Genital Human Papillomavirus Infection in women from Florianópolis - Santa Catarina, Brazil

Infecção genital pelo Papilomavírus Humano em mulheres de Florianópolis - Santa Catarina, Brasil

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ABSTRACT

Introduction: Human Papillomavirus (HPV) infection is the most common sexually transmitted infection in women. About 80% of sexually active women will have contact with this virus at some age in their lives. Most infections will be transient, but when the infection becomes persistent, associated with high oncogenic risk HPV, there may be progression to cancer, especially cervical cancer. The best way to prevent HPV infection is through the use of vaccines. Objective: To assess which are the most prevalent types of HPV in the city of Florianópolis, Brazil and if the majority of the diagnosed types are contained in the HPV vaccines currently available on the market and in the public health sector. Methods: More than 14,727 HPV tests were evaluated for the diagnosis of genital HPV infection in women from Florianópolis. The prevalence of infection was evaluated according to age of the women. HPV detection was performed using molecular biology tests, such as hybrid capture (for diagnosis of the HPV group, high or low oncogenic risk) and PCR (viral genotyping) techniques. Results: The diagnosis of HPV infection was made for women between one and 102 years of age. The highest positivity of the exams was observed in women aged 20–25 years (51% of the exams). The most prevalent age group was 31–35 years old (23.5%), and the lowest was for women aged 70 and above (0.6%). High oncogenic risk HPV was detected in 94.1% of positive samples and was the most frequent in all age groups. Mixed infection (high- and low-risk HPV) was more prevalent in the 66–70 age group (25.6%). The most frequent genotypes were non-16/18 high oncogenic risk HPV (77% of positive cases). HPV 16 was found in 17.1% of positive cases, and HPV 18 in 6.5%. Conclusion: The most prevalent types of HPV in Florianópolis in the last 6 years are non-16/18 high oncogenic risk HPV types, viral types not covered by the current HPV vaccine available in the public health sector in Brazil.

Keywords: Papillomaviridae. HPV types. Uterine cervical neoplasm. Vaccination coverage.

RESUMO

Introdução: A infecção pelo Papilomavírus Humano (HPV) é a infecção sexualmente transmissível mais frequente na mulher. Cerca de 80% das mulheres sexualmente ativas irão entrar em contato com este vírus em algum momento da sua vida. A maioria das infecções será transitória, mas quando a infecção se torna persistente, associada aos HPV de alto risco oncogênico, poderá haver a progressão para o câncer, principalmente o câncer de colo de útero. A melhor forma de prevenção da contaminação pelo HPV é através da utilização das vacinas. Objetivo: Avaliar quais são os tipos de HPV mais prevalentes na cidade de Florianópolis, Brasil, e se a maioria dos tipos diagnosticados estão contidos nas vacinas contra o HPV atualmente disponíveis no mercado e no setor público de saúde. Métodos: Foram avaliados 14.727 exames para diagnóstico da infecção genital pelo HPV em mulheres de Florianópolis, de acordo com a idade das mulheres. A detecção do HPV foi realizada através dos exames de biologia molecular pelas técnicas de captura híbrida (para diagnóstico do grupo de HPV, alto ou baixo risco oncogênico) e PCR (genotipagem viral). Resultados: Foram avaliados exames para diagnóstico da infecção de mulheres entre um e 102 anos de idade. A maior positividade dos exames foi observada em mulheres dos 20–25 anos (51% dos exames). A faixa etária de maior prevalência foi dos 31–35 anos (23,5%), e a menor, após os 70 anos (0,6%). O HPV de alto risco oncogênico foi detectado em 94,1% dos casos positivos e foi o mais frequente em todas as faixas etárias. A infecção mista (HPV de alto e baixo risco) foi mais prevalente na faixa etária dos 66–70 anos (25,6%). Os genótipos mais frequentes foram os HPV de alto risco oncogênico não 16/18 (77% dos casos positivos). O HPV 16 foi encontrado em 17,1% dos casos positivos, e o HPV 18 em 6,5%. Conclusão: Os tipos de HPV mais prevalentes em Florianópolis nos últimos 6 anos são os HPV de alto risco oncogênico não 16/18, tipos virais não cobertos pela atual vacina contra o HPV disponível no setor público de saúde do Brasil.

Palavras-chave: HPV. Tipos de HPV. Câncer de colo de útero. Cobertura vacinal.

INTRODUCTION

Worldwide, genital infection by HPV is the most frequent sexually transmitted infection, both in women and men[1]. There are over 200 different identified types of HPV and about 45 types infect the epithelium of the male and female anogenital tract[2]. Of these, about 18 are considered at high oncogenic risk (HR HPV), mainly types 16 and 18, which are associated with anogenital and aerodigestive tract cancer in men and women[3]. These HPVs are necessary, but not sufficient, to cause virtually all cases of cervical cancer in the world[4]. Low-risk oncogenic HPVs (LR HPV), mainly 6 and 11, cause benign lesions in the anogenital region (warts and low-grade squamous intraepithelial lesions) and in the larynx (recurrent laryngeal papillomatosis), with substantial morbidity and high cost of treatment[3]. From an epidemiological point of view, especially HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82, 26, 53, 66 and 73 are considered to be HR HPV and HPV 6, 11, 40, 42, 43, 44, 54, 61, 72, 81, 70, CP6108 as LR HPV[4].

HPV infection is very common in sexually active women, and 80% of women are expected to have contact with it by the age of 50[5]. Most of these HPV infections are transient and go undetected for more than one to two years[3]. The persistence of infection is greater for HR HPV. And, in relation to these, there is some evidence that HPV 16 can persist for a longer time than the other types. In this way, the spread of high-risk HPVs (particularly HPV 16) is likely to be greater than that of LR HPV, considering the model of sexual contact and transmissibility to be equivalent[1].

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The prevalence of HPV infection in the female population ranges from 2 to 44%[3]. Women with normal cytology had a global adjusted prevalence of 10.41%, with considerable variation according to the region[1]. In Brazil, studies have found positivity for HPV in the general population from 21 to 48%[6-8], with HR HPV found in 48 to 53%. Around 25% of the times, mixed infection with high- and low-risk HPVs is observed[9].

The World Health Organization (WHO) estimates that more than 630 million men and women (1:10 people) are infected with HPV worldwide[10]. We can consider HPV infection as an epidemic in Brazil, as it is estimated that 9 to 10 million people are infected, and that, each year, 700,000 new cases appear[11]. Around 105 million people worldwide are positive for HPV 16 or 18[12]. The highest prevalence of infection is in younger women and decreases with the middle-aged group, with a second peak after 500–60 years, except in Asia[1,13]. Co-infection with multiple HPV types and sequential infection with new types is quite common, and the risk of acquiring a new HPV type appears to be independent of prior infection with other types[3].

Strategies for the cervical cancer prevention consist of avoiding HPV infection and obtaining early diagnosis of precursor lesions, since their progression is slow and curable with treatment[14]. In Brazil, excluding non-melanoma skin tumors, cervical cancer is the third most common type of cancer among women. For the year 2023, 17,010 new cases were estimated, which represents a considered risk of 13.25 cases per 100,000 women. In the regional analysis, cervical cancer is the second most frequent in the North (20.48/100,000) and Northeast (17.59/100,000), and the third in the Midwest (16.66/100,000). In the South region (14.55/100,000) it occupies the fourth position and, in the Southeast region (12.93/100,000), the fifth position[15].

HPV vaccines are the most effective way to prevent HPV infection. At the moment, three vaccines against HPV are available on the market, the bivalent (2HPV) or Cervarix® (against HPV 16 and 18, with the 0, 1 and 6 month schedule), the quadrivalent (4HPV) or Gardasil® (against HPV 6, 11, 16 and 18, with the schedule of 0, 2 and 6 months) and the nonavalent (9HPV) or Gardasil 9® (against HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58, with the 0, 2 and 6 months schedule), which have been shown to be highly effective in clinical trials, with rates of 95–100% of effectiveness for precancerous lesions of the lower genital tract associated with HPV 16 and 18 (2HPV, 4HPV and 9HPV) and for the other 5 high-risk HPV types (31,33,45,52 and 58) for the 9HPV vaccine.

The 4HPV vaccine has been on the public vaccination schedule in Brazil since 2014. Currently, the National Immunization Program (PNI) has adopted the two-dose schedule (0 and 6 months) for girls and boys aged 9 to 14 years, since the two-dose schedule of the vaccine proved to be highly immunogenic and effective for boys and girls in this age group, with a minimum interval between doses of 5 months and a maximum of 15 months[24,25]. Also in the PNI, the vaccine is available for girls/women and boys/men aged 9 to 45 years with some immunosuppressive disease (HIV infection, solid organ and bone marrow transplants and cancer patients), in the traditional 3-dose schedule (0, 2 and 6 months)[25]. Recently, the 9HPV vaccine, licensed since 2017[26], has been approved for sale in Brazil, for the time being only at private immunization clinics[27].

OBJECTIVE

The aim of this study was to identify the types of HPV prevalent in female genital infection in samples from Florianópolis – Santa Catarina, Brazil, and to assess whether the types of HPV most frequently found in these women are protected by the 4HPV vaccine, available in the Brazilian PNI, and the 9HPV vaccine, available only at private immunization clinics in the country.

METHODS

Study design and Population

This is a descriptive observational prevalence study where genital samples of women from the city of Florianópolis, Brazil, were evaluated over a period of 6 years (from January 6, 2016 to December 31, 2021).

This study was approved by the Human Research Ethics Committee (CEPSH) of the Federal University of Santa Catarina (UFSC) under number 5.148.672 (CAAE: 53037521.5.0000.0121).

Sample analysis

All female genital samples from Florianópolis received by the DASA Laboratory in São Paulo were submitted to molecular diagnosis for HPV DNA by Hybrid Capture and PCR (polymerase chain reaction) methods. Most samples were taken from the cervico-vaginal region using a cytobrush. At the extremes of age or when this collection was not possible, a swab was collected from the vaginal introitus.

Through the Hybrid Capture test (from the Digen® Laboratory), the HPV group (high or low risk) present in the sample was detected. The test detection limit was 1 pg/mL of HPV DNA, equivalent to 0.1 virus copy/cell. The test was considered positive (detected) when ≥1 RLU/CO and negative (not detected) when the value was less than 1 RLU/CO. Although some laboratories refer that Hybrid Capture values between 1 and 3 are inconclusive, most studies, like this one, took into account the positivity when ≥1 RLU/CO. The low-risk HPV types detected by the method were types 6, 11, 42, 23 and 44 and the high-risk types were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.

The PCR test detects the type of virus present in the sample (genotyping). Real-time PCR was performed using the TaqMan System (from Abbott® Laboratory). The TaqMan System – Real Time HR HPV has a detection limit of 500 copies/reaction for HPV 16 and 18, and 5,000 copies/reaction for the other HPV types. The TaqMan – Alinity m HR HPV System has a detection limit of 240 copies/test for HPV 16 and 18, 500 copies/test for HPV 45, 2,000 copies/test for HPV 33, 35, 51, 52, 59 and 5,000 copies/test for HPV 31, 39, 56, 58, 66 and 68.

Outcome

The primary endpoint of the study was to assess which type of HPV is the most prevalent in the city of Florianópolis. The secondary endpoint was to assess whether age had any influence on

HPV detection and genotyping. Data analysis was descriptive, with prevalence calculations, using the Epi-Info and Statcalc programs as tools.

RESULTS

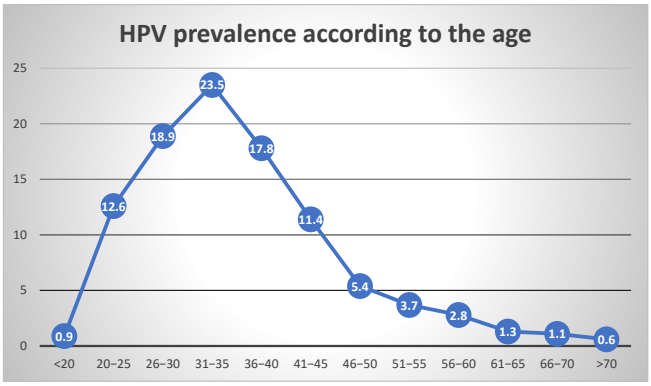
A total of 14,727 samples of the female genital tract of women from Florianópolis (SC, Brazil) were analyzed over a period of six years (2016 to 2021) stored in the Database of the DASA Laboratory in São Paulo. The information obtained from these tests were age, HPV detection according to the oncogenic group (low and high risk) by the Hybrid Capture methodology and genotyping (HPV 16 and 18 alone and types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 in a pool) by the PCR technique. Most samples were negative for HPV infection (71.4%).

The age of the patients in the samples ranged from one to 102 years, with the extremes of age positive for HPV being 12 years (positive for high-risk HPV by the hybrid capture technique) and 87 years (positive for high-risk HPV non-16/18 by the PCR technique). The age group with the highest number of exams was 31 to 35 years old, with 2,825 exams (19.2% of the sample). The age group with the highest percentage of positive tests was 20 to 25 years old, with 51.2% of positive samples, and the lowest, over 70 years old, with 8% (**Table 1**).

HR HPV was the most frequently observed (94.1% of positive samples), being detected alone in 81.2% of the cases, and associated with LR HPV in 12.9%. In all age groups, HR HPV was found in more than 90% of the samples, isolated or associated with LR HPV. Isolated LR HPV was diagnosed in only 5.9% of positive cases, while the ones associated with HR HPV totaled 12.9%. The age group of 31 to 35 years old was the most affected by HPV infection (23.5% of positive samples), and those over 70 years old were the least, with 0.6% (**Figure 1**).

Infection by HR HPV alone was more frequent in the age group under 20 years (86.5%), while LR HPV was from 51 to 55 years (10%). Mixed infection, HR HPV + LR HPV, was more frequent between 66 and 70 years old (25.6%) (**Figure 2**).

HPV genotyping was performed in 8,172 samples using the PCR technique, 1,541 of which were positive (18.9%). The most prevalent HPV genotype was non-16/18 HR HPV type (77%). HPV 16 was detected in 17.1% of the positive samples (isolated in 16.5% and associated with 18 in 0.6%). It had a higher prevalence in the age group of 66 to 70 years (23.1%). HPV 18 was detected in 6.5% of the positive samples (5.9% isolated and 0.6% associated with HPV 16). Its highest prevalence was observed in the age group of 46 to 50 years with 9.3%. The association of HPV 16 and 18 was observed in 0.6% of the positive samples, having appeared only in the 26 to 45 age group (1.1% for the 26 to 30 and 36 to 40 years, and 0.6 % for the 31 to 35 and 41 to 45 years) (**Table 2**).



Source: Data from DASA Laboratory, 2022.

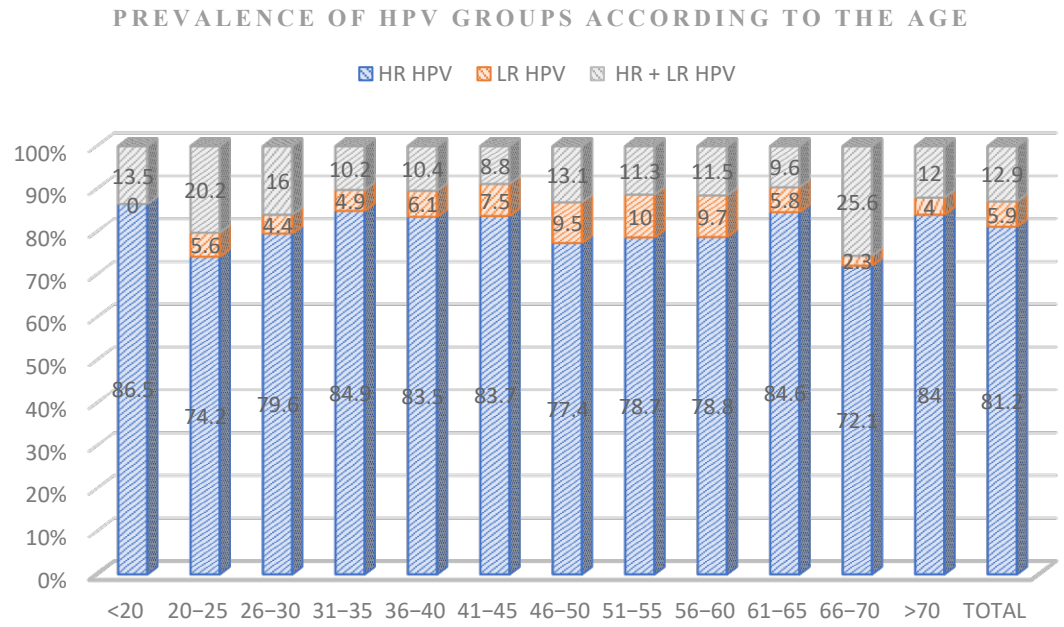
Figure 1. Prevalence of positive HPV cases, according to the age (years) of women from Forianópolis.

Table 1. Distribution of age (years) of women from Florianópolis evaluated according to the HPV group (hybrid capture + PCR).

Age	NEG	POS	HR HPV	LR HPV	HR + LR HPV	Total
(years)	n (%)	n (%)	n (%)*	n (%)*	n (%)*	n (%)
<20	46 (55.4)	37 (44.6)	32 (86.5)	00 (0.0)	5 (13.5)	83 (0.6)
20–25	491 (48.8)	516 (51.2)	383 (74.2)	29 (5.6)	104 (20.2)	1,007 (6.84)
26–30	939 (55.0)	769 (45.0)	612 (79.6)	34 (4.4)	123 (16.0)	1,708 (11.6)
31–35	1,868 (66.1)	957 (33.9)	813 (84.9)	47 (4.9)	97 (10.2)	2,825 (19.2)
36–40	2,039 (73.8)	724 (26.2)	605 (83.5)	44 (6.1)	75 (10.4)	2,763 (18.8)
41–45	1,592 (77.4)	465 (22.6)	389 (83.7)	35 (7.5)	41 (8.8)	2,057 (13.9)
46–50	1,002 (81.9)	221 (18.1)	171 (77.4)	21 (9.5)	29 (13.1)	1,223 (8.3)
51–55	713 (82.6)	150 (17.4)	118 (78.7)	15 (10.0)	17 (11.3)	863 (5.9)
56–60	590 (83.9)	113 (16.1)	89 (78.8)	11 (9.7)	13 (11.5)	703 (4.8)
61–65	438 (89.4)	52 (10.6)	44 (84.6)	3 (5.8)	5 (9.6)	490 (3.3)
66–70	313 (87.9)	43 (12.1)	31 (72.1)	1 (2.3)	11 (25.6)	356 (2.4)
>70	287 (82.0)	25 (8.0)	21 (84.0)	1 (4.0)	3 (12.0)	312 (2.1)
Unknown	200 (59.3)	137 (40.7)	109 (79.6)	10 (7.3)	18 (13.1)	337 (2.3)
Total	**10,518 (71.4)**	**4,209 (28.6)**	**3,417 (81.2)**	**251 (5.9)**	**541 (12.9)**	**14,727 (100.0)**

*HPVgroup/positive cases; NEG: HPV-negative test; POS: HPV-positive test; HR HPV: high-risk HPV; LR HPV: low-risk HPV.
Source: Data from DASA Laboratory, 2022.

With HPV genotyping, we could analyze the additional percentage of protection that we may have when using the nonavalent HPV vaccine (9HPV) (against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58) instead of the quadrivalent (4HPV) vaccine (against types 6, 11, 16 and 18) or bivalent (2HPV) vaccine (against types 16 and 18). Additional protection was 77% for women in Florianópolis (**Figure 3**).



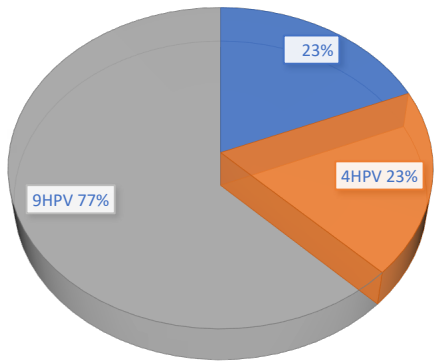
HR HPV: high-risk HPV; LR HPV: low-risk HPV.
Source: Data from DASA Laboratory, 2022.

Figure 2. Prevalence of HPV groups in positive samples, according to the age (years) of women from Florianópolis.

Table 2. Distribution of age (years) of women from Florianópolis, according to the High Risk HPV type detected by the PCR technique.

Age	HPV 16	HPV 18	HPV 16 + 18	HPV nº 16/18	Total
(years)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
<20	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)	16 (100.0)
20–25	22 (11.2)	11 (5.6)	0 (0.0)	163 (83.2)	196 (12.7)
26–30	40 (14.8)	20 (7.4)	3 (1.1)	208 (76.7)	271 (17.6)
31–35	69 (19.3)	15 (4.2)	2 (0.6)	271 (75.9)	357 (23.2)
36–40	49 (18.5)	13 (4.9)	3 (1.1)	200 (75.5)	265 (17.2)
41–45	27 (16.3)	15 (9.0)	1 (0.6)	123 (74.1)	166 (10.8)
46–50	12 (14.0)	8 (9.3)	0 (0.0)	66 (76.7)	86 (5.6)
51–55	10 (20.0)	2 (4.0)	0 (0.0)	38 (76.0)	50 (3.2)
56–60	8 (19.0)	2 (4.8)	0 (0.0)	32 (76.2)	42 (2.7)
61–65	5 (20.0)	2 (8.0)	0 (0.0)	18 (72.0)	25 (1.6)
66–70	3 (23.1)	1 (7.7)	0 (0.0)	9 (69.2)	13 (0.8)
>70	1 (7.1)	1 (7.1)	0 (0.0)	12 (85.8)	14 (0.9)
Unknown	9 (22.5)	1 (2.5)	0 (0.0)	30 (75.0)	40 (2.7)
Total	**255 (16.5)**	**91 (5.9)**	**9 (0.6)**	**1.186 (77.0)**	**1.541 (100.0)**

HPV NO 16/18: HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.
Source: Data from DASA Laboratory, 2022.



Vaccines against HPV: 2HPV (bivalent), 4HPV (quadrivalent) and 9HPV (nonavalent).
The figure shows the percentage of additional protection of the 9HPV (without HPV 16 and 18) compared to 2 HPV and 4HPV.
Source: Data from DASA Laboratory, 2022.

Figure 3. Percentage of HPV types contained in the 2HPV, 4HPV and 9HPV vaccines in the women from Florianópolis.

DISCUSSION

HPV infection is quite frequent in women, and the prevalence and distribution of HPV types in the world vary greatly according to the population studied and the age group in the same population. The highest prevalence of this infection is in younger women, and decreases with the middle-aged group, with a second peak from 50 to 60 years, except in Asia[1]. This same trend is demonstrated in the 2017 WHO data and the 2007 meta-analysis by Sanjosé et al. [13]. We have recently published a study that evaluated HPV infection in genital samples collected throughout the state of Santa Catarina, with results very similar to those found in the state capital[28]. In our study, most of the positive cases for HPV were in the 20 to 25 age group (51.2%), similar to the POP Brazil Study, which included 5,268 women from all over Brazil, showing a higher percentage of HPV in the age group from 16 to 21 years old (57.9%) [29]. Our positivity for women over 50 years old was less than 18%. However, we cannot disregard the average of 12.8% of positive cases for women over 50 years observed in our study.

Is not yet clear the reason for this second peak and its geographic variation, but it may be associated with the reactivation of a previous, undetected infection or the acquisition of the infection through a new sexual contact, both for women and men, mainly as a result of changes in the patterns of sexual behavior in recent decades[3]. Factors such as sexual behavior, religious belief, smoking, parity, contraception, among others, may be responsible for the difference in prevalence in different regions of the world[1]. For example, data from 29 countries indicate that 80% of men and 65% of women age 40 to 80 were sexually active in the year prior to the survey, with the exception of Asia, where both men and women reported less sexual activity[30]. Interestingly, a study of prostitutes also showed a significant decrease in HPV prevalence with age, even with continued high sexual activity, suggesting the development of immunity to type-specific HPV, preventing reinfection[31].

The vast majority of positive cases for HPV were those at high oncogenic risk (94.1% of the positive samples), probably because they were collected as a post-treatment follow-up of induced HPV lesions and not just for diagnosis. In all age groups, HR HPV was prevalent in more than 90% of the cases (whether isolated or associated with LR HPV). The POP Brazil study showed a percentage of 54.6% of positivity for HPV in women aged 16 to 25 years from all over Brazil, with HRHPV in 38.6%. Considering the positive cases for HPV, the study showed HR HPV in 70% of the samples[29]. In a systematic review of more than 50,000 women, Colpani et al. observed HPV infection in 25.4% and 17.6% of women for HR HPV[32]. In a previous study, carried out in Florianópolis, we found a positivity for HPV of 21%, with HR HPV responsible for 58% of positive cases[9].

LR HPV was positive in 18.8% of the positive samples, 5.9% as an isolated infection and 12.9% when associated with HR HPV. The POP Brasil Study also showed a low percentage of infection by LR HPV, being found in 7% of the population of men and women studied[29].

The age group with the highest prevalence of HPV infection was 31 to 35 years (23.5% of positive samples) and the lowest over 70 years (0.6%). Isolated HPV infection with only one viral genotype was more frequent in the population under 20 years of age (86.5% of the cases), while the population aged 66 to 70 years was the one that presented the highest number of mixed infections (25.6% of the cases). Co-infection with multiple types of HPV is a constant in many epidemiological studies. The Brazilian Ludwig-McGill Institute cohort study showed that multiple types of HPV were detected at the same visit in 20% of women positive for HPV (33). The average number of HPV types in women assessed by Winer et al. was three different types per woman, ranging from one to 14[34].

The distribution and prevalence of HPV genotypes vary with the degree of cervical disease, age, and geographic location. The prevalence of HPV 16 and 18 increases according to the severity of the lesion, being associated with approximately 70% of cervical cancer cases worldwide[35]. The most frequently diagnosed genotype in our samples was HR HPV non-16/18 in 77%, followed by HPV 16 (17.1%), 18 (6.5%) and the association of HPV 16 and 18 (0.6%). HPV 31 ranks second in frequency in Europe and HPV 52 in Africa, pointing to the importance of other HR HPV non-16/18 types in certain regions[36]. We also observed geographic variability in Brazil, where HPV 31 and 33 are the second most prevalent types among populations, respectively in the Northeast and Midwest[37,38]. Surprisingly, HPV 66 was detected in 22% of HPV-positive samples in Campo Grande, Mato Grosso do Sul[39]. In the Southeast region, HPV 58 was the most frequent type (19.8%) in HIV-infected women, followed by HPV 53 (15.5%)[40].

The highest prevalence of HPV 16 was observed in the age group of 66 to 70 years (23.1%). In the previous study in Santa Catarina, the most prevalent region of HPV 16 infection was Vale do Itajaí, with 23.8% of positive samples, while in other regions the prevalence was less than 20%[28]. The tests requested in this age group were probably due to some genital lesion (possibly associated with HPV) for diagnostic confirmation or as a cure criterion. In cases of high-grade lesions of the uterine cervix, HPV 16 is known to be the most common. Data from the ICO/IARC-HPV Information Center

in Brazil in 2021 show that HPV 16 was the most frequent type in high-grade lesions (51.2%) and cervical cancer (52.8%)[41].

The age group with the highest prevalence of HPV 18 was younger, 46 to 50 years (9.3%). Evaluating the state of Santa Catarina, it was observed that the most prevalent region of HPV 18 infection was the South of Santa Catarina (16.7%), while in the other regions it did not exceed 10%[28]. In a meta-analysis of 1 million women without cytological alterations, HPV18 was found in many regions as the second most frequent type[36], which was also verified in some Brazilian studies[42-44]. According to the ICO/IARC-HPV Information Center, HPV 18 is the fourth type of HPV in women without any cytological alteration in Brazil (0.7%), and the second in cases of cervical cancer (15.4%)[41]. HPV 18 is closely related to glandular lesions of the cervix and adenocarcinoma (31.8% of the cases for HPV 18, while for squamous cell carcinoma the rate is 8%) and tends to be more aggressive and affect younger women than squamous cell carcinoma[41].

In women without any cytological alteration, the association of HPV 16 and 18 infection is uncommon, being observed in 0.1 to 7% in the USA[45,46] and less than 10% in Paraguay, but there was an increase in these women when they presented a pre-existing cervical lesion, reaching 34%[47]. We observed this infection only in the age group of 26 to 45 years, probably reflecting the presence of a cervical lesion.

If we use the 9HPV vaccine, we will have an additional protection of 77%, compared with the 4HPV vaccine currently available in the National Immunization Program in Brazil. As observed in our previous study, this gain was even greater for the southern region of Santa Catarina (83.4%)[28]. The POP Brazil study also found a low percentage of HPV contained in the 4HPV vaccine, whose prevalence was 14.8%[29]. The most suitable moment for using the vaccine is before exposure to the virus[16], even though the most recent studies also show benefits for women already infected, including those with cervical intraepithelial neoplasia grade 2/3, showing a decrease in relapses by about 75 to 88% for vaccinated women[17]. Although there is an age recommendation by the pharmaceutical industry for the use of vaccines, they have proven to be highly safe, immunogenic and effective also in older men and women[16].

Knowledge about the prevalence of HPV and its types is an important determinant of public policies and fundamental data to define monitoring and treatment strategies for affected patients, and to determine the viral profile of the population, which contributes to the development of HPV prevention policies, for example, assessing prevention coverage by current HPV vaccines. Obtaining these data for the development of research and educational/preventive measures will have a positive impact on the health of the women assisted and that of the community in general, in addition to providing a field for teaching and research in this area.

Strengths

This is a study carried out in Brazil with a significant number of samples for a single city. The high prevalence of non-16/18 high-oncogenic-risk HPVs demonstrates the need to make the nonavalent vaccine against types 6, 11, 16, 18, 31, 33, 45, 52 and 58 available as soon as possible in the health public sector in Brazil, as it is now only provided by immunization private clinics. We cannot neglect the fact that we have observed the prevalence of positivity for HPV in the older population, with over 65 years of age, demonstrating the need to reassess the guidelines for cervical cancer screening in Brazil, which advocate screening up to 64 years of age.

Limitations

This study had some limitations. The evaluation was carried out on the tests requested, probably for different indications, such as screening, evaluation of an existing lesion/disease or as a criterion for post-treatment cure. For this reason, it cannot be analyzed as a study of the prevalence of HPV in the general population of Florianópolis. Likewise, these results reflect what we observe for this city and are not necessarily the same in other cities and/or regions in Brazil. We had no information about the HPV vaccination status of the evaluated women, as this would certainly influence the positivity of the tests or the identified genotypes. The genotyping of non-16/18 HPV types was performed in a pooled manner, not identifying the different viruses separately, which may not faithfully represent the non-16/18 viral types contained in the 9HPV vaccine. Most samples were collected with a cytobrush from the cervico-vaginal region, but at the age extremes (children and advanced post-menopause women) or when this collection was not possible, a collection was performed with a swab from the vaginal introitus, and these group was not evaluated separately.

CONCLUSION

The age group with the highest positivity in the tests for HPV was women between 31 and 35 years old, with high-risk oncogenic HPV present in almost all tests. Non-16/18 HR HPV was the absolute majority of the types found, demonstrating the urgency of using the 9HPV vaccine in the health public programs in Brazil.

Approval by the Human Research Ethics Committee

This study was approved by the Ethics Committee for Research on Human Beings (CEPSH) of Universidade Federal de Santa Catarina (UFSC) under number 5.148.672 (CAAE: 53037521.5.0000.0121).

Participation of each author

ENF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JEL: Data curation, Formal Analysis, Investigation, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare no conflicts of interest.

REFERENCES

1. Burchell NA, Winer RL, Sanjosé S, Franco EL. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. Vaccine. 2006;24(Suppl 3):S52-61. https://doi.org/10.1016/j.vaccine.2006.05.031
2. Muñoz N, Castellsagué X, Berrington de González A, Gissmann L. Chapter 1: HPV in the etiology of human cancer. Vaccine. 2006;24(Suppl 3):S1-10. https://doi.org/10.1016/j.vaccine.2006.05.115
3. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. Vaccine. 2006;24(Suppl 1):S1-15. https://doi.org/10.1016/j.vaccine.2005.09.054
4. Muñoz N, Bosch FX, Sanjose S, Herrero R, Castellagué X, Shah KV, et al. Epidemiologic classification of Human papillomavirus types associated with cervical carcinoma. N Engl J Med. 2003;348(6):518-27. https://doi.org/10.1056/NEJMoa021641
5. Castellsagué X, Bosch FX, Muñoz N. Environmental co-factors in HPV carcinogenesis. Virus Res. 2002;89(2):191-9. https://doi.org/10.1016/s0168-1702(02)00188-0
6. Carvalho MO, Almeida RW, Leite FM, Fellows IB, Teixeira MH, Oliveira LH, et al. Detection of Human papillomavirus DNA by the hybrid capture assay. Braz J Infect Dis. 2003;7(2):121-5. https://doi.org/10.1590/s1413-86702003000200004
7. Franco EL, Villa LL, Sobrinho JP, Prado JM, Rousseau MC, Desy M, et al. Epidemilogy of acquisition and clearence of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. J Infect Dis. 1999;180(5):1415-23. https://doi.org/10.1086/315086
8. Fernandes JV, Meissner RV, Carvalho MGF, Fernandes TAAM, Azevedo PRM, Villa LL. Prevalence of HPV infection by cervical cytologic status in Brazil. Int J Gynecol Obstet. 2009;105:21-4. https://doi.org/10.1016/j.ijgo.2008.12.004
9. Fedrizzi EN, Schlup CG, Menezes ME, Ocampos M. Infecção pelo Papilomavírus humano (HPV) em mulheres de Florianópolis, Santa Catarina. J Bras Doenças Sex Transm. 2008;20(2):73-9. https://doi.org/10.5327/DST-2177-8264-2023351211
10. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108. https://doi.org/10.3322/canjclin.55.2.74
11. Giraldo PC, Silva MJPMA, Fedrizzi EN, Gonçalves AKS, Amaral RLG, Eleutério Júnior J, et al. Prevenção da infecção por HPV e lesões associadas com o uso de vacinas. J Bras Doenças Sex Transm. 2008;20(2):132-40. https://doi.org/10.17765/1983-1870.2018v11n3p431-440
12. Clifford GM, Gallus S, Herrero R, Muñoz N, Snijders PJ, Vaccarella S, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. Lancet. 2005;366(9490):991-8. https://doi.org/10.1016/S0140-6736(05)67069-9
13. Sanjosé S, Diaz M, Castellsagué X, Clifford G, Bruni L, Nuñoz N, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis. 2007;7:453-9. https://doi.org/10.1016/S1473-3099(07)70158-5
14. World Health Organization (WHO). Comprehensive cervical cancer control. A guide to essential practice. 2nd ed. Geneva: WHO; 2014 [cited on Jun 14, 2023]. Available from: https://apps.who.int/iris/bitstream/handle/10665/144785/9789241548953_eng.pdf
15. Instituto Nacional do Câncer (INCA) /Ministério da Saúde (MS). Câncer do Colo de útero – Incidência. [cited on Jun 16, 2023]. Available from: https://www.gov.br/inca/pt-br/assuntos/gestor-e-profissional-de-saude/controle-do-cancer-do-colo-do-utero/dados-e-numeros/incidencia
16. Harper DM. Prophylactic human papillomavirus vaccines to prevent cervical cancer: review of the Phase II and III trials. Therapy. 2008;5(3):313-24. https://doi.org/10.2217/14750708.5.3.313
17. Kang WD, Choi HS, Kim SM. Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN 2/3)? Gynecol Oncol. 2013;130(2):264-8. https://doi.org/10.1016/j.ygyno.2013.04.050
18. Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler CM, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a Phase III double-blind, randomized controlled trial. Lancet. 2007;369(9580):2161-70. https://doi.org/10.1016/S0140-6736(07)60946-5
19. Villa LL, Costa RCR, Petta CA, Andrade RP, Ault KA, Giuliano AR et al. Prophylactic quadrivalent Human papillomavirus (Types 6, 11, 16 and 18) l1 virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicenter phase II efficacy trial. Lancet Oncology. 2005;6(5):271-8. https://doi.org/10.1016/S1470-2045(05)70101-7
20. Ault KA, Future II Study Group. Effect of a prophylactic Human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3 and adenocarcinoma in situ: A combined analysis of four randomized clinical trials. Lancet. 2007;369:1861-8. https://doi.org/10.1016/S0140-6736(07)60852-6
21. Muñoz N, Manalastas Junior R, Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet. 2009;373(9679):1949-57. https://doi.org/10.1016/S0140-6736(09)60691-7
22. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmerón J, et al. Efficacy, safety, and immunogenicity of the Human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomized controlled VIVIANE study. Lancet 2014;384:2213–27. https://doi.org/10.1016/S0140-6736(14)60920-X
23. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372(8):711-23. https://doi.org/10.1056/NEJMoa1405044
24. Programa Nacional de Imunizações, Ministério da Saúde do Brasil. Informe técnico sobre a vacina contra o Papilomavírus humano (HPV) na atenção básica. Brasília, fevereiro de 2015 [cited on Jun 12, 2023]. Available from: http://lproweb.procempa.com.br/pmpa/prefpoa/sms/usu_doc/informe_tecnico__hpv_2015.pdf
25. Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis, Coordenação Geral do Programa Nacional de Imunizações. Nota Informativa referente às mudanças no Calendário Nacional de Vacinação para o ano de 2017. Brasília, fevereiro de 2017 [cited on Jun 12, 2023]. Available from: https://www.saude.go.gov.br/files/imunizacao/legislacao/NI384(MudancasnoCalendarioNacionaldeVacinacao2017).pdf
26. Anvisa. Registrada vacina do HPV contra 9 subtipos do vírus. [cited on Jun 12, 2023]. Available from: http://antigo.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=3875990&_101_type=content&_101_groupId=219201&_101_urlTitle=registrada-vacina-do-hpv-contra-9-subtipos-do-virus&inheritRedirect=true
27. Fernandes S. Vital para evitar câncer, nova vacina para o HPV é lançada no Brasil. Folha de São Paulo [Internet]. 2023 Mar 9 [cited 2023 Jun 12]; Equilíbrio e Saúde. Available from: https://www1.folha.uol.com.br/equilibrioesaude/2023/03/vital-para-evitar-cancer-nova-vacina-para-hpv-e-lancada-no-brasil.shtml
28. Fedrizzi EN, Steffens SM, Menezes ME, Levi JE. Genital infection by Human Papillomavirus (HPV) in women from Santa Catarina/Brazil. J Bras Doenças Sex Transm. 2022;34:e22112. https://doi.org/10.5327/DST-2177-8264-20221212
29. Wendland EM, Villa LL, Unger ER, Domingues CM, Benzaken AS; POP Brazil Study Group. Prevalence of HPV infection among sexually active adolescents and young adults in Brazil: The POP-Brazil Study. Sci Rep. 2020;10(1):4920. https://doi.org/10.1038/s41598-020-61582-2
30. Nicolosi A, Laumann EO, Glasser DB, Moreira Júnior ED, Paik A, Gingell C. Sexual behavior and sexual dysfunctions after age 40: the global study of sexual attitudes and behaviors. Urology. 2004;64(5):991-7. https://doi.org/10.1016/j.urology.2004.06.055
31. Kjaer SK, Svare EI, Worm AM, Walboomers JMM, Meijer CJLM, van den Brule AJC. Human papillomavirus infection in Danish female sex workers: decreasing

prevalence with age despite continuously high sexual activity. Sex Transm Dis. 2000;27:438-45. https://doi.org/10.1097/00007435-200009000-00003
32. Colpani V, Falcetta FS, Bidinotto AB, Kops NL, Falavigna M, Hammes LS, et al. Prevalence of human papillomavirus (HPV) in Brazil: a systematic review and meta-analysis. PLoS ONE. 2020;15(2):e0229154. https://doi.org/10.1371/journal.pone.0229154
33. Rousseau MC, Pereira JS, Prado JC, Villa LL, Rohan TE, Franco EL. Cervical coinfection with human papillomavirus (HPV) types as a predictor of acquisition and persistence of HPV infection. J Infect Dis. 2001;184(12):1508-17. https://doi.org/10.1086/324579
34. Winer RL, Hughes JP, Feng Q, Xi LF, Cherne SL, Oreilly S, et al. Early natural history of incident type-specific human papillomavirus infections in newly sexually active Young women. Cancer Epidemiol Biomarkers Prev. 2011;20(4):699-707. https://doi.org/10.1158/1055-9965.EPI-10-1108
35. Fernandes JV, Meissner RV, Carvalho MG, Fernandes TA, Azevedo PR, Villa LL. Prevalence of HPV infection by cervical cytologic status in Brazil. Int J Gynaecol Obstet. 2009;105(1):21-4. https://doi.org/10.1016/j.ijgo.2008.12.004
36. Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis. 2010;202(12):1789-99. https://doi.org/10.1086/657321
37. Silva MFB, Chagas BS, Guimarães V, Katz LM, Felix PM, Miranda PM, et al. HPV31 and HPV33 incidence in cervical samples from women in Recife, Brazil. Genet Mol Res. 2009;8(4):1437-43. https://doi.org/10.4238/vol8-4gmr677
38. Rabelo-Santos SH, Zeferino L, Villa LL, Sobrinho JP, Amaral RG, Magalhaes AV. Human papillomavirus prevalence among women with cervical intraepithelial neoplasia III and invasive cervical cancer from Goiania, Brazil. Mem Inst Oswaldo Cruz. 2003;98(2):181-4. https://doi.org/10.1590/s0074-02762003000200003
39. Tozetti IA, Scapulatempo IDL, Kawski VL, Ferreira AW, Levi JE. Multiple types of human papillomavirus in cervical samples in women in Campo Grande, MS, Brazil. BJID. 2006;10(5):309-10. https://doi.org/10.1590/s1413-86702006000500001
40. Castilho JL, Levi JE, Luz PM, Cambou MC, Vanni T, Andrade A, et al. A cross-sectional study of high-risk human papillomavirus clustering and cervical outcomes in HIV-infected women in Rio de Janeiro, Brazil. BMC Cancer. 2015;15:478. https://doi.org/10.1186/s12885-015-1486-4
41. Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, et al. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Brazil. 2021 [cited on Jun 24, 2023]. Available from: https://hpvcentre.net/statistics/reports/BRA.pdf
42. Noronha V, Mello W, Villa L, Brito A, Macedo R, Bisi F, et al. Human papillomavirus associated with uterine cervix lesions. Rev Soc Bras Med Trop. 1999;32(3):235-40. Available from: https://www.scielo.br/j/rsbmt/a/7WpwgK964pGpDdHHdnG6w3j/?format=pdf&lang=pt
43. Eluf-Neto J, Booth M, Munoz N, Bosch FX, Meijer CJ, Walboomers JM. Human papillomavirus and invasive cervical cancer in Brazil. Br J Cancer. 1994;69(1):114-9. https://doi.org/10.1038/bjc.1994.18
44. Oliveira-Silva M, Lordello CX, Zardo LM, Bonvicino CR, Moreira MA. Human Papillomavirus in Brazilian women with and without cervical lesions. Virol J. 2011;8:4. https://doi.org/10.1186/1743-422X-8-4
45. Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS, et al. Prevalence of HPV infection among females in the United States. JAMA. 2007;297(8):813-9. https://doi.org/10.1001/jama.297.8.813
46. Wheeler CM, Hunt WC, Cuzick J, Lansfeld E, Pearse A, Montoya GD, et al. A population-based study of human papillomavirus genotype prevalence in the United States: baseline measures prior to mass human papillomavirus vaccination. Int J Cancer. 2013;132:198-207. https://doi.org/10.1002/ijc.27608
47. Mendoza LP, Arbiza J, Paez M, Kasamatsu E, Castro A, Giménez G, et al. Distribution of human papillomavirus genotypes in Paraguayan women according to the severity of the cervical lesion. J Med Virology. 2011;83:1351-7. https://doi.org/10.1002/jmv.22112

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