

# MAIN HUMAN PAPILLOMAVIRUS GENOTYPES IN RIPARIAN WOMEN FROM THE BRAZILIAN AMAZON

*Principais genótipos de papilomavírus humano em mulheres ribeirinhas na amazônia brasileira*

*Principales genotipos del virus de papiloma humano de mujeres ribereñas de la Amazonia brasileña*

Original Article

## ABSTRACT

**Objective:** To assess the distribution of the main oncogenic human papillomavirus (HPV) genotypes in women from riparian and fishing areas in different geographical regions of the Brazilian Amazon. **Methods:** Cross-sectional study conducted from 2013 to 2014. Participants were 516 riparian and fishing women over 13 years old enrolled in the Cervical Cancer Prevention Program (*Programa de Prevenção do Câncer de Colo Uterino – PCCUP*) and submitted to the collection of cervicovaginal material for the Pap test, carried out in loco by a doctor member of the research team, DNA/HPV research and genotyping by Polymerase Chain Reaction (PCR), carried out in the Immunopathology Laboratory of the Federal University of Pará (*Laboratório de Imunopatologia of the Universidade Federal do Pará*) by researchers of the same team. Additionally, information on age and the type of service were also collected by the researchers. All data were analyzed using the Biostat Program 5.0, considering a significant difference when  $p < 0.05$ . **Results:** The mean age of women in the communities A and B were respectively 40 and 39 years, while in communities C, D and E the mean age was 37 years. The prevalence of HPV infection ranged 7.6 to 29.2%. Among the studied oncogenic types, HPV52 ( $n=5$ ; 5.15%), HPV35 ( $n=4$ ; 4.12%) and HPV58 ( $n=3$ ; 3.09%) were the most frequent. The main oncogenic types found are concentrated in the regions of Itaituba (communities A, B) and Bragança (community E). **Conclusion:** All the studied regions presented a high percentage of infection whose HPV type was not identified among the tested individuals, especially communities C and D, with 100% of cases.

**Descriptors:** Papillomaviridae; Genotype; Prevalence; Epidemiology.

## RESUMO

**Objetivo:** Avaliar a distribuição dos principais genótipos do papilomavírus humano (HPV) oncogênicos em mulheres de áreas ribeirinhas e pesqueiras de diferentes regiões geográficas da Amazônia brasileira. **Métodos:** Estudo transversal, realizado no período de 2013 a 2014. Participaram 516 ribeirinhas e pesqueiras maiores de 13 anos, inscritas no Programa de Prevenção do Câncer de Colo Uterino (PCCU) e submetidas à coleta de material cervicovaginal para o Teste Papanicolau, realizado in loco por médico membro da equipe de pesquisadores, pesquisa de DNA/HPV e genotipagem pela Reação em Cadeia da Polimerase (PCR), realizados no Laboratório de Imunopatologia da Universidade Federal do Pará por pesquisadores da mesma equipe, além da coleta de informações como a idade e o tipo de atendimento, também coletados pelos pesquisadores. Todos os dados foram analisados através do Programa Biostat 5.0, considerando diferença significativa quando  $p < 0,05$ . **Resultados:** A média de idade das mulheres nas comunidades A e B foram, respectivamente, 40 e 39 anos, enquanto nas comunidades C, D e E foi de 37 anos. A prevalência da infecção pelo HPV variou de 7,6% a 29,2%. Dentre os tipos oncogênicos pesquisados, os mais frequentes foram HPV52 ( $n=5$ ; 5,15%), HPV35 ( $n=4$ ; 4,12%) e HPV58 ( $n=3$ ; 3,09%). Os principais tipos oncogênicos encontrados estão concentrados na região de Itaituba (comunidades A, B) e Bragança (comunidade E). **Conclusão:** Em todas

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as localidades estudadas foi encontrado um elevado percentual de infecção, cujo tipo de HPV não foi identificado entre os testados, destacando-se as comunidades C e D, com 100% dos casos.

**Descritores:** Papillomaviridae; Genótipo; Prevalência; Epidemiologia.

## RESUMEN

**Objetivo:** Evaluar la distribución de los principales genotipos del virus de papiloma humano (VPH) oncogénicos en mujeres de regiones ribereñas y pesqueras de distintas regiones geográficas de la Amazonia brasileña. **Métodos:** Estudio transversal realizado entre los periodos de 2013 y 2014. Participaron 516 ribereñas y pesqueras mayores de 13 años inscritas en el Programa de Prevención al Cáncer de Cuello Uterino (PCCU) y que realizaron la recogida de material cervicovaginal para el Test de Papanicolaou realizado in loco por un médico miembro del equipo de investigadores, investigación de ADN/VPH y estudio del genotipo a través de la Reacción en Cadena de la Polimerasa (PCR) realizados en el Laboratorio de Inmunopatología de la Universidad Federal de Pará por investigadores del mismo equipo, además de la recogida de informaciones como la edad y el tipo de asistencia. Todos los datos fueron analizados a través del Programa Biostat 5.0 con diferencia significativa para  $p < 0,05$ . **Resultados:** La media de edad de las mujeres de las comunidades A y B fueron, respectivamente, 40 y 39 años, mientras la de las comunidades C, D y E fue de 37 años. La prevalencia de infección por el VPH varió del 7,6% al 29,2%. Entre los tipos oncogénicos investigados los más frecuentes fueron el VPH52 ( $n=5$ ; 5,15%), el VPH35 ( $n=4$ ; 4,12%) y el VPH58 ( $n=3$ ; 3,09%). Los principales tipos oncogénicos encontrados se concentran en la región de Itaituba (comunidades A, B) y Bragança (comunidad E). **Conclusión:** Se encontró un elevado porcentual de infección en todas las localidades estudiadas cuyo el tipo de VPH no ha sido identificado entre los que fueron testados, destacándose las comunidades C y D con el 100% de los casos.

**Descritores:** Papillomaviridae; Genotipo; Prevalencia; Epidemiología.

## INTRODUCTION

Cervical cancer is a serious threat to women's health, especially in developing countries, where prevention and control actions have not achieved the expected success. Reducing the high morbidity and mortality rates associated with this cancer requires knowledge of the factors involved in its pathogenesis, including infection with human papillomavirus (HPV)<sup>(1)</sup>.

This virus is recognized as the main factor involved in the genesis of cervical cancer, although the genotypic characteristics of the virus, the persistent infection and

immunological host factors may influence its malignant transformation. Persistent infection with high-risk HPV, particularly the one caused by HPV16 is associated with the frequency of squamous cell cancer of the uterine cervix and the epithelial covering of other genital organs such as the vagina, the ovaries, the penis<sup>(1)</sup>.

A meta-analysis of HPV infection worldwide including developing countries showed that countries where there is a high incidence of cervical cancer have a high prevalence of this virus, as in Sub-Saharan Africa, Latin America and India. It mainly affects young women and the rates decrease after 30 years old. In Latin America, there was a second peak in the prevalence of HPV in women aged over 55 years<sup>(2)</sup>.

The strategies for prevention and control of human papillomavirus infection and cervical cancer precursor lesions are not yet strong in Brazil given the high prevalence rates recorded, particularly in the North region<sup>(3)</sup>. The smear test done regularly, the appropriate health education and vaccination against HPV are actions being implemented that should be prioritized in primary health care centers in order to reduce morbidity and mortality from cervical cancer<sup>(4,5)</sup>.

It is true that the proportion of infection with high-risk HPV, preventable by vaccine with genotypes 16 and 18, also vary by region, with the highest rates in Europe (and maybe North America) and the lowest rates in Sub-Saharan Africa<sup>(6)</sup>. In China, HPV52 and HPV56 genotypes were the most prevalent and the authors recommended second-generation prophylactic vaccines, including these two genotypes, in order to provide greater protection to women living in the area<sup>(7)</sup>.

In Brazil, the overall prevalence of papillomavirus infection of the cervix ranges between 13.7% and 54.3%, and for women with normal cytology, the rates range between 10.4% and 24.5%<sup>(8)</sup>. In a study conducted in urban and rural of the Amazon, the prevalence of infection was around 15%<sup>(9)</sup>; however, the virus genotypes were not investigated. Estimates for special groups of the Amazon including people from riparian communities are limited; these people do not have the same access to health services as the general population, making it difficult to develop programs with actions targeted to the care of women from riparian areas.

The identification of the types of high-risk HPV is of great value for prevention trials with vaccines, for the monitoring and control of associated lesions and for the adequacy and effectiveness of the actions of the Cervical Cancer Prevention Program (*Programa de Prevenção do Câncer de Colo Uterino - PCCU*) developed in these regions.

Thus, the aim of the present study was to assess the distribution of the main oncogenic human papillomavirus (HPV) genotypes in women from riparian and fishing areas in different geographical regions of the Brazilian Amazon.

## METHODS

This is an observational cross-sectional study conducted from 2013 to 2014. Participants were 516 women enrolled in the Cervical Cancer Prevention Program (*Programa de Prevenção do Câncer de Colo Uterino - PCCU*) developed in riparian communities of four municipalities located in different geographical regions of Pará. Two communities (Communities A and B) are located in the municipality of Itaituba, in Southwestern Pará State, one in the municipality of Limoeiro de Ajurú (Community C), one in the municipality of Acará (Community D) and one fishing community in the municipality of Bragança (Community E) – the latter two are located in Northeastern Pará. The number of participants in each community was represented by about 20% of the female population recorded by the census of the Family Health Strategy of the Ministry of Health. The number of families registered in each community was 250, 192, 215, 65 and 230, in Community A, Community B, Community C, Community D and Community E, respectively.

The study included women aged over 13 years old who had already begun their sexual life, permanently living in the riparian or fishing communities and attending the health facility to perform the Pap test during the period of our visit to the communities. Women whose cervicovaginal materials could not be analyzed for viral identification due to deterioration and/or improper storage of the material were excluded.

Information on the age and type of care was obtained during medical consultation by a researcher of the team prior to the collection of material for the Pap test. The cervicovaginal material was collected by a gynecologist who was part of the research team using endocervical brush and Ayre spatula to perform the Pap test and the deoxyribonucleic acid (DNA) testing for HPV and genotyping by polymerase chain reaction (PCR). The Pap test was performed by a cytopathologist who was also part of the same research team in the community; the results were delivered in the same place.

The DNA/HPV testing by polymerase chain reaction was analyzed in the Immunopathology Laboratory of the Tropical Medicine Center (*Laboratório de Imunopatologia do Núcleo de Medicina Tropical - NMT*) of the Federal University of Pará (*Universidade Federal do Pará - UFPA*) by qualified professionals of the research team following the methodology described by Pinto, Fuzii and Lent<sup>(7)</sup>. The positive samples were subjected to real time PCR using

probes (IDT) for HPV types 6, 11, 16, 18, 31, 33, 35, 52 and 58. Platinum qPCR SuperMix-UDG kit (Invitrogen, Carlsbad, CA) was used for typing. For each reaction we added 100 ng of DNA, 0.5  $\mu$ l of probes, 0.2  $\mu$ l of ROX Reference Dye, 10  $\mu$ l of Platinum qPCR SuperMix-UDG, 0.2  $\mu$ l of MgCl<sub>2</sub>, and 20  $\mu$ l of ultrapure water qsp. Amplification was performed in StepOnePlus Real Time Thermocycler (Applied Life Biosystems® Technologies™) and consisted of 40 cycles of 95° C for 15 sec and 60° C for 60 sec. The results were analyzed in StepOne Plus software (Applied Life Biosystems® Technologies™).

All data were analyzed using the statistical analysis program Biostat 5.0<sup>(10)</sup>. For descriptive analysis of continuous variables, we used mean, standard deviation, absolute (n) and relative (%) frequency for categorical variables. Inferential analysis was performed to compare the mean age between the five communities using ANOVA; and to compare the prevalence of HPV infection, we used the meta-analysis test of various proportions, considering significant difference at  $p < 0.05$ .

The present study followed the ethical guidelines established by Resolution 466/12 of the National Health Council of the Ministry of Health of Brazil and was approved by the Research Ethics Committee of the NMT under Opinion No. 334.524 in July 2013.

## RESULTS

The mean age, the frequency of women who were performing the Pap test for the first time and the prevalence of HPV infection in women of different locations are presented in Table I.

Considering all the participants, the age ranged 13-80 years, and in every community, 75% of participants were under 60 years of age. In all, 13% to 20% of women were performing the Pap test for the first time.

The prevalence of HPV infection in the communities ranged from 7.6% in the coastal fishing community to 29.2% in one of the riparian communities of the municipality of Itaituba, in the Tapajós region. The prevalence in the Community A (municipality of Itaituba), 29.2%, was higher than that observed in other communities; however, the difference was not significant when comparing the prevalence registered in Community A with that registered in Community C, 13.5% ( $p < 0.05$ ), and E, 7.6% ( $p < 0.01$ ), respectively located in Limoeiro do Ajurú (Tocantins region) and Bragança (sea coast). The lowest prevalence was found in the Community E (7.6%) (municipality of Bragança).

Of the HPV types investigated, the most frequent were HPV52 (observed in five isolate cases and in one case

Table I - Prevalence of HPV infection in women from riparian and fishing areas. Pará, 2013 to 2014.

Variables	Itaituba		Limoeiro de Ajurú C	Acará D	Bragança E	<i>p value</i>
	A	B				
	n=195	n=81				
<b>Age (in years)</b>						
Mean	40	39	37	37	37	F:1.7966
Median	37	37	36	37	36	p=0.127
Minimum-maximum	17-80	13-82	14-72	16-71	16-62	
<b>Type of care</b>	n (%)	n (%)	n (%)	n (%)	n (%)	
1 <sup>st</sup> test	39(20.0)	11 (13.5)	19 (17.1)	5 (13.9)	12 (13.0)	
Control	156 (80.0)	70 (86.5)	92 (82.9)	31 (86.1)	80 (87.0)	
HPV/DNA	57 (29.2)	13 (16.0)	15 (13.5)	5 (13.9)	7 (7.6)	p<0.05 (AxC) p<0.01(AxE)

DNA: deoxyribonucleic acid. p<0.05 statistically different; Anova test - one criterion; meta-analysis test of various proportions; p<0.05 (AxC) Community A versus Community C; p<0.01 (AxE) Community A versus Community E;

Note: Communities A and B are located in the municipality of Itaituba and are founded in close geographic proximity.

Table II - Distribution of HPV types in riparian and fishing communities in different geographical regions. Pará, 2013 to 2014.

Regions HPV types	Itaituba A and B	Limoeiro de Ajurú C	Acará D	Bragança E	Total n (%)
	n (%)	n (%)	n (%)	n (%)	
Not identified	52 (74.3)	15 (100)	5 (100)	4 (57.1)	76 (78.4)
Identified	18 (25.7)	0	0	3 (42.9)	21 (21.6)
HPV 6	1 (1.4)	0	0	1 (14.3)	2 (2.1)
HPV 16	1 (1.4)	0	0	0	1 (1.0)
HPV 18	1 (1.4)	0	0	0	1 (1.0)
HPV 31	1 (1.4)	0	0	0	1 (1.0)
HPV 35	4 (5.7)	0	0	0	4 (4.1)
HPV 52	4 (5.7)	0	0	1 (14.3)	5 (5.1)
HPV 58	2 (2.8)	0	0	1 (14.3)	3 (3.1)
HPV 31,18	2 (2.8)	0	0	0	2 (2.1)
HPV 33,58	1 (1.4)	0	0	0	1 (1.0)
HPV 16,52	1 (1.4)	0	0	0	1 (1.0)
Total	70	15	5	7	97

associated with HPV16), HPV35 (four isolate cases), and the HPV58 (observed in three isolate cases and in one case associated with HPV33). The PCR/HPV was positive in 13.5% and 13.9% in communities C and D, respectively; however, the oncogenic types investigated were not found. In communities A and B, in Itaituba, we identified all types

investigated, including dual infections, except for HPV11. In the fishing community (E) located in Bragança, we identified HPV types 6, 52 and 58. In 78.4% of women with infection confirmed by DNA/HPV, the virus type was not identified among the tested types (Table II).

## DISCUSSION

The prevalence of HPV infection in the communities studied ranged from 7.0% to 29.2%, with the highest rates observed in the Tapajós River and the lowest rates in the coastal fishing community in the municipality of Bragança.

We admit that a number of factors specific to the Tapajós region, including the low socioeconomic status<sup>(11)</sup>, the limited availability for performing the test in the community, transportation difficulties for access to preventive screening in the urban area and the increase in male migration to the region resulting from gold prospecting activities, favor viral transmission in the region, contributing to the high prevalence of this infection. On the other hand, the nearest location of the urban area, the fishing community of Bragança, facilitating women's access to prevention services in addition to the absence of gold prospective activities in this region could explain the low circulation of the HPV virus and thus the lower prevalence of this infection. The findings were different from those obtained by a study on riparian communities of Abaetetuba and Tucuruí, which found a higher prevalence in the municipalities that are also part of the Tocantins River region, 11.4% and 14.2%, respectively<sup>(9,12)</sup>.

The few studies carried out in rural and riparian communities in Pará showed prevalence rates with small variations. In Tucuruí, the prevalence was 14.2%<sup>(9)</sup> and in Abaetetuba, 11.4%<sup>(12)</sup>, a result similar to the prevalence found in the riparian communities B (16%), C (13.5%) and D (13.9%). In the past decade, a study conducted with Amerindian women in the State of Pará found a frequency of 42.85% of HPV in cervical samples analyzed by molecular biology methods<sup>(13)</sup>, findings that suggest the need for greater attention to these traditional groups of the Amazon.

In Brazil, most studies of human papillomavirus infection involving urban populations with better access to health services and knowledge of preventive measures reported variable prevalence rates. In the Southeast region, recently, prevalence rates ranged 13.7% to 54.3%<sup>(8)</sup> while in the North region the prevalence in the past decade was 12.6%<sup>(14)</sup>. In women from Southern Brazil, the prevalence was 18.2%<sup>(15)</sup> while women in a northeastern municipality presented a prevalence of 10.68%<sup>(16)</sup>. The results found in most riparian communities are within the range found in women in urban areas; however, the situation is more worrisome given the difficulties of access to prevention and control programs by these women.

Among the nine HPV types tested in the present study, seven high-risk oncogenic types were identified, HPV 16, 18, 31, 33, 35, 52 and 58, corresponding to 22% of the subtyped HPV positive samples. The samples from

women from Limoeiro do Ajurú, Community C, and Acará, Community D, showed no positive results for the subtypes tested. The community studied in the municipality of Bragança, Community E, presented two of the high-risk oncogenic subtypes tested, HPV52 and 58. These same types were found in women with cervical cancer from seven US states; however, when assessing the general population the authors found the HPV16 and HPV18 types as the most prevalent<sup>(17)</sup>, like in other studies conducted with women in Portugal<sup>(18)</sup> and Canada<sup>(19)</sup>.

The subtypes identified in Bragança, Community E, are closer to those found in women in China, where there was a prevalence of HPV52, 16 e 58<sup>(20)</sup>. Another study in China<sup>(21)</sup> identified HPV types 16, 33, 52 and 58 as the most frequent subtypes identified. In Korean women<sup>(22)</sup>, there were higher prevalence rates of HPV 16, 58 and 52 in women with low-grade squamous intraepithelial lesions (LSIL) and HPV58 was the second most prevalent type in women with normal cytology and high-grade squamous intraepithelial lesions (HSIL) and the third most prevalent in women with invasive cancer. These findings suggest that the HPV types identified in Bragança are close to those observed in Asian countries.

Communities A and B of Itaituba showed interesting differences in relation to other communities. All oncogenic subtypes tested were found, with subtypes 18, 35 and 58 as the most frequent and the HPV16 as the least frequent. In a study involving indigenous women from the region, HPV16 was little frequent in relation to the types HPV18 and 58<sup>(13)</sup> and absent in the study with women from riparian areas in the municipality of Abaetetuba, where there was only one case of HPV58 along with other less common types<sup>(12)</sup>. HPV subtypes found in Itaituba, communities A and B, are similar to those of women in Sub-Saharan Africa, who presented a low frequency of type 16, but a high frequency of other oncogenic types such as HPV 31, 33, 35 and HPV18<sup>(6)</sup>. HPV 58, like the prevalence found in a study in China<sup>(7)</sup>, was the most common subtype found among the tested subtypes and was identified in all studies involving women from riparian areas in this region.

It should be noted that the convenience sampling of the study participants was the main limitation of the present study, a feature of most studies involving people from riparian areas that results from difficulties regarding socio-environmental conditions.

## CONCLUSION

The main oncogenic types were HPV35, HPV52 and HPV58, concentrated in Itaituba region (communities A and B) and Bragança (Community E). All the locations studied presented a high percentage of infection whose HPV

type was not identified among those tested, particularly in communities C and D, with 100% of cases. Thus, the risk of developing cervical cancer may be related to subtypes that are not covered by the quadrivalent vaccine, recently distributed in Brazil.

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