 (0.4–2.0)	0.14
Unworker	0.9 (0.4–2.3)	0.536	1.0 (0.4–2.5)	0.27
Marital status				
Single	1.5(0.1–17.3)	0.61	2.3 (0.2–22.6)	0.42
Married	1.3 (0.1–15.4)	0.65	2.1 (0.2–20.3)	0.74
Widow	-	-	-	-
Viral load				
Low	-	0.001	-	0.014
Moderate	3.2 (1.3–8.1)	0.004	3.4 (1.3–8.4)	0.007
High	3.5 (1.4–8.5)		3.6 (1.5–8.9)	

OR : Odds Ratio ; 95% CI : 95% Confidence Interval

Table 3 Correlation between HPV viral load and squamous cell inflammation

Correlation of Pearson		Inflammation	ASCUS	Viral load
Inflammation	Correlation of Pearson	1	-0.155	0.977**
	P-value		0.117	0.001
ASCUS	Correlation of Pearson	-0.155	1	0.061
	P-value	0.117		0.537
Viral load	Correlation of Pearson	0.977**	0.061	1
	P-value	0.001	0.537	

** The correlation is significant at the 0.01 level (two-tailed)

Discussion

Human Papillomavirus (HPV) infection is becoming a real health problem that affects sexually active women every day. It is becoming essential for every health decision-maker to implement effective strategies that can reduce the prevalence of HPV. This involves awareness campaigns, vaccination, and early screening of women to optimize the prevention and surveillance of the virus among women. The objective of this study is to determine the prevalence of high-risk genotypes and to investigate the correlation between squamous cell inflammation and HPV viral load in infected women.

The sociodemographic data of the study participants included only sexually active women. This number

avored women whose age group was between [18–34] and [35–49], with 35.3% and 37.8% respectively. This observation could be justified by a clear motivation of sexually active women to know their status with regard to HPV infection but also the presence or absence of cervical cancer. Similar results were observed in studies conducted in Egypt, Cameroon, and Burkina Faso [19–21]. Concerning profession, level of education, and marital status, the most representative groups were made up of women with a university education level, with 50.6%, and those with a professional activity, with 51.9%. Likewise, single and married women were more representative with 47.8% and 48.2% respectively. This observation could be explained by awareness campaigns during October (Pink October) which urge women to be screened. University-level women easily understand the value of screening for this devastating infection. In addition, many employers encourage their female workers to be screened for cervical cancer for better professional performance. Some studies carried out in certain African countries, namely the Democratic Republic of Congo (DRC), Togo and Cameroon had obtained similar results [22–24].

The prevalence of HPV was high at 26.1% (95% CI: 22.04–30.6) among women with HPV DNA present in the sample. This observation linked to the increase in the prevalence of HPV in women could be justified by a significant circulation of HPV strains in the general population particularly among sexually active women. Some studies conducted in Nigeria (17.3%), Brazil (25.41%), and China (17.7%) obtained similar results from this study [25–28].

The prevalence of circulating HR-HPV genotypes was high (24.8%). And the HR-HPV genotypes that predominated in infected women were composed of HPV-52/16/35/18/59/56. This predominance could be justified by a high prevalence of HPV infection which implies an increased circulation, especially of the majority of HR-HPV genotypes in the female population of the study. Other studies carried out in certain countries such as Cameroon (21.43%), Nigeria (86.2%), Ghana (23%), and China (19.97%) revealed similar results [25, 29–33]. These results will help improve the current screening strategy and surveillance of HR-HPV genotypes in the country. To achieve this, HPV screening should be carried out daily in the country's various medical facilities instead of waiting only for the month of Pink October for mass screening. In addition, this new screening strategy will contribute to improving the clinical management of HPV infection in the country and in other resource-limited settings.

The rate of multiple infections of HPV genotypes among infected women was 29.8%. And the HR-HPV infection rate was 95.2%. This observation could be justified by an exponential circulation of HPV in the population. And this could be accentuated by unprotected

sexual relations with multiple partners, thus exposing one to HPV viral superinfection. Some data from studies in some countries have shown that co-infection is a concern among infected women [24, 34–38].

Logistic regression identified some risk factors associated with squamous cell inflammation. Moderate HPV viral load and high HPV viral load were considered to be risk factors significantly associated with squamous cell inflammation (aOR=3.4 $P=0.014$, and aOR=3.6 $P=0.001$ respectively). These data could be justified by an active viral replication of HPV promoting a cellular aggression thus triggering the inflammation process. Several studies have shown that VL is a predictive marker for cervical epithelial abnormalities caused by HR-HPV but also for progression to cancer [39–42].

Histopathological examination identified cases of squamous cell inflammation and cases of ASCUS. Squamous cell inflammation was significantly correlated with HPV viral load. Squamous cell inflammation is mainly associated with HPV infection, especially caused by HR genotypes. It is therefore important to understand that persistent HPV infection and squamous cell inflammation are responsible for HPV-induced cancer progression [12, 43]. However, the Pearson correlation test was used to investigate the existence of a correlation between squamous cell inflammation and HPV viral load. After analysis, it turns out that the HPV viral load is significantly correlated ($P=0.001$) with the inflammation of squamous cells in women infected with HPV. Mucosal-tropic HPV infects epithelial cells of the genital and oral mucosa. The presence of oncoproteins (E6, E7) plays a critical role in neoplastic progression. The role of inflammation in high-risk HPV infection is complex as it involves responses that can promote the persistence and progression of HPV-associated lesions. Inflammation is considered a key aspect of HPV persistence and the main factor leading to high-risk HPV-related neoplasia. The host inflammatory response can promote the progression of neoplastic lesions. Common genital tract infections and cervical inflammation are considered co-factors in the progression of cervical carcinogenesis. HPV-infected cervical cells secrete large amounts of pro-inflammatory cytokines, which could also support the link between inflammation and HPV infection. The deeper inflammatory state caused by high-risk HPV contributes to the progression of infection to cancer [44, 45]. Note that uterine cervical intraepithelial abnormalities and the development of precancerous and cancerous lesions may also result from complex molecular disturbances at the vaginal level. Reactive oxygen species accompanied by HR-HPV can promote all levels of cervical intraepithelial neoplasia and the development of cancer [46].

Strengths and limitations

This study is, to our knowledge, one of the first studies to have shown the correlation between squamous cell inflammation and HPV infection in Africa. In addition, the study revealed a significant circulation of HR-HPV genotypes among women in Gabon. However, the study had some limitations, including the non-identification of cervical intraepithelial neoplasia lesions (precancerous and cancerous). Indeed, during our study, cytological examination of cervicovaginal smears did not reveal any presence of cervical intraepithelial neoplasia grade lesions in the women included in the study. This could be justified by the size of the sample studied.

Conclusion

The prevalence of HPV among women at the Libreville University Hospital Center in Gabon remains high. This increase in prevalence reflects a significant circulation of human papillomavirus infection among women. The rate of HR-HPV infections remains worrying with significant circulation of HR-HPV genotypes (HPV-52/16/35/18/59/56) among women at the University Hospital Center of Libreville. The rate of multiple HPV infections remains high. A correlation between squamous cell inflammation, and HPV viral load remains significant. Hence the need for the country's health decision-makers to integrate vaccination and early screening in all seasons of the year of HR-HPV genotypes for the prevention of HPV infection but also to guarantee better rapid management and optimal monitoring of HR-HPV circulating in the country. Awareness campaigns and community education are also necessary to prevent HPV infection.

Abbreviations

ASCUS	Atypical Squamous Cells of Undetermined Significance
CSS	Cervical Smear Samples
DNA	DeoxyriboNucleic Acid
HPV	Human Papilloma Virus
HR	High Risk
LR	Low Risk
NPHL	National Public Health Laboratory
PCR	Polymerase Chain Reaction
RPM	Revolution per minute
UHC	University hospital Center
WHO	World Health Organization

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Author contributions

CM and CMM designed the study and CM wrote the article. AKFMO, MT, JABB, LON and NAL participated in data collection. DMB, RMI and GEMK analyzed the data. CM and EA supervised the work. All authors reviewed, read, and accepted the final manuscript.

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Data availability

Datasets used and/or analyzed in this study are available from the corresponding author upon reasonable request.

Declarations**Ethics approval and consent to participate**

The study was approved by the management of the National Cancer Control Program (NCCP) of Gabon and by the Institutional Ethics Committee for Human Health Research (CEIRSH) of the Catholic University of Central Africa. The number of the ethics statement is N° 2024/020635/CEIRSH/ESS/MBV. Informed and written consent was obtained from each participant in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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