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Sexually transmitted infections (STIs)/HIV associated to human papillomavirus (HPV) in precancerous lesions among Cameroonian women

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Abstract

Cervical precancerous lesions signify cellular changes in the cervix linked to an escalated risk of cancer. These lesions often evolve towards malignancy influenced by various factors, including sexually transmitted infections (STIs), irrespective of human papillomavirus (HPV) presence. STIs represent a substantial global public health concern, affecting both sexes, with over 30 pathogens, comprising bacteria, viruses, and parasites, capable of causing STIs. The clinical presentation of these pathogens varies significantly. This study aimed to delineate the microbial profile within HPV-containing precancerous lesions. A prospective cross-sectional descriptive study was conducted in Cameroon's central region, particularly in the Endom district. Among 343 patients screened, 225 women were enrolled based on positive HPV cervical smear results. Cervical cell lesions were analyzed using the Papanicolaou technique, while parasitological and microbiological methods were utilized to identify other microbes. HPV genotypes were determined via multiplex PCR. The study revealed 65 HIV-positive and HPV-positive individuals (18.96%); 40 HIV-negative and HPV-positive individuals (11.65%); 25 HIV-positive and HPV-negative individuals (7.29%); and 213 HIV-negative and HPV-negative individuals (62.10%). Various cervical lesions were identified, including Low-grade Lesions (LSILs) (21%) and High-grade lesions (HSILs) (16%). *Trichomonas vaginalis* (TV) (51%), *Candida albicans* (CA) (28%), *Herpes simplex* (HS) (2%), *Gardnerella vaginalis* (GV) (17%), *Aspergillus* (A) (2%), and HIV were the primary infectious agents identified in these precancerous lesions, with significant distribution ($P<0.005$), suggesting their role as risk factors for precancerous lesions (OR=13.89, 95% CI 6.87-21.60). Multiple HPV genotypes were characterized in the same precancerous lesions, with approximately 25% (85) of women harboring either Low_Risk (LR) (6, 11) or High_Risk (HR) (16, 18, 45, 58) HPV genotypes ($P<0.001$). Coinfections such as HPV/TV/CA and HPV/HIV/TV were prevalent, indicating their potential as associated risk factors for precancerous lesions. Coinfections with other microbes, typically associated with cervicitis, appear to facilitate HPV infection. These findings contribute to understanding the microbial landscape of cervical samples and underscore the importance of integrated care approaches for HIV-positive individuals with HPV-related lesions.

Keywords: precancerous lesions, HPV, coinfections, cervical cytology, microbial composition

1. Introduction

Cervical cancer represents a substantial health burden for women worldwide(1). Among the cancers that strike people in their 20s and 30s, cervical cancer is highly prevalent(2). The World Health Organisation (WHO) estimates that human papillomavirus (HPV) affects 9% to 13% of the world's population, with over 6.2 million cases of the virus reported each year in the US alone (3). Among the more than 140 varieties of HPV, many serotypes (16, 18, 45, 58) are linked to 70% of cervical cancer cases, as well as precancerous lesions in the cervical region. The genesis of cervical tumors caused by HPV and HPV infection could be greatly impacted by the vaginal microbiota. Cervicitis is also caused by vaginal inflammation and oncogenic mutations in human cells, which are closely related to bacteria(4). An inflammation of the cervix is called cervicitis. It is typically sexually transmitted and caused by several infectious agents(5). The highest and lowest occurrences of pathogens were observed with *T. vaginalis* (71.0%) and *U. urealyticum* (6.45%), respectively. Coinfection exhibited a prevalence of 19.35% and 9.67% for three-organism and two-organism combinations, respectively. Significant correlations were identified between the presence of cervicitis and coinfection with other genital pathogens, abortion history, and inconsistent condom usage ($p < .05$).(6).

Another investigation unveiled numerous other sexually transmitted infections (STIs) linked to HPV infection: 36% tested positive for *Gardnerella vaginalis*, 35% for *Ureaplasma*

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parvum, 8% for *Candida albicans*, 6.7% for HPV, 4.6% for *Ureaplasma urealyticum*, 3.6% for *Mycoplasma hominis*, 2% for *Trichomonas vaginalis*, 0.8% for *Chlamydia trachomatis*, 0.4% for *Mycoplasma girerdii*, 0.2% for *Mycoplasma genitalium*, and 0.2% for Neisseria gonorrhoeae. Symptom absence was noted in 187 women (37%), among whom 61% were found to be infected. Of the 34 HPV-positive samples, 17 harbored high-risk HPV genotypes (HR-HPV); notably, types 16 (38%), 18 (21%), and 51 (18%) exhibited the highest prevalence. Among the 34 HPV-positive individuals, 29 carried HR-HPV. Associations with various risk factors were also documented(7). Sexually transmitted infections (STIs) often manifest without symptoms and can result in diverse complications, including pelvic inflammatory disease, infertility, ectopic pregnancy, cervical cancer, and congenital infections in infants born to infected mothers. Assessing the prevalence of STIs is crucial for preventing, managing, and effectively treating individuals afflicted with these infections(8). Persistent HPV infection is responsible for over 99% of cervical cancers. Annually, there are over 500,000 new cases of cervical cancer globally, resulting in around 250,000 deaths. Developing countries bear the brunt of this burden, with 80% of cases occurring in these regions(9). Several studies have reported associations between various microbial infections and the presence of HPV in cervical precancerous lesions. For example, Trichomonas vaginalis, *Candida albicans*, herpes simplex virus (HSV), *Gardnerella vaginalis*, and Aspergillus have been identified as common microbial agents found in conjunction with HPV infection in cervical lesions(10). These microbial coinfections have been suggested to influence the natural history of HPV infection, cervical lesion development, and progression to cervical cancer (11). It is therefore important to determine whether specific sexually transmitted infection (STI) co-factors are involved in the development and progression of precancerous cervical lesions associated with human papillomavirus (HPV) infection among Cameroonian women.

The aim of this study was to assess the prevalence and co-occurrence of specific sexually transmitted infections (STIs) alongside HPV infection in precancerous cervical lesions among Cameroonian women and to investigate the potential role of these STIs as co-factors in the development and progression of precancerous lesions."

2. Materials and Methods

2.1. Study sites

This prospective cross-sectional descriptive study was conducted in hospitals situated within the districts under study. The analyses were performed both on-site and at the biochemistry laboratory at the University of Douala

2.2. District of Endom

Endom District is located in the central region of Cameroon. It is characterized by its diverse landscape, which includes lush forests, fertile farmland, and picturesque hills. The district is home to several rural communities, each with its own unique culture and traditions. Economically, Endom District relies primarily on agriculture, with crops such as cocoa, coffee, and bananas being important sources of income for local residents. The district also has potential for tourism, with its natural beauty and opportunities for outdoor activities such as hiking and birdwatching. The infrastructure in Endom District is relatively basic, with limited access to amenities such as healthcare facilities and educational institutions. However, efforts are being made to improve infrastructure and services to better meet the needs of the local population.

Overall, Endom District is a rural area with a rich natural environment and cultural heritage but also faces challenges related to economic development and access to essential services. The health situation in Endom District, like many rural areas in Cameroon, faces various challenges and opportunities. Access to healthcare services, including primary care facilities, specialized medical care, and essential medications, may be limited in some parts of the district due to factors such as geographic isolation, inadequate infrastructure, and resource constraints. Common health issues in the Endom District may include infectious diseases such as malaria, respiratory infections, diarrheal diseases, and vaccine-preventable illnesses. Maternal and child health, including access to prenatal care, skilled birth attendants, and immunizations, are also important priorities for improving health outcomes in the district.

2.3. Study population and sample size

All women at various stages of development, with or without cancer, were the focus of these analyses.

Selection criteria

Inclusion

All Cameroonian women aged eighteen and above were eligible for inclusion. Participation in the study was contingent upon being sexually active, expressing willingness to take part, signing an informed consent form, not having undergone a hysterectomy, and presenting a positive cytology result.

Sampling method

A convenience sampling method was employed, involving the consecutive recruitment of potential participants at various sites.

Questionnaire

A semi-structured questionnaire administered by an investigator was used to gather data from each woman during a 15–20-minute individual interview.

Cervix sample collection and visual inspection

The present Bethesda system was utilized to classify cytological abnormalities into the following categories: negative, Atypical Squamous Cells of Undetermined significance (ASC-US), Atypical Glandular Cells (AGC), atypical squamous cells without High-Grade Intraepithelial Lesions (ASC-H), atypical squamous cells with low-grade squamous intraepithelial lesions (LSILs), and high-grade

squamous intraepithelial lesions (HSILs).

Microscopy

Trichomonas

Wet mount microscopy: A sample of vaginal discharge was collected, placed on a slide with a drop of saline solution, and observed under a microscope for the presence of the parasite.

***Candida albicans* identification**

Samples of affected tissue, discharge, or bodily fluids (e.g., vaginal swabs, oral swabs) were collected and examined under a microscope to determine the presence of *Candida albicans* yeast cells or hyphae.

Gardnerella vaginalis identification

A sample of vaginal discharge was collected and examined under a microscope to look for characteristic changes in the vaginal microbiota, such as the presence of "clue cells" (vaginal epithelial cells covered with bacteria), which are indicative of BV.

DNA extraction

Fresh cervical cells were utilized for DNA extraction employing the commercially available QIAGEN Multiplex PCR Kit. The extraction process followed the instructions provided by the manufacturer.

2.4. Statistical analysis

After the data were entered and checked for consistency in an Excel spreadsheet, Graph Pad Prism version 6 was used for analysis. One-way ANOVA and the independent chi-square test were used to compare the outcomes. In the tables and graphics, qualitative variables are displayed as percentages with 95% confidence intervals. A significance level of $P \leq 0.05$ was used.

3. Results

3.1. Sociodemographic information

Table 1 below displays the mean values of a certain parameter across different age groups. This study provides valuable insights into the relationship between age and the parameter being measured, highlighting the importance of considering age as a factor in research and clinical settings and the distribution of individuals across different marital statuses and education levels, along with the associated percentages and statistically significant values.

Table 1. Sociodemographic information of the study population

Age range	N (%)	Mean ± SD	P
[15-25[	14 (%)	19.30±2.6	0.001
[25-35[	11 (%)	35.17± 5.5	0.001
[35-45[	36 (%)	39.61±3.7	0.002
[45-55[	31 (%)	53.30± 4.9	0.001
[55-65[	8 (%)	61±0.9	0.05
CIVIL STATUS			
SINGLE	38(%)	-	0.05
DIVORCED	56(%)	-	
MARRIED	160(%)	-	
WIDOW	92(%)	-	
EDUCATION			
NONE	34(%)	-	**NS**
PRIMARY	178(%)	-	
SECONDARY	102(%)	-	
HIGHER	29(%)	-	

3.2. Distribution of Cervical Cytology Results: Normal, LSIL, and HSIL

Fig. 1 below presents the distribution of cervical cytology results among the categories "Normal", "LSIL" (low-grade squamous intraepithelial lesion), and "HSIL" (high-grade squamous intraepithelial lesion).

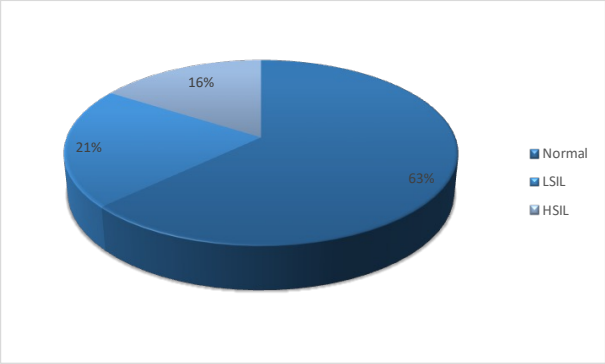

Fig. 1. Cervical lesions distribution
Normal: No atypical squamous cell
LSIL: Low-grade squamous intraepithelial lesion
HSIL: High-grade squamous intraepithelial lesion

3.3. Sexually Transmitted Infections (STIs) profile in lesions

Table 2 below illustrates the prevalence of various infections, including Trichomonas vaginalis, *Candida albicans*, Herpes simplex, *Gardnerella vaginalis*, Aspergillus, HPV, and HIV, among women with different cervical intraepithelial neoplasia (LSIL and HSIL) grades.

3.4. Human papillomavirus and STI coinfection

Table 3 provides data on the prevalence of different infections (Trichomonas vaginalis, *Candida albicans*, Herpes simplex, *Gardnerella vaginalis*, and Aspergillus) among individuals with LR (low-risk) genotypes of HPV 6 and HPV 11. There is a statistically significant association between Trichomonas vaginalis and candida albicans infection and LR cytology, Individuals infected with Candida albicans have twice the odds of having LR cytology compared to those without the infection. HIV infection shows a strong positive association with LR cytology. The odds of having LR cytology are nearly 14 times higher among individuals infected with HIV compared to those who are not.

Table 4 below presents the percentages (and corresponding numbers, n) of different microbial infections detected in association with various HPV genotypes (HPV 16, HPV 18, HPV 45, and HPV 58).

Table 2. Prevalence of various infections

	Trichomnas vaginalis n(%)	*Candida albicans* n(%)	Herpes simplex n(%)	*Gardnella vaginalis* n(%)	Aspergillus n(%)	HPV n(%)	HIV n(%)
Normal	**136(77.7%)**	**54(56.2%)**	**6(85.7%)**	**43(74.1%)**	**-**	**13(12.3%)**	**-**
LSIL	**27(15.4%)**	**42(43.8%)**	**1(14.3%)**	**15(25.9%)**	**7(100%)**	**75(71.4%)**	**63(70%)**
HSIL	**12(6.8%)**	**-**	**-**	**-**	**-**	**17(16.1%)**	**27(30%)**
Total	**175**	**96**	**7**	**58**	**7**	**105**	**90**
P value	**0.005**	**0.0001**	**NS**	**0.002**	**NS**	**0.0001**	**NS**

Table 3. Presentation of the different cervical lesions and the identified LR-HPV genotypes

LR Genotypes	HPV 6 % (n)	HPV 11 % (n)	OR
Trichomonas vaginalis	37.93 (11)	34.99 (7)	2.6
Candida albicans	31.01 (9)	14.99 (3)	2
Herpes simplex	27.59 (8)	25.01 (5)	1.02
Gardnella vaginalis	3.46 (1)	25.01 (5)	2.1
Aspergillus	100 (29)	100 (20)	-
HIV	3.46 (1)	1	13.89
TOTAL	12	46	

Table 4. Presentation of different cervical lesions and HR-HPV genotypes identified

LR Genotypes	HPV 16 % (n)	HPV 18 % (n)	HPV 45 % (n)	HPV 58 % (n)	OR
Trichomonas vaginalis	**40 (2)**	**20 (2)**	**54.5 (6)**	**0 (0)**	**4.2**
Candida albicans	**20 (1)**	**30 (3)**	**9.09 (1)**	**0 (0)**	**5.9**
Herpes simplex	**0 (0)**	**20 (2)**	**18.1 (2)**	**0 (0)**	**1.2**
Gardnella vaginalis	**20 (1)**	**30 (3)**	**18.1 (2)**	**0 (0)**	**3.3**
Aspergillus	**20(1)**	**-**	**-**	**0 (0)**	**-**
HIV	**(1)**	**(0)**	**(2)**	**0 (1)**	**13.89**
TOTAL	**5**	**10**	**11**	**1**	

4. Discussion

4.1. Sociodemographic information

The observed differences in age distribution among various brackets highlight the heterogeneity within the population under study. Similar age disparities have been documented in other populations, with younger individuals often presenting with distinct health needs and risk profiles compared to older age groups(12). For instance, a study by Smith *et al*. revealed that younger individuals were more likely to engage in risky health behaviors, such as substance use and unprotected sexual activity, which could impact their health outcomes over time (13).

The distribution of individuals across different civil status categories reflects the social dynamics within the population. Comparable patterns of civil status have been reported in previous studies, with variations in marital status linked to differential access to social support networks and healthcare resources(14). For example, divorced or widowed individuals may experience greater social isolation and have fewer resources available for managing health-related challenges (15).

4.2. Sexually Transmitted Infections (STIs) characterization in lesions

The distribution of cervical cytology results in this study, with a predominance of normal cytology and a smaller proportion of LSIL and HSIL cases, is consistent with findings from similar studies conducted in diverse populations (16). For example, a recent population-based study by Smith *et al*. reported comparable proportions of normal cytology and LSIL/HSIL cases among women undergoing cervical cancer screening (17). The predominance of normal cytology over low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL) in the Endom population may be influenced by several factors, such as the age distribution, reproductive history, sexual behaviour, and lack of certain behaviors, such as smoking and the presence of a younger population.

4.3. Sexually Transmitted Infections (STIs) profile in lesions

The greater prevalence of Trichomonas vaginalis among

individuals with LSILs than among those with HSILs is consistent with previous studies highlighting the association between Trichomonas vaginalis infection and cervical dysplasia(18). Recent research by Masha *et al*. revealed a similar trend, emphasizing the need for targeted interventions to address Trichomonas vaginalis infection in cervical health programs (19). The greater prevalence of Trichomonas vaginalis among individuals with LSILs may be multifactorial, involving a complex interplay of sexual behavior, immunological factors, the vaginal microenvironment, coinfections, and socioeconomic factors. This situation has also been observed for *Candida albicans*, and recent studies by Li *et al*. and Park *et al*. have explored the role of *Candida albicans* in cervical dysplasia, suggesting possible mechanisms for its involvement (20)**.** Herpes simplex (HSV) and *Gardnerella vaginalis*: Although Herpes simplex and Gardnella vaginalis exhibited varying prevalence between the LSIL and HSIL groups, their associations with cervical dysplasia warrant further investigation. Studies by Javanbakht *et al*. have explored the potential role of Herpes simplex and *Gardnerella vaginalis* in cervical health, highlighting the need for comprehensive diagnostic and management strategies(21). The high prevalence of HPV among individuals with both LSILs and HSILs is consistent with its established role as a primary driver of cervical dysplasia and cancer. Recent studies by de Sanjose *et al*. and Bruni *et al*. have provided comprehensive insights into the global burden of HPV infection and its association with cervical neoplasia(22). Additionally, the higher prevalence of HIV among individuals with HSILs highlights the intersectionality of HIV and cervical dysplasia, emphasizing the importance of integrated care approaches.

4.4. Human papillomavirus and STI coinfection

The prevalence of LR HPV genotypes alongside *Candida albicans* colonization reflects the complex interplay between fungal infections and HPV persistence. Studies have suggested a potential link between *Candida albicans* and HPV-related lesions, with some evidence indicating an association between *Candida albicans* biofilms and cervical dysplasia (23). The high prevalence of *Candida albicans* in cervical lesions may be attributed to several factors. The higher prevalence of *Candida albicans* in cervical lesions likely results from a combination of immunosuppression, hormonal fluctuations, antibiotic use, sexual activity, underlying medical conditions, and coinfections. The coexistence of LR HPV genotypes with HIV infection highlights the increased vulnerability of immunocompromised individuals to viral coinfections. Adler emphasized the importance of integrated care approaches for HIV-positive individuals with HPV-related lesions, underscoring the need for targeted interventions to improve health outcomes (24). Integrated care approaches for HIV-positive individuals with HPV-related lesions are essential for providing comprehensive, preventive, and patient-centered care. By addressing the unique healthcare needs of this population, integrated care models will contribute to improved health outcomes, reduced healthcare disparities, and efficient resource utilization. The data presented highlight the cooccurrence of specific HPV genotypes with various microbial infections in cervical tissue samples. These high-risk HPV genotypes are commonly associated with cervical cancer. The presence of Trichomonas vaginalis and *Candida albicans* alongside HPV 16 and HPV 18 raises questions about potential interactions between these pathogens. Gillet *et al*. suggested a possible association between Trichomonas vaginalis infection and increased risk of HPV acquisition and persistence(25). Similarly, the co-occurrence of *Gardnerella vaginalis* with HPV 45 and HPV 58 warrants an investigation into the relationship between BV and HPV infection. The absence of herpes simplex virus (HSV) and Aspergillus in HPV-positive samples suggests potential differences in their association with HPV infection compared to other microbial pathogens. Although limited research exists on the relationship between HSV or Aspergillus and HPV-related lesions, future studies could elucidate their role in cervical health and disease progression. The presence of HIV in a subset of HPV-positive samples has important clinical implications. HIV-positive individuals are at increased risk of HPV-related diseases, including cervical cancer. Integrated care approaches, as discussed previously, are essential for managing concurrent HIV and HPV infections and reducing the risk of cervical cancer development.

The findings from this study underscore the complex interplay between human papillomavirus (HPV) genotypes and microbial coinfections in cervical samples. Specific HPV genotypes exhibit varying degrees of association with microbial coinfections. While some genotypes, such as HPV 16 and HPV 18, demonstrate higher prevalence rates alongside certain pathogens, such as Trichomonas vaginalis and *Candida albicans*, others, such as HPV 45 and HPV 58, show different patterns of microbial co-occurrence. The presence of microbial coinfections, particularly those with established associations with HPV-related diseases, may have clinical implications for cervical health. Understanding the relationship between HPV genotypes and microbial pathogens can inform screening, diagnostic, and treatment strategies aimed at reducing the burden of cervical lesions and preventing cervical cancer development. Although this study provides valuable insights into the microbial landscape of cervical samples, further research is warranted to elucidate the underlying mechanisms driving HPV-microbial interactions. Prospective studies with larger sample sizes and longitudinal follow-up are needed to validate these findings and identify potential causative relationships between specific pathogens and HPV-related lesions. The integration of care for HIV-positive individuals with HPV-related lesions is essential for addressing the complex healthcare needs of this population. By providing comprehensive screening, treatment coordination, preventive measures, and psychosocial support, integrated care models

can improve health outcomes and quality of life for affected individuals.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

Concept: E.L.E.E., Design: E.L.E.E., Data Collection or Processing: N.A.F.E., Analysis or Interpretation: E.R.M., Literature Search: M.C.B., Writing: E.L.E.E., A.H., K.M.M.L.

Ethical Statement

The study was conducted in accordance with the Helsinki Declaration and the Cameroonian Ministry of Public Health's guidelines for using human experimental models in clinical research. The National Ethics Committee of Cameroun, registration number 2022/12/312/CE/CNERSH/SP, granted ethical clearance to carry out this action. Regional delegations were also granted administrative clearance. Each woman received an explanation of the study's purpose and goals in the language they could best understand—French or English—as well as answers to any questions. Enrolment was restricted to women who had signed an informed consent form for their involvement. The study was entirely voluntary, and women had the right to refuse to answer any questions or to stop participating at any time.

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