High prevalence of HPV infection in the remote villages of French Guiana: an epidemiological study

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Short Summary: A Study among women living in remote Amazonian villages found a high prevalence of HPV infections, with a U-shaped age distribution. Twenty seven percent of HPV-positive women had normal cytology.

Abstract

Background
Cervical cancer is the second most frequent cancer in women in French Guiana. Studies have shown that populations living in the remote areas of the interior have early sexual debut and that multiple sexual partnerships are common. The objective of the present study was thus to determine the prevalence of HPV infection in these areas.

Methods
A study was conducted in women aged 20-65 years with previous sexual activity. Women were included on a voluntary basis after using local media and leaders to inform them of the visit of the team. HPV infection was defined by the detection of HPV DNA using the GREINER-BIO-ONE kit. In addition to HPV testing cytology was performed.

Results
The overall age-standardized prevalence rate was 35%. There was a U shaped evolution of HPV prevalence by age with women over 50 years at highest risk for HPV, followed by the 20 to 29 years group. Twenty seven percent of women with a positive HPV test had normal cytology.
Conclusions

Given the high incidence of cervical cancer in French Guiana the present results emphasize the importance of using HPV testing given its better sensitivity than cytology and the potential operational simplification of screening in these remote areas. Vaccination against HPV, preferably with a nonavalent vaccine, also seems an important prevention measure. However, in this region where a large portion of the population has no health insurance, this still represents a challenge.
Introduction

Cervical cancer is a global public health problem caused by persistent HPV infection leading to malignancy. For women, it ranks second in terms of cancer incidence and mortality worldwide, and first in several developing countries. The global burden estimates suggest that annual incidence is 510,000 and mortality is 288,000 each year worldwide.

In France, cervical cancer is ranked number 8 in terms of cancer incidence. In the French overseas territories in the Americas the incidence rates are situated between what is observed in mainland France and the Caribbean, one of the most affected regions worldwide. In French Guiana, cervical cancer is the second most frequent cancer in females still causing significant mortality. In 2002-2005, the standardized incidence of cervical cancer was 30.3 per 100,000 women, which was close to that of neighboring Brazil. French Guiana is a sparsely populated region covered by primary forest, with populations living in remote parts of the territory only accessible by boat. Despite a network of health centers connected to the main hospital, there are some difficulties to access care. It was recently shown that despite the absence of significant difference in incidence between rural areas and urban areas, there were some differences in the diagnostic delays with 77% of the women from the rural areas with lesions metastasizing beyond the cervix versus 44% for women living in urban areas. Health professionals concur that given the early start of sex life in populations living in these remote parts, the risk of cervical lesions due to HPV should be high. In these remote areas, sexual transmission is also seen for the HIV epidemic, which has soared from zero to over 1% within a decade. Given that HPV 16-18 are involved in 73% of cervical cancers in Europe, vaccination against these genotypes is now recommended in France. However, little is known about the epidemiology of HPV in French Guiana, a French territory with very different
populations and a very different pathogen environment from that of mainland France. The relative isolation of Amerindian and maroon populations may thus lead to singular epidemiologic features. The objective of the present study was thus to describe the prevalence of HPV infections in general, the prevalence of the different genotypes, and of cytological anomalies in women aged 20-65 years living in the remote areas of French Guiana.

Methods

Study population: the source population was women living in the remote villages on the Maroni and Oyapock rivers. The target population was women aged 20-65 years having previously had sexual activity. The inclusions took place between Dec 2012 and Sept 2014.

Inclusion criteria: All women from the target population. Non inclusion criteria: women having had hysterectomy, pregnant women (>3 months pregnant).

Data collection: at the time of inclusion a short questionnaire was filled to collect socio-economic and demographic data, gynecological and obstetrical history.

Study conduct: Before starting inclusions, communication missions in all the villages sensitized the local populations on this public health problem. Traditional authorities, health centers’ workers were also informed. Local radio messages informed the population of the dates of the study team’s presence in the village. During the inclusion, women wishing to be screened came to the health center where the project was explained to them, and where the
questionnaire was filled and samples were taken and transferred in a cooler until the end of
the mission. The samples were then send to the Virology laboratory of Fort de France
Hospital, in Martinique where extraction and genotyping were performed using an automated
method in order to reduce the risk of error and contamination. DNA extraction was performed
using a minimum of 2 ml of sample in liquid phase.
HPV infection was defined by the detection of HPV DNA using the GREINER-BIO-ONE kit,
used at the Virology laboratory in Fort de France University Hospital. This kit allows the
identification of High risk HPV genotypes : 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59,
66, 68, 70, 73, 82 and of low risk HPV genotypes: 6, 11, 40, 42, 43, 44, 55. This kit allowed
the identification of multiple infections. Cytologic anomalies were described using the 2001
Bethesda classification.

All results were sent to attending physicians for medical care. When HPV was positive and
cytology was negative, a gynecological follow up was recommended to verify if HPV
positivity disappeared or if cytologic lesions appeared. If both HPV and cytology was
positive colposcopy was proposed.

Ethical and regulatory aspects:
Although it has been shown that HPV tests are superior to cytology for the detection of
cervical cancer, in France, the HPV test is only reimbursed when the patient has a cytological
examination revealing ASCUS. Here, all patients received the HPV test and cytology free of
charge. All included subjects gave written informed consent. Regulatory and ethical approval
was given by the Comité d'Evaluation Ethique de l'Inserm (CEEI), approval n° 12-064; the
Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le
domaine de la Santé (CCTIRS), n° 12.310 ; the Commission Nationale de l'Informatique et
des Libertés (CNIL), n° 912459 ; and the Comité de Recherche Clinique (CoRC) Pasteur
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Data analysis

Prevalence was obtained by dividing the number of women infected by at least one HPV genotype (high grade or low grade) by the total number of women included. For specific genotypes, prevalence was obtained by the number of women infected by that specific genotype by the total number of women included in the study. Prevalence of cytological anomalies was obtained by dividing the number of women with at least one cytological anomaly by the total number of women with an interpretable cytological examination.

The standardized HPV prevalence rate used the direct standardization method with the world population as a reference.

Unconditional multiple logistic regression was used to predict the variables associated with having a positive HPV test. Different age group-specific models were performed. Categorical variables were transformed into indicator variables. The data was analyzed using STATA 13© (College Station, Texas, USA). Mapping was performed using Mapinfo 12.0© (Troy, NY, USA).

Results

Overall the population of women living in the remote villages was estimated at 5712 on the Maroni and 1209 on the Oyapock. A total of 643 women (406 on the Maroni and 237 on the Oyapock) were included and 51 were not included because they had an exclusion criteria. On the Maroni 117 were included in Apatou, 69 in Grand Santi, 86 in Papaïchtton, 65 in
Maripasoula, 32 in Taluen, and 37 in Antecume Pata. On the Oyapock 98 were included in Saint Georges, 60 in Camopi, and 79 in Trois Sauts. The ratio between the number of women included in each village and the estimated target population number in each village ranged between a minimum of 6% in Grand Santi to 41.7% in Camopi. Overall, 9.3% of women from the target population entered the study. Overall, sexual relations started at a young age with 27% percent of the surveyed women had their first sexual relation before age 15, and 50% before age 16.

Table one shows very high HPV prevalence notably for high risk viruses. The overall age-standardized prevalence rate was 35%. Figure 1 shows there was a U shaped evolution of overall HPV prevalence by age and high risk HPV prevalence by age, with women over 50 years at highest risk for HPV, followed by the 20 to 29 years group. Maroon language was associated with a greater HPV prevalence whereas Portuguese language was associated with a lower prevalence. Other risk factors such as number of sex partners, parity, age at first sex, education, contraception, or smoking were not significantly linked to differences in HPV prevalence. None of the women had declared receiving the HPV vaccine.

Figure 2 shows the geographical differences in HPV prevalence with the lower part of the Maroni river having the highest prevalence. Table 2 shows that HPV 52 was the most frequent high risk virus. HPV16 was the second most frequent genotype in women aged less than forty years. It seemed less frequent in women above 40 years. Overall, the prevalence of HPV 16 or 18 exceeded 5% of tested women.

Overall 139 women had single HPV infections, 53 had double infections, and 22 had 3 or more different HPV genotypes.

A very large proportion (N=147, 27.2%) of women with normal cytology had in fact a positive HPV test.
Table 3 and table 4 show multiple regression analysis models predicting HPV positivity for different covariates. Few variables predicted HPV positivity. In the global models women aged 20-29 and women aged 50-64 years were at higher risk of having a positive HPV test, and of having a high risk genotype than other age groups as shown in Fig 1. Table 4 shows that education was independently associated with HPV positivity in women 20-29 years but that among women aged 30-39 years, intermediate or high education were independently associated with a lower risk of having a positive HPV test. A number of reported sex partners of 2 or more in the past year was associated with an increased risk of having a positive HPV test in women aged 30-39 years.
**Discussion**

The overall prevalence of HPV infection in the remote areas of this French territory was much higher than in mainland France. Moreover, the standardized HPV prevalence rate was comparable and even higher than published studies around the world\(^{10}\). The level of prevalence observed was comparable to what is usually observed in developing countries. High HPV prevalence levels are consistent with the high incidence of cervical cancer observed in French Guiana, which also resembles more what is observed in developing countries than what is observed in France. The age at first sex was lower than in mainland France with differences between the Maroon regions, and the Amerindian regions.

The HPV prevalence varied according to age, and was highest in the Maroon villages. As observed elsewhere, and notably in Latin America and Africa, there was a U-shaped curve of HPV prevalence by age group\(^{11,12}\). The prevalence rate reflects the combination of incidence, new infections, and the duration of infection. The U shape may have reflected new infections in these age groups and/or a slower clearance of viruses in older parous women\(^{13}\). As other studies elsewhere, apart from age few variables were able to predict the risk of having a positive HPV test\(^{13,14}\).

The study limitations were that inclusion was voluntary, and that women living far from the health centers may have been less likely to be included in the study. Finally, cytology and histology from cervical biopsies would have been important to compare the frequency of the genotypes in all women receiving the HPV tests and in women with actual cervical lesions. Nevertheless, this is the first study conducted in this border region.

Despite studies repeatedly showing the superior sensitivity of HPV tests over cytology, HPV tests are not reimbursed by the French health insurance as screening tools. They are only reimbursed if cytology shows ASCUS lesions or worse. The present results combined to the
studies showing a high incidence of cervical cancer suggest that HPV testing would be a better method than the default method which did not detect over 27% of women with HPV infection. HPV testing can also be performed using self tests, which could make it more acceptable for some women and less human resources-intensive. Given the high prevalence of HPV infection and the high incidence of cervical cancer in French Guiana, emphasis on vaccination and expanded and innovative screening seems important. The exact HPV vaccine coverage in these remote territories is unknown, but it is presumably very low. None of the surveyed women reported having been vaccinated. Given the early age of sexual life initiation, the optimal age of vaccination may need to be shifted downwards when compared to recommendations in mainland France. When looking at the variety of HPV genotypes present in these remote territories of French Guiana, the nonavalent HPV vaccines would seem more appropriate that the bivalent or tetravalent vaccines, which do not cover other circulating high risk genotypes. This nonavalent vaccine has been recommended in France and it would presumably have an even greater added value in French Guiana. Presently, given the large proportion of the population that do not have health insurance in these remote areas, the cost of the vaccine is prohibitive. Given the present results, Health authorities should tackle these economic obstacles to ensure that populations have access to this vaccine.

Overall, the present results show that over a third of women were infected with HPV, and that over a quarter of women with high risk HPV infection had normal cytology. Given the high incidence of cervical cancer in French Guiana and the relative delay in diagnosis, these results emphasize the importance of vaccination, preferably with a nonavalent vaccine. However, in this region where a large portion of the population has no health insurance, this still represents a challenge. Finally, the results underscore the importance of expanded screening using HPV tests given their better sensitivity than cytology, and their potential for
operational simplification in a region where health resources are limited and overstretched.\textsuperscript{15}

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References


