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Molecular detection of high-risk papillomaviruses and vaccination status in normal cytology in Congo

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Abstract

Objective: The aim of this study was to identify the molecular prevalence of high-risk HPV infection and the distribution of genotypes present in normal cytology, as well as to determine the vaccination status of our study population.

Methods: 110 cervical samples were taken from individuals, and 1 ml of each sample was added to the Xpert HPV cartridge in the sample compartment before it was placed in the Cepheid GeneXpert system. Detection was performed simultaneously via amplification of the *E6* and *E7* genes in five fluorescent channels (HPV16, HPV18/45, HPV31/33/35/52/58, HPV51/59, and HPV39/56/66/68a).

Results: 36/110 (33%) of all samples tested were positive for HPV DNA. The predominant genotypes were HPV16 (12.7%) and other pooled HR-HPV types (8.2%). All women who received the Gardasil-9 vaccine (3.6%) had HPV, and infection was associated with travel outside Africa. 96.4% of the screened individuals had not received any HPV vaccine.

Conclusion: Our research confirms a widespread HR-HPV infection in our population and extends the importance of studies on the molecular prevalence of HPV, particularly in women with normal cytology and apparent good health, in view of the cruel lack of public awareness of HPV infections.

Keywords: *High-risk Human Papillomavirus; normal cytology; vaccination status; molecular epidemiology; HPV genotypes*

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Ethics approval. The study was conducted with the informed consent of the patients. The study protocol was approved by the Health Sciences Research Ethics Board (HSRB) (Protocol No. 251/MRSIT/IRSSA/CERSSA dated January 20th, 2023).

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Молекулярная диагностика папилломавирусов высокого риска и статус вакцинации среди женщин с нормальной цитологией в Конго

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Резюме

Цель: Цель данного исследования – определение молекулярными методами распространенности ВПЧ-инфекции высокого риска и распределения генотипов вируса среди женщин с нормальной цитологией, а также определение статуса вакцинации в исследуемой когорте.

Методы: Исследованы 110 цервикальных образцов, по 1 мл каждого образца вносили в картридж Xpert HPV в отсеке для образцов перед помещением в систему Cepheid GeneXpert. Одновременная детекция всех мишеней при амплификации генов *E6* и *E7* проводилась в 5 флуоресцентных каналах (HPV16, HPV18/45, HPV31/33/35/52/58, HPV51/59 и HPV39/56/66/68a).

Результаты: Из всех исследованных образцов 36/110 (33%) были положительными по ДНК ВПЧ. Преобладающими генотипами были ВПЧ-16 (12,7%) и прочие объединенные генотипы ВПЧ высокого риска (8,2%). Все женщины, получавшие вакцину Gardasil-9 (3,6%), имели ВПЧ-инфекцию, предположительно ассоциированную с поездками за пределы Африки. Остальные участницы исследования (96,4%) никакой вакцины против ВПЧ не получали.

Заключение: Наше исследование подтверждает широкую распространенность инфекции, вызванной ВПЧ высокого риска, в нашей популяции и подчеркивает важность изучения распространенности ВПЧ молекулярными методами, особенно у здоровых женщин с нормальной цитологией, в связи с высоким уровнем неосведомленности населения о ВПЧ-инфекции.

Ключевые слова: *ВПЧ высокого риска; нормальная цитология; статус вакцинации; молекулярная эпидемиология; генотипы ВПЧ*

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Introduction

Cervical cancer (CC) is a serious health problem that kills many people every year. It accounts for 10% of all malignant tumours and is the fourth most common cancer in women worldwide, with an incidence of 604,127 new cases (13,3%) [1–3]. Sub-Saharan Africa is one of the regions with the greatest impact of CC, with low screening rates and delayed diagnosis and treatment [4, 5]. In 2020, cervical cancer had a 25.5% increase in incidence rate[1] and 14.2% of cancer deaths were caused by CC in the Congo [3, 6, 7]. More than 95% of cervical cancers are caused by sexually transmitted HPV, with 90% of these women living in low- or middle-income countries [8].

[1]IARC. Cancer Today. Available at: http://gco.iarc.fr/today/home

Human papillomavirus (HPV) is a common sexually transmitted infection that is diagnosed worldwide [4]. Currently, 202 different HPV genotypes have been identified, according to the International HPV Reference Center [5]. It is estimated that HPV causes 610,000 new cases of cancer and 250,000 deaths per year [9, 10]. Sub-Saharan Africa is the region most affected, with a 24% prevalence of HPV infection in women with normal cytology [11]. In the Republic of Congo, recent studies of HPV in normal cytology have identified the main characteristics of HPV16, HPV35 and HPV33 infection [12–15]. The increase in HPV prevalence is the result of both a lack of CC screening and a lack of awareness among young Congolese.

The benefits of HPV vaccination are evident in high-income countries that introduced national HPV vaccination programmes earlier. In contrast, many countries in sub-Saharan Africa have not yet implemented national HPV vaccination programmes and still face low vaccination coverage in implementing countries [16, 17]. The new recommendation from the Strategic Advisory Group of Experts on Immunization (SAGE) is underpinned by concerns about the slow introduction of the HPV vaccine into vaccination programmes and the low overall population coverage, particularly in the poorest countries [8]. The HPV vaccine is highly effective in preventing HPV serotypes 16 and 18, which cause 70% of cervical cancers. Currently, the licensed HPV vaccines available are classified as bivalent, quadrivalent, and non-valent, depending on the number of HPV strains targeted [17]. In order to highlight the importance of cervical cancer screening and the value of introducing vaccination programmes in the Congo, we undertook this study with the aim of identifying the molecular prevalence of high-risk HPV infection and the geographical distribution of genotypes present in normal cytology, as well as determining the vaccination status of our study population.

Material and methods

Study site

The study was carried out in the anatomo-cytopathology unit of the Centre Hospitalier et Universitaire de Brazzaville (CHU-B).

Participants and type of study

This was a descriptive cross-sectional study with retrospective data conducted in April 2023. The sampling method used was a random selection of 110 cervical samples, which were taken from women who had undergone a speculum examination.

Inclusion criteria

– Have a normal cervical smear cytology result in the CHU-B cytology report register.
– Have a contact number that can be reached.
– Be physically fit for the clinical examination.
– Have agreed to have the smear taken again and have given informed consent.
– Have a confirmed diagnosis of normal cytology after resampling.

Exclusion criteria

– Not having given consent.
– Have an abnormal cytological examination.
– Menstruating.
– Under antibiotic treatment.

The study was conducted with the informed consent of the patients. The study protocol was approved by the Health Sciences Research Ethics Board (HSRB) (Protocol No. 251/MRSIT/IRSSA/CERSSA dated January 20th, 2023).

Data and sample collection

A survey questionnaire, including information on socio-demographic characteristics, was completed for each patient. Smears were obtained using an Ayre spatula and an endocervical cytobrush and were stored in special tubes containing 4 ml of PreservCyt transport medium kept at −80 °C until processing.

DNA extraction and analysis of the DNA extract

DNA extraction was performed on all samples. A conventional PCR of a 268-bp fragment of the beta-globin gene with primers GH20 and PC0431 was performed to ensure the quality of the extract. The presence of the housekeeping gene and the absence of inhibitors were confirmed in all samples (100%).

HPV detection and genotyping

Genotyping was carried out by real-time PCR using GeneXpert technology in order to differentiate the HPV DNA present by molecular typing. The Xpert HPV Assay enables simultaneous detection via amplification of the *E6* and *E7* genes in 3 fluorescent channels (HPV16, HPV18/45, and other HR-HPVs such as HPV31/33/35/52/58/51/59/39/56/66/68a).

The assay also includes a human control gene (hydroxymethylbilane synthase [HMBS]) to verify the validity of the sample and amplification. An internal Probe Verification Control (PCC) is used to check reagent rehydration, filling of the PCR tube into the cartridge, probe integrity, and dye stability [18].

Execution of the test

For the execution of the test, 1 mL of sample was added to the cartridge in the sample compartment. The cartridge was then inserted into the device and the test started. After 60 minutes of the run, the typing result, interpreted by the Xpert software, was obtained in the form of a pool [18].

Statistical analysis

The correlation between HPV seroprevalence and independent variables was analysed using Pearson's chi-squared test and/or Fisher's exact test and Odd ratio. P values less than 0.05 were considered statistically significant. Microsoft Excel 2019 was used to create the database, and statistical analyses were performed using RStudio 2023.06.0+421 Mountain Hydrangea Release with R version 4.2.2.

Table 1. General characteristics of the study population associated with HPV infection
Таблица 1. Общая характеристика исследуемой популяции, связанной с инфекцией ВПЧ

Variables Характеристики	HPV / ВПЧ							
	Overall / Всего *n*	(%)	HPV– / ВПЧ– *n*	HPV– / ВПЧ– (%)	HPV+ / ВПЧ+ *n*	HPV+ / ВПЧ+ (%)	OR (IC 95%) / ОШ (95% ДИ)	*p*-value
Age Возраст								
17–27	27	24.5	15	13.6	12	10.9	Ref. / Реф.	0.3
28–37	37	33.6	25	22.7	12	10.9	0.60 (0.35–2.36)	
38–47	26	23.6	18	16.4	8	7.3	0.55 (0.32–1.65)	
48–57	11	10.0	8	7.3	3	2.7	0.46 (0.21–3.25)	
58–67	7	6.4	7	6.4	0	0.0	–	
68–71	2	1.8	2	1.8	0	0.0	–	
Alcohol consumption Употребление алкоголя								
No Нет	61	55.5	43	39.1	18	16.4	Ref. / Реф.	0.2
Yes Да	49	44.5	32	29.1	17	15.5	1.26 (0.56–2.83)	
Age of first sexual intercourse Возраст первого сексуального контакта								
< 18	70	63.6	48	43.6	22	20.0	Ref. / Реф.	0.01
≥ 18	40	36.4	27	24.5	13	11.8	1.05 (1.02–2.41)	
Tobacco consumption Употребление табака								
No Нет	92	83.6	64	58.2	28	25.5	Ref. / Реф.	0.1
Yes Да	18	16.4	11	10.0	7	6.4	1.45 (0.51–4.14)	
Multiple sexual partner Несколько сексуальных партнеров								
< 5	57	51.8	40	36.4	17	15.5	Ref. / Реф.	0.07
≥ 5	53	48.2	35	31.8	18	16.4	1.21 (0.54–2.70)	
Past STI								
No	88	80.0	59	53.6	29	26.4	Ref. / Реф.	0.06
Yes	22	20.0	16	14.5	6	5.5	0.76 (0.27–2.15)	
Number of pregnancies Число беременностей								
Aucun Не было	30	27.3	18	16.4	12	10.9	Ref. / Реф.	0.3
< 5	46	41.8	31	28.2	15	13.6	0.72 (0.21–2.07)	
≥ 5	34	30.9	26	23.6	8	7.3	0.46	
Contraceptive use Использование контрацептивов								
No Нет	40	36.4	31	28.2	9	8.2	Ref. / Реф.	0.05
Yes Да	70	63.6	44	40.0	26	23.6	2.03 (0.83–4.93)	
Risky sexual behavior Рискованное сексуальное поведение								

For continuation of Table 1, see page 3
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Variables Характеристики	HPV / ВПЧ							
	Overall / Всего *n*	(%)	HPV− / ВПЧ− *n*	HPV− / ВПЧ− (%)	HPV+ / ВПЧ+ *n*	HPV+ / ВПЧ+ (%)	OR (IC 95%) / ОШ (95% ДИ)	*p*-value
No Нет	58	52.7	45	40.9	13	11.8	Ref. / Реф.	0.02
Yes Да	52	47.3	30	27.3	22	20.0	2.53 (1.11–5.80)	
Multiple Infection HR-HPV Множественная инфекция ВПЧ высокого риска								
Yes Да	13	11.8	0	0.0	13	11.8	–	
No Нет	23	20.9	0	0.0	23	20.9	–	
Types of HPV / Типы ВПЧ							Ref. / Реф.	0.4
HPV16 / ВПЧ-16	14	12.7	7	6.4	7	6.4	2.89 (0.86–6.24)	
Others HR-HPV / Другие ВПЧ высокого риска	9	8.2	6	5.5	3	2.7	1.44 (0.46–2.56)	
HPV18/45 / ВПЧ-18/45	3	2.7	1	0.9	2	1.8	5.78 (0.67–8.94)	
HPV16/18/45 / ВПЧ-16/18/45	2	1.8	1	0.9	1	0.9	2.89 (0.32–4.15)	
HPV16/Others HR-HPV ВПЧ-16/Другие ВПЧ высокого риска	8	7.3	5	4.5	3	2.7	1.73 (0.11–4.79)	
HPV Vaccination Вакцинация против ВПЧ								
No Нет	106	96.4	71	55.4	35	31.8	Ref. / Реф.	0.08
Yes Да	4	3.6	4	3.6	0	0.0	0.70 (0.02–6.88)	
Number of vaccine injections Число инъекций вакцины							Ref. / Реф.	0.1
No injection Не было инъекций	106	96.4	71	55.4	35	31.8	–	
1 or 2 injections 1 или 2 инъекции	1	0.9	1	0.9	0	0.0	–	
3 injections 3 инъекции	3	2.7	3	2.7	0	0.0	–	
Travel outside Africa Путешествие за пределы Африки								
No Нет	106	96.4	72	65.5	35	31.8	Ref.	0.09
Yes Да	4	3.6	4	3.6	0.0	0.0	0.70 (0.07–7.03)	

Note. Age of first sexual intercourse, Risky sexual behavior, Contraceptive use ($p \leq 0.05$).

Примечание. Возраст первого полового акта, рискованное сексуальное поведение, использование контрацептивов ($p \leq 0{,}05$).

Results

Analysis of socio-demographic characteristics

With extremes ranging from 17 to 71 years of age, a peak in frequency (33.6%) was observed between 28 and 37 years of age, and the mean age of all women was 36.59 ± 12.86 years. We studied certain risk factors associated with HPV infection in women with cervical cancer, the frequencies of which are shown in **Table 1**.

HPV molecular prevalence and genotyping

Of the 110 samples, in line with our results, 36/110 (33%) of all samples were tested positive for HPV DNA.

Prevalence of HR-HPV with univariate risk factors

In this univariate logistic regression analysis, risky sexual behaviour and contraceptive use were positively associated with HR-HPV as predominant risk factors in our population (**Table 2**). The predominant genotypes

Table 2. Some characteristics of the study population associated with HPV vaccination
Таблица 2. Некоторые характеристики исследуемой популяции, связанные с вакцинацией против ВПЧ

Variables Характеристики	HPV Vaccination Вакцинация против ВПЧ					
			No Нет		Yes Да	
	n	(%)	*n*	(%)	*n*	(%)
Age Возраст						
17–27	27	24.5	27	24.5	0	0.0
28–37	37	33.6	35	31.8	2	1.8
38–47	26	23.6	24	21.8	2	1.8
48–57	11	10.0	11	10.0	0	0.0
58–67	7	6.4	7	6.4	0	0.0
68–71	2	1.8	2	1.8	0	0.0
Number of vaccine injections Число инъекций вакцины						
No injection Не было инъекций	106	96.4	106	96.4	0	0.0
1 or 2 injections 1 или 2 инъекции	1	0.9	0	0.0	1	0.9
3 injections 3 инъекции	3	2.7	0	0.0	3	2.7
Travel outside Africa Путешествие за пределы Африки						
No Нет	106	96.4	106	96.4	0	0.0
Yes Да	4	3.6	0	0.0	4	3.6

were HPV16 (12.7%) and other grouped HR-HPV types (8.2%). It should be noted that multiple HR-HPV infections were identified in 13cases. All the women who received the Gardasil-9 vaccine had HPV (3.6%), and infection was associated with travel outside Africa.

Vaccination status according to socio-demographic factors

Table 2 shows the distribution of HPV vaccination status by age in the population. It can be seen that the 28–37 and 38–47 age groups were those who had received the Gardasil-9 vaccine. 96.4% of the screened women had not received any HPV vaccine.

Discussion

In the management of women with ambiguous cytology results, HPV DNA testing for the early detection of precancerous cervical lesions is now widely recognised as a reliable and validated option. Recently, there has also been interest in the use of HPV testing in cervical samples from asymptomatic women without cytological abnormalities [19]

The prevalence of HPV infection (33%) was high in our study. In 2013, Boumba et al. revealed that 23.5% of Congolese women with normal cytology had HPV+. 10 years after this pioneering study, our observations show an increase in the prevalence of HPV infection, and this finding clearly shows that prevention methods to date have not improved at all since the study by Boumba et al. [20].

Univariate logistic regression analysis between HPV infection and the risk factors collected revealed an association with age at first sexual intercourse, risky sexual behavior, and contraceptive use. Risky sexual practices were highly prevalent in this area. Studies of healthy African women under 25 years of age show high sexual activity associated with high HPV prevalence (70.0 to 84.0%) [21, 22] which confirms the different risk factors found in our study linked to women's sexual behaviour.

The distribution of the genotypic profile showed 32.7% HR-HPV in women with a normal cytology diagnosis. These results confirm the strong presence of HR-HPV and corroborate the study by Boumba et al. (2013), who found 60.4% and Tsimba et al. (21.5%) of oncogenic genotypes in normal cytology.

This study also identified 3 distinct oncogenic HPV genotypes: HPV16/18 and 45, the most prevalent of which was HPV type 16 (12.7%). The pooled genotyping of the other HR-HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) had the second highest frequency (8.2%), showing the hypothesis that beyond HPV16 and 18, the other HR-HPV types are needed to be identified in Africa, although

the mechanism of CC carcinogenesis in Central Africa remains to be determined. This hypothesis is in line with the results of a recent HPV study that found six frequently encountered HR-HPV infections (25%), including HPV-35, HPV-56, and HPV-68, are not targeted by the Gardasil-9 vaccine [13].

These results show the importance of carrying out studies on the existing molecular epidemiology of unidentified HPV infections throughout the Congolese territory, which are common in Africa.

The HPV vaccine is highly effective in preventing HPV genotypes 16 and 18, which cause 70% of cervical cancers. Vaccination status in our population was very low (3.6%), confirming the slowness and non-existence of prevention programmes through the introduction of the HPV vaccine and the low overall population coverage, particularly in low-resource countries [8]. It should be noted that the women who received the various injections or doses (1 or 2 injections, or 3 injections) were all HPV-positive, which may suggest that these women had acquired protection against HR-HPV. SAGE therefore strongly encourages all countries to set up HPV vaccination programmes and to give priority to older girls who have not yet been vaccinated. The aim of these recommendations is to enable more girls and women to benefit from vaccination and thus prevent cervical cancer and its consequences throughout their lives [8].

Conclusion

Our research confirms the existence of widespread HR-HPV infection in our population and extends the importance of studies on the molecular prevalence of HPV, particularly in women with normal cytology and apparent good health. These results underline the importance of including HPV testing in cervical cancer screening and diagnosis, in addition to cervical smear testing, in order to significantly improve health programmes. Given the imperative of increasing HPV vaccination coverage in sub-Saharan Africa, and now with the announcement of the WHO's cervical cancer elimination strategy, it is essential to put in place implementation strategies to overcome barriers and reach target populations.

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