Genital infection by Human Papillomavirus (HPV) in women from Santa Catarina/Brazil

Infecção genital pelo Papilomavírus Humano (HPV) em mulheres de 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 point in their lives. Most infections will be transient, but when the infection becomes persistent and associated with a high oncogenic risk of Human Papillomavirus, there may be progression to cancer, especially cervical cancer. The best way to prevent Human Papillomavirus infection is through the use of vaccines, which have been available to the public in Brazil since 2014. **Objective:** This study aimed to assess the most prevalent types of Human Papillomavirus in the state of Santa Catarina, Brazil, and its mesoregions and if the majority of diagnosed types are contained in the Human Papillomavirus vaccines currently available on the market. **Methods:** A total of 20,000 Human Papillomavirus tests were evaluated for the diagnosis of genital Human Papillomavirus infection in women from the state of Santa Catarina, Brazil. The prevalence of infection was evaluated according to age and the city of origin of the exams. Human Papillomavirus detection was performed using molecular biology tests, such as hybrid capture (for diagnosis of the Human Papillomavirus group, high or low oncogenic risk) and polymerase chain reaction (viral genotyping) techniques. **Results:** The diagnosis of Human Papillomavirus infection was performed on women between 1 and 102 years of age. The age with the highest Human Papillomavirus positivity, as expected, was 20–25 years (45.6%) and the lowest after 70 years (7.1%). The highest Human Papillomavirus positivity of the exams was observed in the Serrana region of Santa Catarina state (58.9% of the exams). A high-oncogenic-risk Human Papillomavirus was detected in 93% of positive samples and was the most frequent in all age groups. Mixed infection (high- and low-risk Human Papillomavirus) was more prevalent in the 66–70 age group (29.3%) and in the Southern Region of Santa Catarina (26.4%). The most frequent genotypes in the state of Santa Catarina were non-16/18 high oncogenic risk Human Papillomavirus (76.9% of positive cases). Human Papillomavirus 16 was found in 17.1% of positive cases and Human Papillomavirus 18 in 6.6%. **Conclusion:** The most prevalent types of Human Papillomavirus in the state of Santa Catarina in the past 6 years are the non-16/18 high oncogenic risk Human Papillomavirus types, which are viral types not covered by the current Human Papillomavirus vaccines available in Brazil.

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

RESUMO

Introdução: A infecção por Papilomavírus Humano é a infecção sexualmente transmissível mais frequente na mulher. Cerca de 80% das mulheres sexualmente ativas entrarão em contato com esse vírus em algum momento. A maioria das infecções será transitória, mas quando ela é persistente, associada aos Papilomavírus Humano de alto risco oncogênico, poderá progredir para câncer, principalmente de colo de útero. A melhor forma de se prevenir da contaminação pelo vírus é por meio de vacina, disponível no sistema público do Brasil desde 2014. **Objetivo:** Avaliar os tipos de Papilomavírus Humano mais prevalentes no estado de Santa Catarina e suas mesorregiões, e se a maioria dos tipos diagnosticados estão contidos nas vacinas contra o Papilomavírus Humano atualmente disponíveis no mercado. **Métodos:** Foram avaliados 20 mil exames para diagnóstico da infecção genital pelo Papilomavírus Humano em mulheres de todo o estado. A prevalência da infecção foi comparada de acordo com a idade e a procedência dos exames. A detecção do Papilomavírus Humano deu-se pelos exames de biologia molecular pelas técnicas de captura híbrida (para diagnóstico do grupo de Papilomavírus Humano, alto ou baixo riscos oncogênicos) e de PCR (genotipagem viral). **Resultados:** Foram avaliados exames para diagnóstico da infecção de mulheres entre um e 102 anos de idade. A faixa etária de maior positividade, como era de ser esperado, foi dos 20 aos 25 anos (45.6%) e a menor depois dos 70 anos (7.1%). A maior positividade dos exames foi observada na região Serrana do estado (58.9% dos exames). O Papilomavírus Humano de alto risco oncogênico foi detectado em 93% dos casos positivos e foi o mais frequente em todas as faixas etárias. A infecção mista (Papilomavírus Humano de alto e baixo riscos) foi mais prevalente na faixa etária dos 66 aos 70 anos (29.3%) e na região Sul Catarinense (26.4%). Os genótipos mais frequentes no estado foram os Papilomavírus Humano de alto risco oncogênico não 16/18 (76.9% dos casos positivos). O Papilomavírus Humano 16 foi encontrado em 17.1% dos casos positivos e o Papilomavírus Humano 18 em 6.6%. **Conclusão:** Os tipos de Papilomavírus Humano mais prevalentes no estado de Santa Catarina, nos últimos seis anos, são os Papilomavírus Humano de alto risco oncogênico não 16/18, tipos virais não cobertos pelas atuais vacinas contra o Papilomavírus Humano disponíveis no Brasil.

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

INTRODUCTION

Genital Human Papillomavirus (HPV) infection is the most common sexually transmitted infection both in women and men worldwide[1]. Currently, there are more than 200 identified types of HPV, of which more than 100 are completely genetically sequenced and more than 120 with partial sequencing. About 45 types infect the male and female anogenital tract epithelium[2]. Of these, 18 are considered to be at high oncogenic risk, 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]. Those with low oncogenic risk, 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 treatment costs[3]. From an epidemiological point of view, mainly HPVs 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82 are considered high oncogenic

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risk and low-risk HPVs 6, 11, 40, 42, 43, 44, 54, 61, 72, 70, 81, and CP6108[4].

It is estimated that at least 50% of sexually active individuals will come into contact with HPV at some point in life and that 80% of women will have this contact by the age of 50 years[5].

Most HPV infections detected by molecular biology techniques are transient and have not been detected for more than 1 or 2 years[3]. High-risk HPV infections persist longer than low-risk ones. Regarding the high-risk types, there is some evidence that 16 persists longer than the others. Therefore, it is likely that the spread of high-risk HPVs (particularly 16) is greater than that of low-risk HPVs, considering the model of sexual contact and transmissibility to be equivalent[1].

In the female population, the prevalence of HPV infection varies from 2–44%[3]. In a recent meta-analysis, with 78 published studies, women with normal cytology had an adjusted global prevalence of 10.41% (95%CI 10.2–10.7), with considerable variation according to region[1]. Studies carried out in Brazil found positivity for HPV in the general population, from 21–48%[6-8], with high oncogenic risk detected in 48–53%.

In about a quarter of the time, mixed infection with high- and low-risk HPVs was observed[9].

According to the World Health Organization (WHO), more than 630 million men and women (1:10 people) are infected with HPV[10]. For Brazil, it is estimated that 9–10 million people are infected by this virus, and that each year, 700,000 new cases appear, which can therefore be considered an epidemic disease[11]. Around 105 million people are positive for HPV 16 or 18 worldwide[12]. The highest prevalence of infection is in younger women and decreases in the middle-aged group, with a second peak after the age of 50 years, except in Asia[1,13]. Coinfection with multiple types of HPV and sequential infection with new types are common, and the risk of acquiring a new type of HPV seems to be independent of the previous infection with other types[3].

Cervical cancer prevention strategies consist of preventing HPV infection and early diagnosis of pre-invasive lesions, since their progression is slow and combatable with treatment[14]. The consolidated data on the incidence of cervical cancer by the National Cancer Institute (INCA) of the Ministry of Health for the triennium 2020–2022 is 16,710 cases in Brazil (adjusted incidence rate of 15.38/100,000 women), 970 cases in Santa Catarina (adjusted incidence rate of 12.6/100,000 women), and 70 cases in Florianópolis (adjusted rate of 21.41/100,000 women)[15].

Currently, the most effective way to prevent HPV infection is through vaccines. At the moment, three immunizers against HPV are available on the market: bivalent or Cervarix®, against types 16 and 18, with a 0, 1 and 6 month schedule; quadrivalent or Gardasil®, against 6, 11, 16 and 18, with the regimen of 0, 2 and 6 months; and the nonavalent or Gardasil 9®, against types 6, 11, 16, 18, 31, 33, 45, 52 and 58, with a 0, 2 and 6 month schedule, which were highly effective in clinical trials with 95–100% efficacy rates for precancerous lesions of the lower genital tract associated with HPV 16 and 18 (bi-, quad-, and nonavalent vaccines) and against the other five high-risk HPV types for the nonavalent vaccine. All three proved to be highly immunogenic and safe, most often associated with nonserious local adverse events, such as pain, discomfort, hyperemia, and edema[11,16-23].

Since March 2014, the quadrivalent HPV vaccine has been available on the public vaccination schedule in Brazil. Currently, the National Immunization Program (PNI) has adopted the two-dose schedule (0 and 6 months) for girls and boys aged 9–14 years, since the two-dose schedule of the vaccine proved to be highly immunogenic and effective for boys and girls aged 9–14 years, with a minimum interval between doses of 5 months and a maximum of 15 months[24,25].

In the PNI, the vaccine is available for girls/women and boys/men aged 9–45 years with an immunosuppressive disease (HIV infection, transplanted solid organs and bone marrow, and cancer patients) in the traditional three-dose regimen (0, 2 and 6 months)[25].

OBJECTIVE

The objective of this study was to identify the types of HPV prevalent in female genital infection in samples from the state of Santa Catarina and to assess whether the most frequently found HPV types in women are preventable by quadrivalent vaccines (against types 6, 11, 16 and 18), available at the National Immunization Program in Brazil, and nonavalent (against types 6, 11, 16, 18, 31, 33, 45, 52 and 58), licensed but not yet marketed in Brazil.

METHODS

Study design and population

This is a descriptive observational study of prevalence, in which the genital samples of women from the state of Santa Catarina (SC) were evaluated for 6 years (from January 6,2016, to December, 31,2021), tabulated according to cities and mesoregions. The state was geographically divided by the Brazilian Institute of Geography and Statistics (IBGE) into six mesoregions: Greater Florianópolis, South Santa Catarina, Vale do Itajaí, North Santa Catarina, Serrana, and West Santa Catarina. In turn, these mesoregions are formed by 20 microregions, according to geographic location. The Greater Florianópolis mesoregion encompasses the microregions of Florianópolis, Tijucas, and Tabuleiro (21cities). In the South Santa Catarina are the microregions of Tubarão, Criciúma, and Araranguá (46 cities). Vale do Itajaí includes microregions of Itajaí, Blumenau, Rio do Sul, and Ituporanga (54 cities). In the North Santa Catarina are the microregions of Joinville, Canoinhas, and São Bento do Sul (26 cities). Serrana has the microregions of Curitibanos and Campos de Lages (30 cities), while in West Santa Catarina there are the microregions of Chapecó, Xanxerê, Joaçaba, Concórdia, and São Miguel do Oeste (118 cities)[26].

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 samples received by the DNA Análises Laboratory in Florianópolis and DASA in São Paulo, from Santa Catarina for the

analysis of possible female genital HPV infection, were submitted to molecular diagnosis for HPV DNA research using hybrid capture and polymerase chain reaction (PCR) methods.

Using the hybrid capture method, from the Digen® Laboratory, the group of HPV (high or low risk) present in the sample was detected. The detection limit of the test is 1 pg/mL HPV DNA, equivalent to 0.1 virus copy per 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 report that hybrid capture values between 1 and 3 are inconclusive, most studies, as well as this one, took positivity into account when ≥1 RLU/CO. The low-risk HPVs detected by the method were types 6, 11, 42, 23, and 44, and the high-risk HPVs were types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.

In turn, the PCR test detects the type of virus present in the sample (genotyping), which was performed in real time by the TaqMan System of the Abbott® Laboratory. The Real-Time HR HPV version of this system limits detection to 500 copies per reaction for types 16 and 18 and 5,000 for others, while the Alinity m HR HPV limits detection to 240 copies per test for HPV types 16 and 18; 500 for 45; 2 million for 33, 35, 51, 52 and 59; and 5,000 for 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 state of Santa Catarina. Secondary endpoints were to assess whether age and state mesoregions 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 20,000 samples from the female genital tract of women from Santa Catarina were analyzed for 6 years (2016–2021) and stored in the database of the DNA Análises laboratories, in Florianópolis, and DASA, in São Paulo. Most of these examinations were from the Greater Florianópolis mesoregion (18,181 samples) followed by Vale do Itajaí (608 samples). The information obtained from these examinations were age, origin, HPV detection according to the oncogenic group (low and high risk) and genotyping (HPVs 16 and 18 alone and 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 in pool).

The age of the patients in the samples ranged from 1 to 102 years, where the age extremes positive for HPV were 3 years (positive for high-risk HPV by the hybrid capture technique) and 87 years (positive for high-risk HPV but not 16-18 by the PCR technique). The age group with the highest number of exams was from 31 to 40 years, with 7,645 exams (38.2%). The age group with the highest percentage of positive tests was from 20 to 25 years, with 45.6% of positive samples, and the lowest, after 70 years (7.1%) (**Table 1**). The mean age of HPV-infected women was similar in all mesoregions, ranging from 34.1 years for the Serrana mesoregion to 37.7 years for Greater Florianópolis (**Figure 1**).

Table 1 – Distribution of demographic characteristics of women from Santa Catarina evaluated according to HPV group (hybrid capture + PCR).

	NEG N	POS N	HR HPV n (%)*	LR HPV n (%)*	HR + LR HPV n (%)*	Total n (%)**
Age (years)						
<20	75	49	36 (73.5)	01 (2.0)	12 (24.5)	124 (39.5)
20–25	802	673	481 (71.4)	43 (6.4)	149 (22.1)	1,475 (45.6)
26–30	1,528	935	715 (76.4)	48 (5.1)	172 (18.4)	2,463 (37.9)
31–35	2,829	1034	842 (81.4)	60 (5.8)	132 (12.7)	3,863 (26.7)
36–40	3,022	760	612 (80.5)	55 (7.2)	93 (12.2)	3,782 (20.0)
41–45	2,327	502	406 (80.8)	42 (8.3)	54 (10.7)	2,829 (17.7)
46–50	1,471	245	186 (75.9)	26 (13.9)	33 (13.4)	1,716 (14.2)
51–55	1,075	155	113 (72.9)	19 (12.3)	23 (14.8)	1,230 (12.6)
56–60	812	117	87 (74.3)	13 (11.1)	17 (14.5)	929 (12.6)
61–65	558	67	55 (82.0)	04 (5.9)	08 (11.9)	625 (10.7)
66–70	376	41	27 (65.8)	02 (4.8)	12 (29.3)	417 (9.8)
>70	324	25	21 (84.0)	01 (4.0)	03 (12.0)	349 (7.1)
Unknown	112	86	59 (68.6)	10 (11.6)	17 (19.7)	198 (43.4)
Total	15,311	4,689	3,640 (77.6)	324 (7.0)	725 (15.4)	20,000 (23.4)
Mesoregion						
Greater Fpolis	14,243	3,938	3,134 (79.6)	252 (6.4)	552 (14.0)	18,181 (21.6)
South SC	161	136	92 (67.6)	08 (6.0)	36 (26.4)	297 (45.8)
Vale do Itajaí	407	201	130 (64.6)	24 (12.0)	47 (23.4)	608 (33.0)
North SC	175	127	100 (78.7)	07 (5.6)	20 (15.7)	302 (42.0)
Serrana	17	22	15 (68.2)	02 (9.1)	05 (22.7)	39 (56.4)
West SC	317	255	159 (62.3)	31 (12.2)	65 (25.5)	572 (44.6)

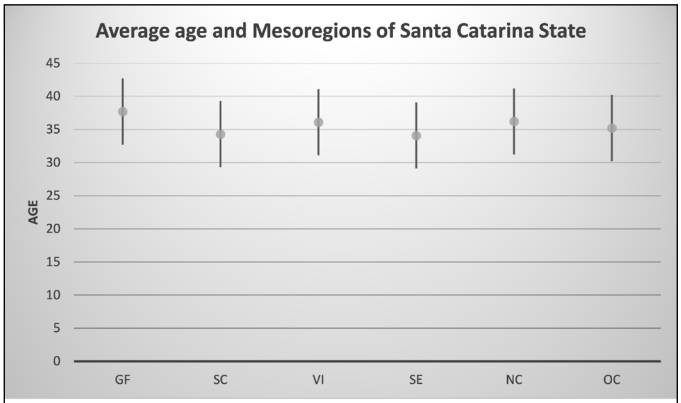
*HPV group/positive cases; **positive cases/total tests. NEG: HPV-negative test; POS: HPV-positive test; HR HPV: high-risk HPV; LR HPV: low-risk HPV; Fpolis: Florianópolis. Source: Data from DNA Laboratories Analysis and DASA, 2022.

The highest prevalence of positivity for HPV infection in the samples was in the Serrana mesoregion with 58.9%, despite being the one with the lowest number of samples collected (39 samples). Greater Florianópolis, despite having the largest number of samples collected (18,181), had the lowest percentage of HPV infection detected (21.6%). The age group from 20 to 25 years was also the one that presented the highest percentage of positivity for HPV for most of the mesoregions of Santa Catarina (**Table 2** and **Figure 2**).

High-risk HPV (HR HPV) was the most frequently observed (93% of positive samples), detected alone in 77.6%, and associated with low-risk HPV in 15.4%. In all age groups, HR HPV was found in more than 90%, isolated or associated with HPV of low oncogenic risk (LR HPV). LR HPV alone was diagnosed in only 7% of positive cases and associated with HR HPV in 22.3%. The age group from 46 to 50 years was the most affected with simple infection (13.9% of positive samples) and from 66 to 70 years, the most frequently associated with mixed infection, HR HPV + LR HPV (29.3%) (**Table 1**).

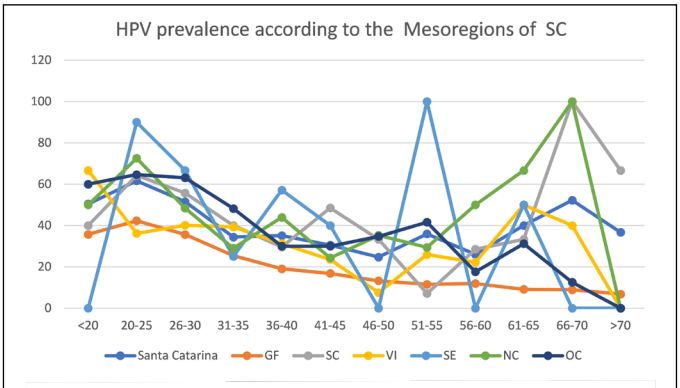
Isolated HR HPV was more prevalent in the Greater Florianópolis mesoregion (79.6%), but when associated with LR HPV, the Southern region of Santa Catarina was more prevalent (26.4%). LR HPV isolated or associated with HR HPV was more commonly diagnosed in the West Santa Catarina mesoregion (37.7%) (**Table 1** and **Figure 3**).

Regarding HPV genotyping, it was performed in 11,991 samples using the PCR technique, 13.2% of which were positive. The most prevalent HPV genotype was non-HR HPV 16/18 (76.9%), followed by HPV 16 (16.5%), 18 (6%) and the HPV 16 and 18 association at 0.6%. HPV 16 was more frequent in the Vale do Itajaí region (23.8%),



The mean age of HPV-positive cases was: GF (Greater Florianópolis): 37.7 years; SC (South SC): 34.3 years; VI (Vale do Itajaí): 36.1 years; SE (Serrana): 34.1 years; NC (North SC): 36.2 years; OC (West SC): 35.2 years. Source: Data from DNA Laboratories Analysis and DASA, 2022.

Figure 1 – Average age of HPV-positive women, according to the mesoregions of Santa Catarina.



GF: Greater Florianópolis; SC: South Catarinense; VI: Vale do Itajaí; SE: Serrana; NC: North SC; OC: West SC. The distribution of cases according to age group is quite homogeneous and follows the trend of the state of Santa Catarina, except for the Serrana mesoregion, which presents extreme results, associated with the low number of samples. Source: Data from DNA Laboratories Analysis and DASA, 2022.

Figure 2 – Prevalence of positive HPV cases, according to age and mesoregions of Santa Catarina.

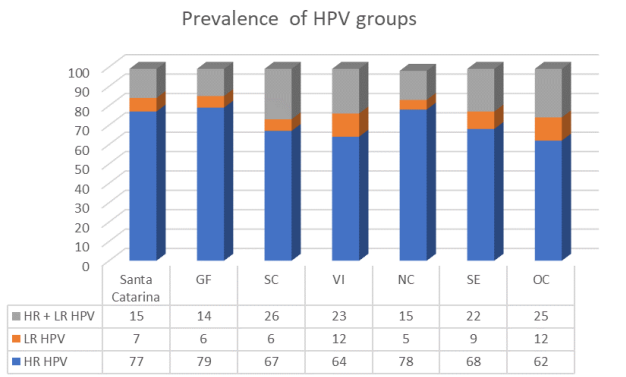
Table 2 – Prevalence of positive HPV cases, according to age and mesoregions of Santa Catarina.

DNA HPV	Mesoregion				
	GF n (%)	SC n (%)	VI n (%)	SE n (%)	NC n (%)
<20	35/98 (35.7)	02/05 (40.0)	04/06 (66.6)	0	02/04 (50.0)
20–25	507/1,197 (42.3)	36/56 (64.2)	29/80 (36.2)	09/10 (90.0)	29/40 (72.5)
26–30	749/2,103 (35.6)	39/70 (55.7)	47/117 (40.1)	04/06 (66.6)	31/64 (48.4)
31–35	894/3,517 (25.4)	16/40 (40.0)	50/127 (39.3)	02/08 (25.0)	16/55 (29.0)
36–40	663/3,488 (19.0)	16/54 (29.6)	35/112 (31.2)	04/07 (57.1)	18/41 (43.9)
41–45	443/2,634 (16.8)	17/35 (48.5)	16/68 (23.5)	02/05 (40.0)	09/37 (24.3)
46–50	211/1,587 (13.2)	03/09 (33.3)	03/40 (7.5)	0	12/34 (35.2)
51–55	132/1,147 (11.5)	01/14 (7.1)	07/27 (25.9)	01/01 (100)	05/17 (29.4)
56–60	105/881 (11.9)	02/07 (28.5)	04/18 (22.2)	0	03/06 (50.0)
61–65	54/593 (9.1)	01/03 (33.3)	04/08 (50.0)	01/02 (50.0)	02/03 (66.6)
66–70	36/404 (8.9)	01/01 (100)	02/05 (40.0)	0	01/01 (100)
>70	23/334 (6.8)	02/03 (66.6)	0	0	0
Unknown	86/198 (43.4)	0	0	0	0
Total	3,938/18,181 (21.6)	136/297 (45.7)	201/608 (33.0)	23/39 (58.9)	128/302 (42.3)

GF: Greater Florianópolis; SC: South Catarinense; VI: Vale do Itajaí; SE: Serrana; NC: North SC; OC: West Catarinense. Source: Data from DNA Laboratories Analysis and DASA, 2022.

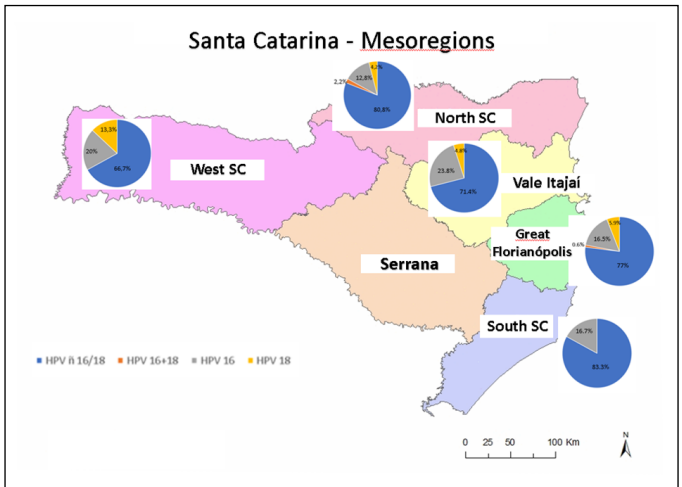
being less than 20% in the other mesoregions and had a higher prevalence from 66 to 70 years (23%). HPV 18 was detected in 6.6% of positive samples, more frequently detected in the Southern mesoregion of Santa Catarina (16.7%), and less than 10% in most regions. The age group with the highest prevalence of this viral type was from 41 to 45 years (8.8%). The association of HPVs 16 and 18 was only diagnosed in the regions of Greater Florianópolis (0.6%) and Northern Santa Catarina (2.2%), being more frequent in the age group from 36 to 40 years (1%). The Serrana mesoregion, on the other hand, did not have any HPV genotyping tests (**Table 3** and **Figure 4**).

Observing HPV genotyping, we can see the additional percentage of protection when using the nonavalent vaccine (9HPV), against types 6, 11, 16, 18, 31, 33, 45, 52 and 58 instead of the quadrivalent (4HPV),



HR HPV: high-risk HPV; LR HPV: low-risk HPV; GF: Greater Florianópolis; SC: South Santa Catarina; VI: Vale do Itajaí; SE: Serrana; NC: North Santa Catarina; OC: West Santa Catarina. Source: Data from DNA Laboratories Analysis and DASA, 2022.

Figure 3 – Prevalence of HPV groups in positive samples, according to the mesoregions of Santa Catarina.



Serrana mesoregion did not have any genotyped samples. HPV no 16/18: high-risk HPV types not 16 and/or 18 (HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Source: Data from DNA Laboratories Analysis and DASA, 2022.

Figure 4 – Prevalence of HPV types, according to the mesoregions of Santa Catarina.

Table 3 – Distribution of demographic characteristics of women from Santa Catarina evaluated according to the type of HPV detected by PCR technique.

Variable	HPV*						
	NEG N	POS N	16 n (%)	18 n (%)	16+18 n (%)	HR no 16/18 n (%)	Total n (%)**
AGE (years)							
<20	48	17	0	0	0	17 (100)	65 (26.1)
20–25	498	216	26 (12.0)	12 (5.5)	01 (0.4)	177 (81.9)	714 (30.2)
26–30	951	301	43 (14.2)	25 (8.3)	03 (0.9)	230 (76.4)	1,252 (24.0)
31–35	1,884	368	72 (19.5)	15 (4.0)	02 (0.5)	279 (75.8)	2,252 (16.3)
36–40	2,051	276	50 (18.1)	13 (4.7)	03 (1.0)	210 (76.0)	2,327 (11.8)
41–45	1,606	170	28 (16.4)	15 (8.8)	01 (0.5)	126 (74.1)	1,776 (9.5)
46–50	1,011	92	14 (15.2)	08 (8.7)	0	70 (76.1)	1,103 (8.3)
51–55	718	51	10 (19.6)	02 (3.9)	0	39 (76.4)	769 (6.6)
56–60	592	46	09 (19.5)	02 (4.3)	0	35 (76.1)	638 (7.2)
61–65	439	28	05 (17.8)	02 (7.1)	0	21 (75.0)	467 (5.9)
66–70	314	13	03 (23.0)	01 (7.7)	0	09 (69.2)	327 (3.9)
>70	287	14	01 (7.1)	01 (7.1)	0	12 (85.7)	301 (4.6)
Total	10,399	1,592 (13.2)	261 (16.5)	96 (6.0)	10 (0.6)	1,225 (76.9)	11,991 (100)
Mesoregion							
Greater Fpolis	10,320	1,503	247 (16.5)	90 (5.9)	09 (0.6)	1,157 (77.0)	11,823 (12.7)
South SC	01	06	0	01 (16.7)	0	05 (83.3)	07 (85.7)
Vale do Itajaí	26	21	05 (23.8)	01 (4.8)	0	15 (71.4)	47 (44.7)
North SC	45	47	06 (12.8)	02 (4.2)	01 (2.2)	38 (80.8)	92 (51.0)
Serrana	0	0	0	0	0	0	0
West SC	07	15	03 (20.0)	02 (13.3)	0	10 (66.7)	22 (68.2)

*HPV type/positive cases; **positive cases/total examinations. NEG: HPV-negative test; POS: HPV-positive test; HR HPV: high-risk HPV; no 16/18: HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68; Fpolis: Florianópolis. Source: Data from DNA Laboratories Analysis and DASA, 2022.

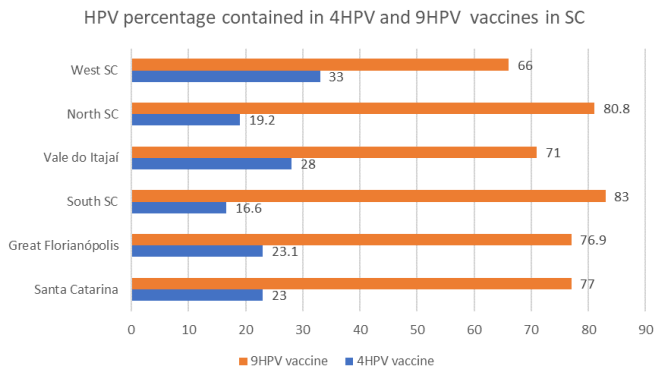
against types 6, 11, 16, and 18. Additional protection was 77% for Santa Catarina. Not counting protection against HPV types 16 and 18 (common to both vaccines), the 9HPV immunizing agent increased protection by more than 80% in the North and South Santa Catarina mesoregions (80.9% and 83.4%, respectively). The lowest percentage of increase – and even so important – was 66.7% for the West of Santa Catarina (**Figure 5**).

DISCUSSION

The prevalence and distribution of HPV types in the world vary greatly, according to the population studied and its age group. The highest prevalence of this infection is seen in younger women, decreasing in the middle-aged group, and having its second peak after the age of 50 years, except in Asia[1]. This same trend is demonstrated in the 2017 WHO data and in the meta-analysis by Sanjosé et al. (2007)[13]. In our study, the majority of positive cases for HPV were in the age group of 20-25 years (45.6%), similar to the POP Brazil Study, which included 5,268 women from all over Brazil and showed a higher percentage of HPV in the age group of 16–21 years (57.9%)[27]. Our positivity for women over 50 was less than 15%. However, we cannot ignore the 7.1% of positive cases for women over 70 years of age observed in our study.

The reason for this second peak and its geographic variation is unclear, but it may be associated with the reactivation of a previously undetected infection or the acquisition of infection by a new sexual contact of both women and men, mainly as a result of changes in patterns of sexual behavior in recent decades[3].

Factors such as sexual behavior, religion, smoking, parity and 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 aged 40–80 years were sexually active in the year prior to the study, with the exception of Asia, where men and women reported less sexual activity[28]. Interestingly, a study with prostitutes also showed a significant decrease in the prevalence of HPV with age, even with continued high sexual activity, suggesting the development of immunity to type-specific HPV, preventing reinfection[29].



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

Figure 5 – Types of HPV contained in the 4HPV and 9HPV vaccines, according to the mesoregions of Santa Catarina.

Although we observed higher positivity of HPV infection in the Serrana region of Santa Catarina (58.9%) and lower in Florianópolis (21.6%), we cannot conclude that the real prevalence is higher in the former than in the latter, because several of these exams must have been collected not only for diagnosis but also as a post-treatment follow-up of HPV-induced lesions. However, the POP Brazil Study also showed a different prevalence of HPV, according to the region of Brazil, whose highest detection occurred in the northeast (58.1%) and the lowest in the south (49.7%)[27].

The majority of HPV-positive cases in our study was for high-risk types (93%), such as simple infection (77.6%), or associated with low-risk types (15.4%). In all age groups, the HR HPV was prevalent in more than 90% (isolated or associated with LR HPV). The POP Brazil Study showed a percentage of 54.6% of positivity for HPV in women aged 16–25 years throughout Brazil, with HR HPV in 38.6%. Considering the positive cases, the study showed HR HPV in 70% of the samples[27].

In a systematic review of more than 50,000 people, Colpani et al. observed HPV infection in women in 25.4 and 17.6% for HR HPV[30]. In a previous study carried out in Florianópolis, we found a positivity rate for HPV of 21%, with the high risk being responsible for 58% of positive cases[9]. Low risk was positive in 6.9% of samples as an isolated infection and in 22.3% when associated with HR HPV. The POP Brazil Study also showed a low percentage of infection by LR HPV found in 7% of the population of men and women studied[27].

Isolated HPV infection, with only one viral genotype, was more frequent in the population aged 46–50 years (13.9%), while the population aged 66–70 years presented the most mixed infection (27.3%). Coinfection with multiple types of HPV is a constant in many epidemiological studies. The Ludwig-McGill Institute Brazilian cohort study showed that multiple types of HPV were detected at the same visit in one-fifth of HPV-positive women[31]. The mean number of HPV types in women evaluated by Winer et al. was of three types per woman, ranging from 1–14[32].

When we evaluated the regions of Santa Catarina, we observed that isolated HR HPV infection was more frequent in the Greater Florianópolis mesoregion (79.6%), while isolated LR HPV infection was more frequent in the West of Santa Catarina (37.6%). The mixed HR HPV infection associated with LR HPV was more frequent in the southern mesoregion of Santa Catarina (26.4%).

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, which is associated with approximately 70% of cervical cancer cases worldwide[33]. The genotype most frequently diagnosed in our samples was HR HPV non 16/18 in 77.4%, followed by HPV 16 (16.5%), 18 (6%) and the association of types 16 and 18 in 0.6%. Type 31 ranks second in frequency in Europe and 52 in Africa, pointing to the importance of HPV types other than 16/18 in certain regions[34].

We also observed geographic variability in Brazil, where HPV 31 and 33 are the second-most prevalent types among populations, in the northeast and midwest, respectively[35,36]. Surprisingly, type 66 was detected in 22% of samples positive for HPV in Campo Grande (Mato Grosso do Sul)[37]. In the southeast region, HPV 58 was the most frequent type (19.8%) in HIV-infected women, followed by HPV 53 (15.5%)[38].

The age group with the highest prevalence of HPV 16 was from 66–70 years (23%) and the most prevalent region was Vale do Itajaí,

with 23.8% of positive samples, while in the other regions the prevalence was less than 20%. The tests requested in this age group were probably as a result of some genital lesion (possibly associated with HPV) for diagnostic confirmation or as a cure criterion. In cases of high-grade cervical lesions, HPV 16 is known to be the most common. Data from the ICO/IARC-HPV Information Center in Brazil in 2021 showed that this was the most frequent type in high-grade lesions (51.2%) and cervical cancer (52.8%)[39]. The age group with the highest prevalence of HPV 18 was younger, from 41–45 years (8.8%), and the most prevalent region was the South of Santa Catarina (16.7%), while in the other regions, it did not exceed 10%.

In a meta-analysis of 1 million women without cytological alterations, HPV 18 was found in many regions as the second-most frequent type[34], also verified in some Brazilian studies[40-42]. According to the ICO/IARC-HPV Information Center, HPV 18 is the fourth type found in women without any cytological alterations in Brazil (0.7%) and the second in cases of cervical cancer (15.4%)[39]. It is related to cervical glandular lesions and adenocarcinoma (31.8% of cases by HPV 18, while for squamous cell carcinoma it is 8%) and tends to be more aggressive and affect younger women than squamous cell carcinoma[39].

Mixed infection with HPV 16 and 18 is uncommon in women without any cytological alteration, observed in 0.1–7% in the USA[43,44] and in less than 10% in Paraguay, but there was an increase in these women when they presented a pre-existing cervical lesion, reaching 34%[45]. We observed this infection only in the 20–45 age group, probably reflecting the presence of some cervical lesions. This association was more frequent in the North of Santa Catarina (2.2%).

When we evaluated the types of HPV protected by vaccines available on the market, we observed a gain in protection with 9HPV vaccine of 77%, with this gain even greater for the South region of Santa Catarina, at 83.4%, compared to the vaccine currently available in the PNI of Brazil, to 4HPV. The POP Brazil Study also observed a low percentage of HPVs contained in the 4HPV vaccine, whose prevalence was 14.8%[27]. The most appropriate time to use the vaccine is before exposure to the virus[16]; however, more recent studies also show benefits for already infected women, including those with moderate and high-grade cervical intraepithelial neoplasia (NIC 2/3), showing a decrease in relapses in about 75–88% of vaccinated women[17]. Although there is a recommendation of age in the package insert for the use of vaccines, they have also been proved to be highly safe, immunogenic and effective in older men and women[16].

This study had some limitations. The evaluation was performed in tests requested, probably for different indications, such as screening, evaluation of an existing lesion/disease or as a post-treatment cure criterion. Therefore, it cannot be analyzed as a study of the prevalence of HPV in the general population. Likewise, these results reflect what we observed for the state of Santa Catarina and are not necessarily the same in other states and/or regions of Brazil, a continental country. We did not have information on the HPV vaccination status of the women evaluated, as this would certainly influence the positivity of the tests or the genotypes identified. Genotyping of non-16/18 HPV types was performed as a pool, and the different viruses were not identified in isolation and may not faithfully represent the non-16/18 viral types contained in the 9HPV vaccine. Finally, in some cities that entered the analysis, there were few tests, probably influencing the results for their region.

The prevalence of HPV and its types is a determinant of public policies and fundamental data for the definition of monitoring and treatment strategies for affected patients, as well as the determination of the viral profile of the population, which contributes to the development of HPV infection and 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 served and on the community in general, in addition to providing a field for teaching and research in this area.

CONCLUSION

The age group with the highest positivity of the HPV tests was the young woman, up to the age of 25 years, with high-oncogenic-risk HPV present in almost all the tests. Among these, non-16/18 high-risk HPVs were the absolute majority, demonstrating the urgency of using the nonavalent HPV vaccine in our country.

Positive points of the study

This is the only study carried out in Brazil with such a high number of samples for a single state. The high prevalence of non-16/18 high-oncogenic-risk HPVs demonstrates the need to make available the nonavalent vaccine against types 6, 11, 16, 18, 31, 33, 45, 52 and 58 as soon as possible in Brazil, since it has been licensed by the National Health Surveillance Agency (ANVISA) since 2017. We cannot neglect the fact that we have observed the prevalence of positivity for HPV in the older population, 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.

Approval by the Human Research Ethics Committee

This study was approved by the Ethics Committee for Research on Human Beings (CEPSH) of the Federal University of 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. SMS: Data Curation, Formal Analysis, Investigation, Validation, Visualization, Writing – review & editing. MEM: Data Curation, Formal analysis, Investigation, Validation, Visualization, 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.

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