High genotypic diversity of human papillomavirus among women in Cameroon: implications for vaccine effectiveness

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A R T I C L E   I N F O

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A B S T R A C T

Background: The burden of human papillomavirus (HPV) is high in Cameroon, but knowledge on high-risk oncogenic HPV (HR-HPV) is limited. Our study sought to ascertain the HR-HPV genotypes circulating in Cameroon. Methods: A cross-sectional study was conducted among non-vaccinated women in Cameroon. Detection of HR-HPV was performed by real-time PCR on cervico-vaginal swabs. Predictors of HR-HPV were determined following logistic regression analysis, with p < 0.05 considered statistically significant. Results: In total, 364 women were enrolled, with a median age of 41 (34–50) years. Of these, 3.0% were smokers and 26.0% reported having more than three sexual partners. The overall HR-HPV positivity rate was 21.43% (95% CI 17.21–25.64). Predictors of HR-HPV were young age, i.e. < 41 years (aOR: 95% CI) 0.408 (0.194–0.862); p = 0.018), smoking (aOR 5.199 (1.314–20.575); p = 0.018), and having more than three sex partners (aOR: 2.335 (1.133–4.811); p = 0.022). Overall, 12 HR-HPV genotypes were identified, with 26.98% women coinfectected with at least two HR-HPVs, including one case of a triple coinfection. According to the circulating genotypes, potential vaccine effectiveness was 47% for the 4-valent vaccine and 70% for the 9-valent vaccine. Conclusion: Within the Cameroonian context, at least one out of five women is likely to be an HR-HPV carrier, especially among young people, smokers, and those with multiple sexual partners. Importantly, HR-HPV infection is highly diversified, with vaccine efficacy ranging from about 47% (4-valent) to 70% (9-valent).

Background

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the world, particularly affecting sexually active adolescent and young adult women (Akom et al., 2003; Ali et al., 2019). More than 75% of women are estimated to have had at least one contact with the virus during their sexual life (Bansal et al., 2014; Obiri-Yeboah et al., 2017; Olesen et al., 2014). Fortunately, despite the high

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genetic diversity of HPV, more than 90% of immunocompetent women undergo significant viral clearance 12 to 24 months after new infections (Garland et al., 2017; UN, 2020). Currently, more than 120 HPV genotypes circulate in the world, divided into two groups: low-risk oncogenic human papillomaviruses (LR-HPV) and high-risk oncogenic human papillomaviruses (HR-HPV). At least 14 genotypes of HR-HPV have already been identified: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 66. Importantly, HPV16 and HPV18 remain the most prevalent and virulent HR-HPV genotypes, causing about 70% of all invasive cervical cancers (ICCs) worldwide, although there have been recent rises in other HR-HPV genotypes (Banister et al., 2017; Muñoz et al., 2009; Prakash et al., 2016).

Cervical cancer is associated with persistent infection with one HR-HPV genotype, with an estimated 500,000 new cases and nearly 500,000 deaths worldwide each year (Ferlay et al., 2015; Glesen et al., 2014). According to the World Health Organization (WHO), the annual number of new cases of cervical cancer is expected to increase from 500,000 to 700,000 between 2018 and 2030. During the same period, the annual number of deaths is expected to increase from 311,000 to 400,000, with 98% of these deaths occurring in resource-limited settings (RLS). This is particularly true in sub-Saharan Africa (SSA), where the HIV epidemic and other well-known risk factors favour HPV infection and subsequent occurrence of cervical cancer (Ferlay et al., 2015; WHO, 2015).

The high burden of diseases associated with HR-HPV in sub-Saharan Africa therefore highlights the urgent need to discriminate between HR-HPV genotypes in some African regions such as Cameroon, where the prevalence of HR-HPV appears to be high (38.49% and 30.1%, respectively, in studies by Sosso et al. and Njouom et al.) (Sosso et al., 2020; Centre Pasteur du Cameroun, s.d.). Moreover, several European and American countries are already using the new 9-valet HR-HPV vaccine, which has shown 97.4% effectiveness in Europe and 96.7% in America, proving effective against seven HR-HPV genotypes (16, 18, 31, 33, 45, 52, and 58), in contrast to the bivalent and quadrivalent vaccines adopted by several SSA countries, covering only HR-HPV genotypes 16–18 (ANSM, 2006; De Vuyst et al., 2015; Garland et al., 2017; Kabyene et al., 2015; Sosso et al., 2020; Veldhuizen et al., 2012).

Thus, in a context of poor vaccination strategy, primary prevention against HR-HPV in SSA should be supported by evidence-based studies establishing HR-HPV genotypes circulating in these settings. Optimizing primary prevention, alongside other prevention strategies (secondary and tertiary) already in place in SSA, would therefore help to overcome the high burden of cervical cancer across the continent (Beyazit et al., 2018; Bouassa et al., 2017; Mboumba Bouassa et al., 2019). The aim of our study was to determine the prevalence of HR-HPV positivity and its associated factors, to ascertain the genetic diversity of HR-HPV genotypes, and to assess the adequacy of vaccine strategies in SSA settings such as Cameroon.

**Methods**

**Study design**

A cross-sectional and analytical study was conducted among patients attending routine consultation in two reference hospitals in Cameroon.

**Study sites and period**

The study was conducted from June 2020 to May 2021 at the Gyneco-obstetric and Pediatric Hospital in Yaoundé (GOPHY) and the Laquintinie Hospital in Douala (LHD), which are reference health facilities for the clinical management of cervical cancer in the two major cities of the country.

**Study population and enrolment process**

Following a convenient sampling, eligible women (sexually active, aged ≥ 18 years, and non-vaccinated) who consented to participate in the study were enrolled. Pregnant women and those who had undergone a total hysterectomy were excluded. A standardized questionnaire was administered to all participants, covering sociodemographic characteristics, and gyneco-obstetric and reproductive history. Whole-blood and cervical samples were then collected.

**Sample collection and analysis**

A minimum sample size of 313 women was obtained using the following statistical formula:

\[
N = p(1 - p)(Z_a^2 / d^2)
\]

Where \(N\) was the minimum number of participants, \(p\) was the prevalence of cervical cancer among women in Cameroon in 2016 (\(p = 23.6\%\)), and \(Z_a\) was the 95% confidence interval (\(Z_a = 1.96\)), with \(d\) being the error rate set at 5\% (\(d = 0.05\)). Ultimately, 364 women took part in the study.

Blood and cervical samples were collected from all consenting women, with HIV testing, CD4 cell counts, and HPV genotyping performed at the Chantal Biya International Reference Centre for Research on HIV/AIDS Prevention and Care (CIRCB) in Yaoundé, Cameroon (http://ciscb.cm/btc_ciscb/web/). Briefly, the CIRCB is a reference centre for HIV/AIDS, performing laboratory analysis with external quality control and proficiency testing for HIV screening (CDC DTS), early infant diagnosis of HIV (CDC PT programme), and CD4 and viral load testing (QASI, Canada).

**HIV screening test**

HIV screening was performed following a two-step serial algorithm, according to the Cameroon national guidelines and as previously described (Billong et al., 2017).

**CD4 lymphocyte counts**

Whole blood from EDTA tubes for each participant was used to ascertain the CD4 T lymphocyte count, using flow cytometry on a FACSCalibur® (Becton Dickinson), as previously described (wwwbdbiosciences.com/en-us/instruments/clinical-instruments/clinical-cell-analyzers).

**Cervical smear**

Cervico-vaginal smear (CVS) slides were prepared using the standard Papanicolaou staining protocol (http://www.lhcworld.com_/protocols/special_stains/papanicolaou_stain.htm). Interpretation of slides was performed by specialised pathologists, according to the Bethesda 2001 guidelines (Appar et al., 2003). Grading of the CVS profiles observed was classified as follows: normal cytology results (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).

**Genotyping algorithm**

Genotyping was performed using two types of real-time PCR. First, Abbott™ real-time PCR was used for initial screening, with only the Abbott-positive samples retained for further HR-HPV genotype characterization using the second real-time PCR — https://maxanim.com/genetics/pcr/hpv-genotypes-14-rt-pcr-quant-ce-v67-100rtr/. The Abbott™ real time PCR was performed as per the manufacturer’s instructions (www.molecular.abbott/int/en/products/infectious-disease/realtime-high-risk-hpv).
Briefly, viral DNA was extracted and amplified using the Abbott real-time PCR, with simultaneous detection and genotyping of HPV 16 and HPV 18, and a pooled detection of 12 other HR-HPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

The Sacace® Biotechnologies genotyping platform HPV Genotypes 14 Real-TM Quant (www.sacace.com/manuals.htm) was used for in vitro real-time amplification for the qualitative or quantitative detection and genotyping of HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. The analytical specificity of the HPV Genotypes 14 Real-TM Quant kit was ensured by the selection of specific primers and probes, with PCR conditions as described elsewhere (Kuassi-Kpede et al., 2021).

**Data analysis**

Data were collected using Excel 2016, and analyses were performed using Epi-info version 7 and Graph pad prism version 6. The odds ratio (OR) was calculated to determine whether the variable was a risk or protective factor. A logistic regression model was used to identify factors independently associated with HR-HPV positivity; the confidence interval (CI) for statistical tests was set at 95%, and the null hypothesis was rejected at a threshold of 5%. Chi-square or Fisher exact tests were used whenever appropriate. All p-values ≤ 0.2, obtained in univariate analysis, were taken into account in the multivariate analysis.

**Ethical considerations**

Ethical approval was obtained from the National Ethics Committee (ref. 2020/06/1249/CE/CNERSH/SP) and administrative authorizations were provided by the study sites (GOPHY and LHD). Written informed consent (in both national languages) was obtained from the participants, and laboratory results were provided free of charge to participants for their own clinical benefit.

**Results**

**Baseline characteristics of the study population**

Overall, 364 women were enrolled, with a median age (interquartile range, IQR) of 41 (34–50) years; of these, 51.92% resided in Douala and 48.07% in Yaoundé. Regarding socio-demographic parameters, women with high education (secondary school and university) were more represented than those with lower education (illiterate and primary school) — 85.98% versus 14.02, respectively. Single women (38.73%) were less represented than those who were married, divorced, or widowed (61.26%). There were more Christian women (53.57%) than those practicing other religions (46.43%). Women with regular or irregular sources of income (52.74%) were more represented than those with low incomes (47.25%). Finally, women with more than four children were more represented (77.47%) than those with fewer than four children (22.52%).

Regarding sexuality, the majority of women enrolled had a median of over three sexual partners (74%), with 81.04% having their first sexual intercourse before the age of 20 years. In terms of clinical features, 3.02% of the women were smokers, 3.55% were HIV-positive, 53.02% used contraceptives, and 7.41% had a positive smear test.

**HR-HPV positivity rate and associated factors**

The overall HR-HPV positivity rate was 21.43% (78/364), with young women (< 41 years) showing a higher rate than the older group (21% vs 14%, respectively). With regard to education, women who had left school at primary level had the highest positivity rate (24%), followed by women with a higher education level (17%; p = 0.629). Regarding sources of income, underpaid women had the highest positivity rate (20%), followed by paid women (15%; p = 0.335). Marital status data revealed that single women (22%) were more positive for HR-HPV than widows (20%; p = 0.142). The region with the highest proportion of HR-HPV-positive women in this study was the western region (18%), followed by the central region (16%; p = 0.847). In terms of religion, Catholic women (18%) had the highest rate of HR-HPV positivity, followed by Muslims (9%; p = 0.178). Data on age of first intercourse (coitarche) among the participants showed that those who were sexually active at 15–20 years had the highest rate of HR-HPV positivity (19%), followed by those sexually active after the age of 20 (13%; p = 0.428). With regard to the number of sexual partners, women with more than three partners had the highest positivity rate (24%; p = 0.005). Among the participants with high-grade intraepithelial cervical lesions, 25% were infected with HR-HPV, although there was no statistically significant association (p = 0.443, OR = 1.62, 95% CI 0.42–6.17). Regarding the consumption of tobacco, participants who used tobacco had a higher positivity rate (55%) than those who did not use tobacco (16%; p = 0.005).

**Table 1** gives a detailed breakdown of the overall distribution of HR-HPV positivity and associated factors following bivariate analysis. After linear regression adjustment, age, multiple sex partners, and smoking were identified as predictors of HR-HPV positivity (p = 0.01, p = 0.02 and p = 0.01, respectively, as shown in **Table 2**).

**Molecular epidemiology of HR-HPV in the study population**

The Abbott Real-Time PCR platform revealed that 78/364 of the women were infected with HR-HPV (21.43%; 95% CI 17.21–25.64). Of the 78 HR-HPV-positive samples, the Sacace® Biotechnologies platform successfully characterized 80.76% (63/78). Overall, 12 HR-HPV genotypes were identified: 18 (30.15%; 9/63), 16 (19.04%; 12/63), 39 (17.46%; 11/63), 58 (15.87%; 10/63), 66 (9.52%; 6/63), 59 (7.93%; 5/63), 35 (6.34%; 4/63), 52 (6.34%; 4/63), 33 (3.17%; 2/63), 45 (3.17%; 2/63), 56 (1.58%; 1/63), and 68 (1.58%; 1/63) (**Figure 1**). Around 22.22% (14/63) of these women were coinfected with at least two HR-HPVs. These included genotypes 16 and 18 (2/24), 16 and 51 (1/14), 16 and 59 (1/14), 18 and 35 (1/14), 18 and 59 (1/14), 18 and 66 (1/14), 39 and 33 (1/14), 39 and 52 (1/14), 39 and 59 (1/14), 59 and 35 (1/14), 66 and 58 (1/14), and a triple co-infection involving genotypes 18, 39, and 58. Overall, this distribution was similar between women residing in Yaoundé and those residing in Douala (all p > 0.05).

**Potential vaccine effectiveness**

Based on the current local vaccine strategy (bivalent or quadrivalent vaccines, protecting against HR-HPV 16 and 18), 47% (30/63) of cases in our study population would have been covered (**Figure 2a**). A much greater proportion (70%; 44/63 — **Figure 2b**) would have been protected with the 9-valent vaccine (effective against HR-HPV 16, 18, 31, 33, 45, 52, and 58).

**Discussion**

This study aimed to describe the distribution of circulating high-risk oncogenic human papillomavirus (HR-HPV) genotypes and to identify the determinants of this infection in Cameroon. The results showed an HR-HPV positivity rate of 21.43%, which was very high compared with the global prevalence (11–12%) but still below the overall positivity rate found in SSA (26%) (Beyazit et al., 2018; Gravitt et al., 2007; Prakash et al., 2016). In line with a study by Atashili et al. in Nigeria (Atashili et al., 2012; Sosso et al., 2020), the most represented age group in our study population (median age 41 years) was 30–39 years. This observation may be supported by the fact that young people (aged 19–39 years) are predominant in Cameroon and SSA in general, are more at risk of a surge in HR-HPV (Al-Awadhi et al., 2019; Sellors et al., 2000), and account for more than 50% of infections worldwide (Beyazit et al., 2018; Gravitt et al., 2007; Prakash et al., 2016).
Interestingly, after bivariate and multivariate analysis, only three factors remained statistically associated with HR-HPV in our study population: a young age (<41 years), multiple sex partners (>3), and the consumption of tobacco. As previously discussed, young women stand a higher risk of HR-HPV in several RLS, which is also partly due to the immaturity of the cervix during adolescence, as many among them engage in sex at early age (Al-Awadhi et al., 2019; Beyazit et al., 2018; Gravitt et al., 2007; Prakash et al., 2016; Sellors et al., 2000). Furthermore, several studies have shown a significant increase in HR-HPV among women having sex with multiple partners (Castellsagué and Muñoz, 2003; Hernandez et al., 2008; Sellors et al., 2000). Additionally, smoking may act as a cocarcinogen, increasing the risk of developing cancer by causing additional DNA damage to HPV-infected cells, and may lead to overexpression of viral proteins E6 and E7. Furthermore, tobacco significantly reduces the production of immune cells, which in turn decreases the host immune response to HPV. (Castellsagué et al., 2014; Castellsagué and Muñoz, 2003; Kuassi-Kpede et al., 2021; Parkin, 2006).

Twelve HPV genotypes were identified in this study — 16, 18, 33, 35, 39, 45, 52, 56, 58, 59, 66, and 68 — with a predominance of genotypes 18, 16, 39, and 58, respectively. This finding illustrates high heterogeneity in the distribution of the HR-HPV genotypes among women in SSA, as reported previously (Mbulawa et al., 2018; Petrelli et al., 2016; Sangvaa-Lugomaa et al., 2011). Although the predominance of HR-HPV genotypes 18 and 16 is in line with the global epidemiology (Clifford et al., 2017; Veldhuijzen et al., 2012), our findings suggest a growing trend for other HR-HPV genotypes in SSA, and especially 39 and 58. This finding is supported by studies by Jary et al. in Mali.
and Ferre et al. in Togo, where this unusual distribution of the different genotypes was also observed, with large proportions of the other genotypes (Jary et al., 2021; Chinyowa et al., 2018; Ferré et al., 2019; Mboumba Bouassa et al., 2019; Obiri-Yeboah et al., 2017).

Of all the genotypes identified in this study, only two could have been covered by the quadrivalent vaccines available locally. Importantly, our results suggest that a prophylactic vaccination based on quadrivalent or bivalent vaccines would have guaranteed a vaccine efficacy of just 47% in the study population. Alternatively, the 9-valent vaccine (not available in Cameroon and in most RLS) would have covered six of the HR-HPV genotypes found in this study, protecting 70% of the target population. This finding supports the use of a multivalent vaccine (specifically the 9-valent vaccine) among young adolescents girls (i.e. uninfected targets) for adequate protection against HR-HPV in order to ensure an optimal prevention of cervical cancer, as suggested in the study by Mboumba et al. in Bangui and Chad, which suggested that this vaccine could be beneficial for the prevention of HPV-associated diseases (Catarino et al., 2016; Doh et al., 2017; Kunckler et al., 2017; Mboumba Bouassa et al., 2018, 2019). Furthermore, updating current vaccines for the newly detected genotypes in our context would secure the control of HR-HPV and aid the elimination of cervical cancer in RLS (Badial et al., 2018; Kaldy, 2018). Implementing such strategies, including free vaccination campaigns for girls aged 12–13 and for boys in secondary schools (as is the case in parts of the western world) would support countries in the elimination of HPV-associated cervical cancers (de Sanjose et al., 2010; Kaldy, 2018). With vaccine coverage now reaching 80% among Australian girls and 75% among Australian boys aged 15 and above, circulation of the virus, and therefore the risk of new infections and cervical cancers, would now be hampered according to epidemiological modelling (de Sanjose et al., 2010; Kaldy, 2018).

In our study, cases of cervical lesions were also found among those negative for HR-HPV. Although this is uncommon, other factors, such as infections caused by herpes viruses or Chlamydia trachomatis (not investigated in our study), are also responsible for cervical lesions. Moreover, reasons for gynecological consultations among women with cervical lesions include post-conization follow-up (conization refers to a surgical intervention that aims to remove HPV-induced lesions on the cervix). This suggests the need for further investigations in our context.

One limitation of this study was that, among the cases of HR-HPV reported, there was found to be a discrepancy between both analytic platforms, which led to the non-characterization of 15 samples. This demonstrates the value of implementing HPV sequencing to further charac-
terize viral lineages, and thus possibly adapting national guidelines towards an optimal vaccination strategy to prevent HPV infection.

Conclusion

In this SSA setting, with about one in five women likely to be an HR-HPV carrier, the risk of infection is driven by young age, smoking, and multiple sexual partners. Importantly, HR-HPV infection is highly diversified, with vaccine efficacy ranging from about 50% (quadrivalent) to 70% (nonavalent). Furthermore, some HR-HPV genotypes (e.g. 39, 59, and 66) are not covered by current vaccines. This evidence calls for more in-depth studies to further adapt local vaccination strategies to circulating genotypes.

List of 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 papillomavirus
HR-HPV: high-risk oncogenic human papillomavirus
LR-HPV: low-risk oncogenic human papillomavirus
PLHV: People living with HIV
RT-PCR: real-time polymerase chain reaction
WHO: World Health Organization

Declarations

Ethical approval and consent to participate

This study obtained ethical clearance from the CIRCB Ethics Committee on (project no. 1810) and also authorization from CIRCB for where the study was conducted. The participants freely signed informed consent forms, which were written in French and English (according to the first language of the participant), while the minor participants provided their assent.

Consent for publication

Not applicable.

Disclosure statement

The 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 declare that this study is without conflicts of interest.

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Authors’ contributions

Michel Carlos Tommo Tchouaket, Joseph Fokam, Samuel Martin SOSso, Ezechiel Ngoufack Jagni Semengué, and Bouba Yagai initiated the manuscript. Michel Carlos Tommo Tchouaket, Joseph Fokam, Samuel Martin SOSso, Ezechiel Ngoufack Jagni Semengué, Bouba Yagai, Rachel Kamgaing Simo, Zacharie Sando, Alex Durand Nka, Gaëlle Panka Tchinda, Désiré Takou, Nadine Fainguem, Collins Chenwi, Aude Chris-telle Kae, Aissatou Abba, Marie Krystel Nnomo Zam, Carlo-Federico Perno, Vittorio Colizzi, and Alexis Ndjolo substantially revised the manuscript. Michel Carlos Tommo Tchouaket, Joseph Fokam, Samuel Martin SOSso, Ezechiel Ngoufack Jagni Semengué, Bouba Yagai, Desire Takou, Nadine Fainguem, Collins Chenwi, Aude Christelle Kae, Aissatou Abba, and Marie Krystel Nnomo Zam contributed to the data acquisition and analyses. Michel Carlos Tommo Tchouaket, Joseph Fokam, Ezechiel Ngoufack Jagni Semengué, Bouba Yagai, Désiré Takou, Zacharie Sando, Carlo-Federico Perno, Vittorio Colizzi, and Alexis Ndjolo contributed to data interpretation. All the authors approved the final version for publication.

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Approval

Not required.

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