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

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27 **Key words :** HPV, epidemiology, French Guiana, prevalence

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

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35 **Abstract**

36 **Background**

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

41 **Methods**

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

46 **Results**

47 The overall age-standardized prevalence rate was 35%. There was a U shaped evolution of
48 HPV prevalence by age with women over 50 years at highest risk for HPV, followed by the
49 20 to 29 years group. Twenty seven percent of women with a positive HPV test had normal
50 cytology.

51 **Conclusions**

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

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62 **Introduction**

63 Cervical cancer is a global public health problem caused by persistent HPV infection
64 leading to malignancy¹. For women, it ranks second in terms of cancer incidence and
65 mortality worldwide, and first in several developing countries. The global burden estimates
66 suggest that annual incidence is 510 000 and mortality is 288 000 each year worldwide.

67 In France, cervical cancer is ranked number 8 in terms of cancer incidence.² In the French
68 overseas territories in the Americas the incidence rates are situated between what is observed
69 in mainland France and the Caribbean³, one of the most affected regions worldwide⁴. In
70 French Guiana, cervical cancer is the second most frequent cancer in females⁵ still causing
71 significant mortality⁶. In 2002-2005, the standardized incidence of cervical cancer was 30.3
72 per 100 000 women, which was close to that of neighboring Brazil⁷. French Guiana is a
73 sparsely populated region covered by primary forest, with populations living in remote parts
74 of the territory only accessible by boat. Despite a network of health centers connected to the
75 main hospital, there are some difficulties to access care. It was recently shown that despite the
76 absence of significant difference in incidence between rural areas and urban areas, there were
77 some differences in the diagnostic delays with 77% of the women from the rural areas with
78 lesions metastasizing beyond the cervix versus 44% for women living in urban areas⁵. Health
79 professionals concur that given the early start of sex life in populations living in these remote
80 parts⁸, the risk of cervical lesions due to HPV should be high. In these remote areas, sexual
81 transmission is also seen for the HIV epidemic, which has soared from zero to over 1% within
82 a decade⁹. Given that HPV 16-18 are involved in 73% of cervical cancers in Europe,
83 vaccination against these genotypes is now recommended in France. However, little is known
84 about the epidemiology of HPV in French Guiana, a French territory with very different

85 populations and a very different pathogen environment from that of mainland France. The
86 relative isolation of Amerindian and maroon populations may thus lead to singular
87 epidemiologic features. The objective of the present study was thus to describe the prevalence
88 of HPV infections in general, the prevalence of the different genotypes, and of cytological
89 anomalies in women aged 20-65 years living in the remote areas of French Guiana.

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94 **Methods**

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

99

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

102

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

105 *Study conduct*: Before starting inclusions, communication missions in all the villages
106 sensitized the local populations on this public health problem. Traditional authorities, health
107 centers' workers were also informed. Local radio messages informed the population of the
108 dates of the study team's presence in the village. During the inclusion, women wishing to be
109 screened came to the health center where the project was explained to them, and where the

110 questionnaire was filled and samples were taken and transferred in a cooler until the end of
111 the mission. The samples were then send to the Virology laboratory of Fort de France
112 Hospital, in Martinique where extraction and genotyping were performed using an automated
113 method in order to reduce the risk of error and contamination. DNA extraction was performed
114 using a minimum of 2 ml of sample in liquid phase.

115 HPV infection was defined by the detection of HPV DNA using the GREINER-BIO-ONE kit,
116 used at the Virology laboratory in Fort de France University Hospital. This kit allows the
117 identification of High risk HPV genotypes : 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59,
118 66, 68, 70, 73, 82 and of low risk HPV genotypes: 6, 11, 40, 42, 43, 44, 55. This kit allowed
119 the identification of multiple infections. Cytologic anomalies were described using the 2001
120 Bethesda classification.

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

126 *Ethical and regulatory aspects:*

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

135 Institute, n° 2012-15. The study was funded by the European Regional Development Fund
136 (FEDER presage n° 30814).

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138 *Data analysis*

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

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

148 Unconditional multiple logistic regression was used to predict the variables associated with
149 having a positive HPV test. Different age group-specific models were performed. Categorical
150 variables were transformed into indicator variables. The data was analyzed using STATA
151 13© (College Station, Texas, USA). Mapping was performed using Mapinfo 12.0© (Troy,
152 NY, USA).

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155 **Results**

156 Overall the population of women living in the remote villages was estimated at 5712 on the
157 Maroni and 1209 on the Oyapock. A total of 643 women (406 on the Maroni and 237 on the
158 Oyapock) were included and 51 were not included because they had an exclusion criteria. On
159 the Maroni 117 were included in Apatou, 69 in Grand Santi, 86 in Papaïchton, 65 in

160 Maripasoula, 32 in Taluen, and 37 in Antecume Pata. On the Oyapock 98 were included in
161 Saint Georges, 60 in Camopi, and 79 in Trois Sauts. The ratio between the number of women
162 included in each village and the estimated target population number in each village ranged
163 between a minimum of 6% in Grand Santi to 41.7% in Camopi. Overall, 9.3% of women from
164 the target population entered the study. Overall, sexual relations started at a young age with
165 27% percent of the surveyed women had their first sexual relation before age 15, and 50%
166 before age 16.

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

175
176 Figure 2 shows the geographical differences in HPV prevalence with the lower part of the
177 Maroni river having the highest prevalence. Table 2 shows that HPV 52 was the most
178 frequent high risk virus. HPV16 was the second most frequent genotype in women aged less
179 than forty years. It seemed less frequent in women above 40 years. Overall, the prevalence of
180 HPV 16 or 18 exceeded 5% of tested women.

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

183 A very large proportion (N=147, 27.2%) of women with normal cytology had in fact a
184 positive HPV test.

185 Table 3 and table 4 show multiple regression analysis models predicting HPV positivity for
186 different covariates. Few variables predicted HPV positivity. In the global models women
187 aged 20-29 and women aged 50-64 years were at higher risk of having a positive HPV test,
188 and of having a high risk genotype than other age groups as shown in Fig 1. Table 4 shows
189 that education was independently associated with HPV positivity in women 20-29 years but
190 that among women aged 30-39 years, intermediate or high education were independently
191 associated with a lower risk of having a positive HPV test. A number of reported sex partners
192 of 2 or more in the past year was associated with an increased risk of having a positive HPV
193 test in women aged 30-39 years.

194

195 **Discussion**

196 The overall prevalence of HPV infection in the remote areas of this French territory was much
197 higher than in mainland France. Moreover, the standardized HPV prevalence rate was
198 comparable and even higher than published studies around the world¹⁰. The level of
199 prevalence observed was comparable to what is usually observed in developing countries.
200 High HPV prevalence levels are consistent with the high incidence of cervical cancer
201 observed in French Guiana, which also resembles more what is observed in developing
202 countries than what is observed in France. The age at first sex was lower than in mainland
203 France with differences between the Maroon regions, and the Amerindian regions.

204 The HPV prevalence varied according to age, and was highest in the Maroon villages. As
205 observed elsewhere, and notably in Latin America and Africa, there was a U-shaped curve of
206 HPV prevalence by age group^{11, 12}. The prevalence rate reflects the combination of incidence,
207 new infections, and the duration of infection. The U shape may have reflected new infections
208 in these age groups and/or a slower clearance of viruses in older parous women¹³. As other
209 studies elsewhere, apart from age few variables were able to predict the risk of having a
210 positive HPV test^{13, 14}.

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

216 Despite studies repeatedly showing the superior sensitivity of HPV tests over cytology, HPV
217 tests are not reimbursed by the French health insurance as screening tools. They are only
218 reimbursed if cytology shows ASCUS lesions or worse. The present results combined to the

219 studies showing a high incidence of cervical cancer suggest that HPV testing would be a
220 better method than the default method which did not detect over 27% of women with HPV
221 infection. HPV testing can also be performed using self tests, which could make it more
222 acceptable for some women¹⁵ and less human resources-intensive. Given the high prevalence
223 of HPV infection and the high incidence of cervical cancer in French Guiana, emphasis on
224 vaccination and expanded and innovative screening seems important^{16, 17}. The exact HPV
225 vaccine coverage in these remote territories is unknown, but it is presumably very low. None
226 of the surveyed women reported having been vaccinated. Given the early age of sexual life
227 initiation, the optimal age of vaccination may need to be shifted downwards when compared
228 to recommendations in mainland France. When looking at the variety of HPV genotypes
229 present in these remote territories of French Guiana, the nonavalent HPV vaccines would
230 seem more appropriate than the bivalent or tetravalent vaccines, which do not cover other
231 circulating high risk genotypes¹⁸. This nonavalent vaccine has been recommended in France¹⁹
232 and it would presumably have an even greater added value in French Guiana. Presently, given
233 the large proportion of the population that do not have health insurance in these remote areas,
234 the cost of the vaccine is prohibitive. Given the present results, Health authorities should
235 tackle these economic obstacles to ensure that populations have access to this vaccine.

236

237 Overall, the present results show that over a third of women were infected with HPV, and that
238 over a quarter of women with high risk HPV infection had normal cytology. Given the high
239 incidence of cervical cancer in French Guiana and the relative delay in diagnosis^{6, 20}, these
240 results emphasize the importance of vaccination, preferably with a nonavalent vaccine.
241 However, in this region where a large portion of the population has no health insurance, this
242 still represents a challenge. Finally, the results underscore the importance of expanded
243 screening using HPV tests given their better sensitivity than cytology, and their potential for

244 operational simplification in a region where health resources are limited and overstretched¹⁵.
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