HPV Infection and Cancer Control in Brazil: The Important Role of Vaccination

Infecção por HPV e Controle do Câncer no Brasil: O Importante Papel da Vacinação

Infección por VPH y Control del Cáncer en el Brasil: El Importante Papel de la Vacunación

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ABSTRACT

Introduction: HPV vaccination is crucial for cancer control in Brazil. Despite efforts, the country has not yet met the global targets projected for 2030, which could lead to the eradication of cervical cancer after 2050. **Objective:** To describe HPV vaccination coverage, analyze hospital morbidity, and assess mortality trends of HPV-related cancers in Brazil. **Method:** Data on HPV vaccination coverage in Brazil, hospital morbidity, and mortality rates of specific HPV-related cancers, namely cervical, vulvar, vaginal, oropharyngeal, anal, and penile cancers, were analyzed. **Results:** The HPV vaccination coverage for the first dose among girls from 2013-2021 was 76%, and among boys from 2017-2021, it was 52%. The state of Acre has the lowest vaccination coverage. A total of 260,784 patients were analyzed from 2006-2020. Over 80% of patients with oropharyngeal cancer are diagnosed at advanced stages. Anal and anal canal cancer showed an average annual increase in mortality of 7.1% among men and 4.4% among women. **Conclusion:** HPV vaccination is essential and extends beyond the prevention of cervical cancer. The vaccination coverage in Brazil is still insufficient to meet eradication targets, underscoring the need for integrated and effective actions to reduce the morbidity and mortality of HPV-related cancers.
Key words: Human Papillomavirus Viruses; Vaccination Coverage; Neoplasms/mortality; Mortality/trends.

RESUMO

Introdução: A vacinação contra o papilomavírus humano (HPV) é crucial para o controle do câncer no Brasil. Apesar dos esforços, o país ainda não atingiu as metas globais projetadas para 2030 que podem levar à erradicação do câncer do colo do útero após 2050. **Objetivo:** Descrever a cobertura vacinal contra o HPV, analisar a morbidade hospitalar, além da tendência da mortalidade dos cânceres associados a esse vírus no Brasil. **Método:** Foram analisadas as informações sobre a cobertura vacinal contra o HPV no Brasil, a morbidade hospitalar e a mortalidade de alguns tipos de cânceres que são relacionados ao HPV, a saber: colo do útero, vulva, vagina, orofaringe, ânus e pênis. **Resultados:** A cobertura vacinal contra o HPV na primeira dose nas meninas, de 2013-2021, foi de 76% e nos meninos, de 2017-2021, de 52%. O Estado do Acre apresenta a menor cobertura vacinal. Foram analisados 260.784 pacientes, no período de 2006-2020. Mais de 80% dos pacientes com câncer de orofaringe têm seus diagnósticos feitos em estádios avançados. O câncer de ânus e canal anal apresentou um aumento na mortalidade em média de 7,1% ao ano entre os homens e 4,4% ao ano entre as mulheres. **Conclusão:** A vacinação contra o HPV é fundamental e vai além da prevenção para o câncer do colo do útero. A cobertura vacinal no Brasil ainda é insuficiente, o que reforça a necessidade de ações integradas e eficazes para reduzir a morbidade e mortalidade dos cânceres relacionados ao HPV.
Palavras-chave: Papillomavírus Humano; Cobertura Vacinal; Neoplasias/mortalidade; Mortalidade/tendências.

RESUMEN

Introducción: La vacunación contra el virus del papiloma humano (VPH) es clave para el control del cáncer en el Brasil. A pesar de los esfuerzos, el país aún no ha alcanzado las metas globales proyectadas para 2030, que podrían erradicar el cáncer de cuello uterino después de 2050. **Objetivo:** Describir la cobertura de vacunación contra el VPH, analizar la morbilidad hospitalaria y evaluar la tendencia de mortalidad de los cánceres relacionados con el VPH en el Brasil. **Método:** Se analizaron datos sobre la cobertura de vacunación contra el VPH en el Brasil, la morbilidad hospitalaria y la mortalidad de cánceres relacionados con el VPH, como cuello uterino, vulva, vagina, orofaringe, ano y pene. **Resultados:** La cobertura de la primera dosis de la vacuna contra el VPH en niñas, de 2013 a 2021, fue del 76%, y en niños, de 2017 a 2021, del 52%. Acre tiene la menor cobertura vacunal. Se analizaron 260 784 pacientes entre 2006 y 2020. Más del 80% de los casos de cáncer de orofaringe se diagnostica en etapas avanzadas. El cáncer de ano y canal anal mostró un aumento de la mortalidad del 7,1% anual en hombres y del 4,4% anual en mujeres. **Conclusión:** La vacunación contra el VPH es fundamental y va más allá de la prevención del cáncer de cuello uterino. La cobertura vacunal en el Brasil sigue siendo insuficiente, lo que subraya la necesidad de acciones integradas y eficaces para reducir la morbilidad y mortalidad de cánceres relacionados con el VPH.
Palabras clave: Virus del Papiloma Humano; Cobertura de Vacunación; Neoplasias/mortalidad; Mortalidad/tendencias.

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INTRODUCTION

In the last 40 years, one of the most significant findings in the investigation of the causes of cancer was the identification of the link between human papillomavirus (HPV) and cervical cancer[1]. Since the relationship between HPV and cancer was first identified in the 1970s[2,3], the presence of HPV in 99.7% of cases of cervical cancer represents the highest specific cause attribution ever documented for cancer in humans[2,4,5].

Persistent infection by oncogenic HPV types can cause several cancers, not just cervical cancer. In 2024, more than 23 thousand new cases of HPV-related cancers are estimated in Brazil, of which 17 thousand are cervical, 2 thousand oropharynges, 1,2 thousand of anus and anal canal, 700 vulvar, 300 vaginal, and a thousand penile cancer[6]. Vaccination is the main control strategy, as well as enabling continuous monitoring of the infection to evaluate the effectiveness of vaccination programs[7,8].

Currently, HPV, a sexually transmitted virus, is known to cause up to 3.8% of new cancers worldwide[9,10]. Most of them occur in the anogenital area. The impact of HPV infection on the development of oropharynx, anus, vulvar, vaginal, and penile cancers is significant[11,12]. The most frequent anogenital cancer is cervical cancer, which accounted for about 604 thousand new cancer cases and 342 thousand deaths worldwide in 2020. Other sites of anogenital cancer associated with HPV include anal, penile, vaginal, and vulvar cancer, with a global burden of 150 thousand new cases worldwide in 2020[13-15].

HPV infection is a risk factor for anogenital cancers, and the vaccine makes its prevention a Public Health priority[7]. HPV vaccination prevents not only cervical cancer but also other tumors, such as oropharynx, anus, vulva, vagina and penis. Extensive vaccination coverage is essential to reduce morbidity and mortality of these cancers over time[7,16].

In Brazil, the Ministry of Health incorporated the quadrivalent vaccine (types 6, 11, 16, and 18) into the Brazilian National Health System (SUS) in 2014[17]. The initial vaccination scheme, which provided for three doses (0, 6, and 60 months), was changed in 2016 to two doses (0 and 6 months) according to the recommendation of the World Health Organization (WHO), except for the immunosuppressed population[18]. In 2024, the single-dose vaccine scheme for HPV vaccine was adopted by the National Immunization Program (PNI)[19].

HPV vaccine is currently recommended for boys and girls aged 9 to 14 years, immunosuppressed people (aged 15 to 45 years), HIV pre-exposure prophylaxis users, recurrent respiratory papillomatosis carriers, and victims of sexual violence[19]. Early immunization, before sexual activity begins, is essential to prevent the disease and reduce the risk of cancer[20]. Broad and accessible vaccination campaigns are vital to protecting public health[7,21].

Although cancer affects many, it is unacceptable to ignore the primary prevention available. With HPV present in up to 88% of anus and 25% of oropharynx cancers, prevention would reduce cases and relieve the healthcare system[1,15]. This study aimed to describe the coverage of HPV vaccination in boys and girls, to analyze hospital morbidity and mortality trends of cancers related to this virus in Brazil and its Regions. The results showed the current burden of morbidity and mortality of HPV-related cancers, highlighting the importance of vaccination in the future prevention of these tumors. The analysis was performed independently, with no intention of establishing causal relationships between vaccination coverage, hospital morbidity, and mortality.

METHOD

The present study analyzed information on vaccination coverage against HPV in Brazil and on hospital morbidity and mortality of some types of cancers that are related to HPV, namely: cervical, vulvar, vaginal, oropharynx, anal, and penile cancer.

Information from the Brazilian Ministry of Health's databases on HPV vaccination was used, containing information on vaccination coverage, by sex and age group between 9 and 14 years, considering the second dose may have been applied at 15 years of age, in the periods from 2013 to 2021 for females and from 2017 to 2021 for males, corresponding to the years of inclusion of the vaccine in the Brazilian PNI for both sexes.

The study also used information on hospital morbidity of HPV-related cancers – namely oropharynx (C09-10), anal (C21), vulvar (C51), vaginal (C52), cervical (C53), and penile (C60) – for Brazil and Regions, available for the period 2006 to 2020 from Hospital-based Cancer Registry (RHC)[22] that sent their databases to the RHC Integrator. The morphologies ended in /2 and /3 (*in situ* and malignant neoplasm, respectively) were selected.

Frequencies were calculated for the following variables: Gender (male and female), age group (≤24 years, 25 to 44 years, 45 to 64 years, and ≥65 years), race/skin color (yellow, white, indigenous, brown and black), education (none, incomplete elementary, complete elementary, complete high school, and complete higher education), clinical staging (0, I, II, III, IV). The time variable between diagnosis and treatment was divided into two categories: Patients who arrived at the health unit without diagnosis and treatment and patients who arrived at the health

unit with diagnosis and without treatment. The analyzed categories for both were: Up to 30 days, 31 to 60 days, and above 60 days.

For this study, information on mortality from six types of HPV-related cancer was analyzed in both sexes: Cervical cancer (C53), oropharynx cancer (C09-10), anus and anal canal cancer (C21), vulvar cancer (C51), vaginal cancer (C52), and penile cancer (C60). Mortality rates were calculated using the microdata from the Mortality Information System (SIM)[23] for the 2000-2022 period, per 100,000 inhabitants, in Brazil and Regions. Ages were adjusted to the standard 1960 world population. The denominator for calculating mortality rates in Brazil and Regions was the census (2000 and 2010) and intercensal (2001 to 2020) populations.

The Joinpoint[24] regression model, which adjusts, on a logarithmic scale, linear trends and changes in those trends (inflection points), was used for trend analysis (mortality). The values presented in this study correspond to the values estimated by the statistical adjustment test, that uses the Monte Carlo permutation method. The direction and magnitude of the trend, in the whole period, were estimated through average annual percent change (AAPC), considering a statistical significance level of 0.05.

Statistical analyses were performed using the Joinpoint Regression software, version 5.20[24], and R software, version 4.3.2[25].

Since this study dealt with public domain secondary data, it was not subjected to a Research Ethics Committee, according to Resolution number 510[26], April 7, 2016, of the National Health Council.

RESULTS

HPV vaccination coverage in girls aged 9 to 14 in Brazil was 75.8% for the first dose and 57.4% for the second dose, with lower adherence in the second dose in all regions. The North presented the lowest coverage (68.5% and 50.2%, respectively), and the South, the highest (87.8% and 62.0%). Among boys aged 11 to 14 years, coverage was even lower, with 52.2% in the first dose and 36.5% in the second dose; the North again had the lowest adherence (41.6% and 28.1%), and the South had the highest (63.8% and 43.0%). Acre recorded the lowest coverage among all states, while Paraná had the highest coverage, both for boys and girls. (Figure 1).

The database included 260,784 patients with diagnoses of the six selected cancers: 27,969 oropharyngeal, 12,536
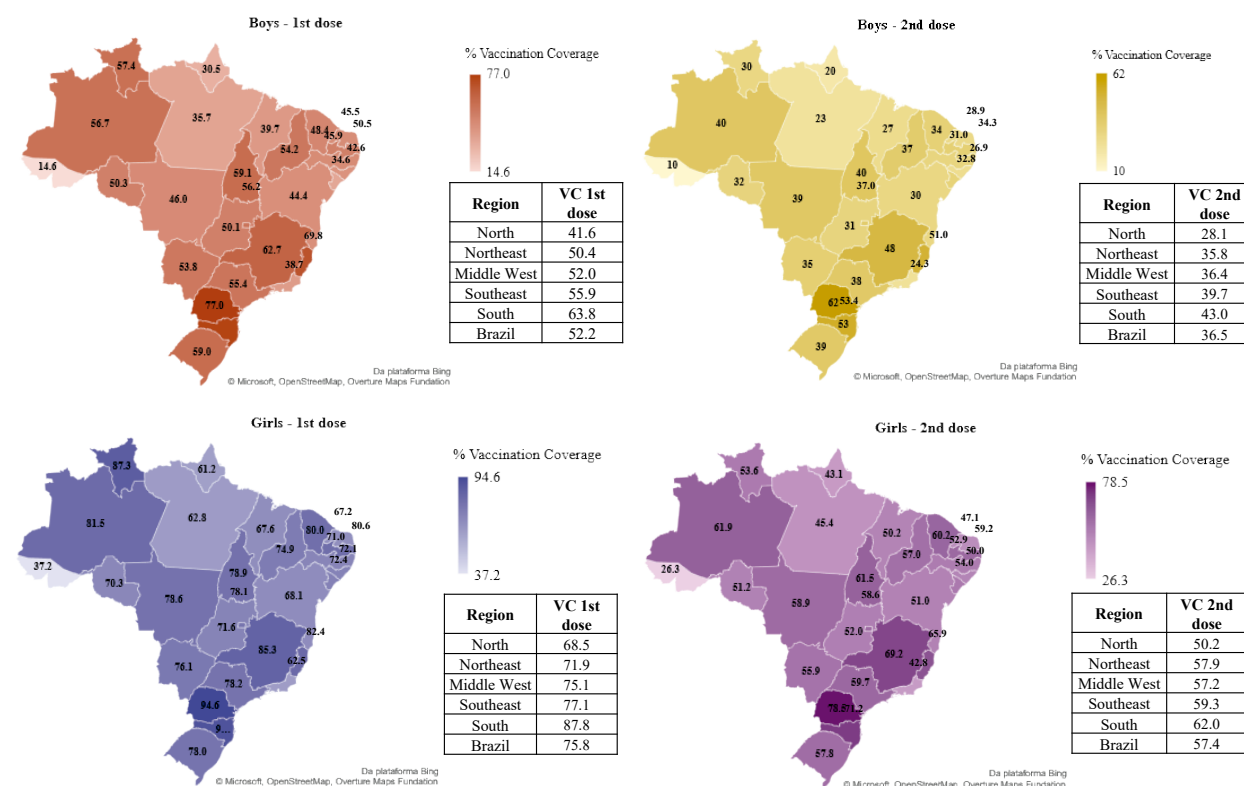
Figure 1. HPV vaccination coverage, male population aged 11 to 14 years old – 2017 to 2021 – and female population aged 9 to 14 years old – 2013 to 2021 –, Brazil, Regions, and States

Source: Based on PNI[19] data.

anal, 8,804 vulvar, 3,144 vaginal, 198,860 cervical, and 9,471 penile. The relative frequencies of each variable were calculated, including the "no information" cases (Table 1).

The profile of analyzed patients revealed that 86% were women, 61% were over 45 years old and 45% identified themselves as brown or black. Regarding education, 33% had only incomplete elementary education, and 29% had advanced staging (III and IV) (values not shown in Table 1).

Oropharyngeal cancers are those with the highest percentage of patients reaching hospitals in stages III and IV (more than 80%), for both sexes. For anal, penile, vulvar, and vaginal cancers, the values range from 30% to 50% (Figure 2).

Between 2000 and 2022, mortality rates from oropharyngeal cancer remained stable in Brazil for both sexes, but the Northeast region showed an average increase

Table 1. Variables description, Brazil, RHC, 2006 to 2020

Variables	C09-10	C21	C51	C52	C53	C60
	%	%	%	%	%	%
Total value (N)	**27,969**	**12,536**	**8,804**	**3,144**	**198,860**	**9,471**
Sex						
Male	85.2	27.6	-	-	-	100.0
Female	14.8	72.4	100.0	100.0	100.0	-
Age group						
Less than 25	0.3	0.4	1.4	2.9	3.2	0.8
25 to 44	7.9	10.9	11.9	16.1	45.0	15.2
45 to 64	65.1	50.6	34.8	42.5	36.8	45.0
65 and over	26.7	38.1	51.9	38.4	15.0	39.0
Race/skin color						
Yellow	0.6	0.7	0.6	0.8	0.9	1.2
White	30.1	29.9	33.8	28.4	26.1	24.2
Indigenous	0.1	0.1	0.1	0.1	0.2	0.3
Brown	30.5	32.9	28.5	31.5	42.3	43.6
Black	5.0	4.5	3.6	3.8	4.4	4.7
No information	33.7	31.9	33.4	35.4	26.0	25.9
Education						
None	8.7	8.4	14.3	12.1	9.2	16.2
Incomplete elementary	38.0	30.2	35.3	31.3	32.1	38.5
Complete elementary	16.5	14.7	13.6	13.4	15.0	12.9
Complete high school	11.0	15.6	10.2	11.1	16.9	7.8
Complete higher education	2.9	5.5	3.2	4.5	3.7	1.5
No information	23.0	25.5	23.4	27.7	23.2	23.2
Staging						
0	0.4	1.7	10.2	9.2	20.5	2.4
I	2.6	4.1	14.2	8.7	10.4	12.3
II	5.1	21.5	9.3	10.1	16.0	14.5
III	13.7	26.1	14.7	12.3	19.6	12.6
IV	44.6	6.8	10.9	11.6	5.6	9.7
No information	33.6	39.9	40.8	48.1	27.9	48.4
Time from diagnosis to treatment						
No diagnosis and no treatment	**9,948**	**3,037**	**3,083**	**1,065**	**58,183**	**3,758**
Up to 30 days	39.7	41.3	50.0	44.1	45.6	68.1
31 to 60 days	24.9	23.1	15.4	20.4	19.1	14.6
Over 60 days	35.5	35.5	34.6	35.5	35.2	17.3
With diagnosis and no treatment	**13,812**	**7,704**	**4,129**	**1,422**	**110,254**	**3,584**
Up to 30 days	13.0	12.6	7.4	12.4	9.5	13.1
31 to 60 days	24.9	25.0	18.5	20.7	19.0	25.4
Over 60 days	62.1	62.5	74.1	66.9	71.4	61.4

Source: Based on RHC[22] data.
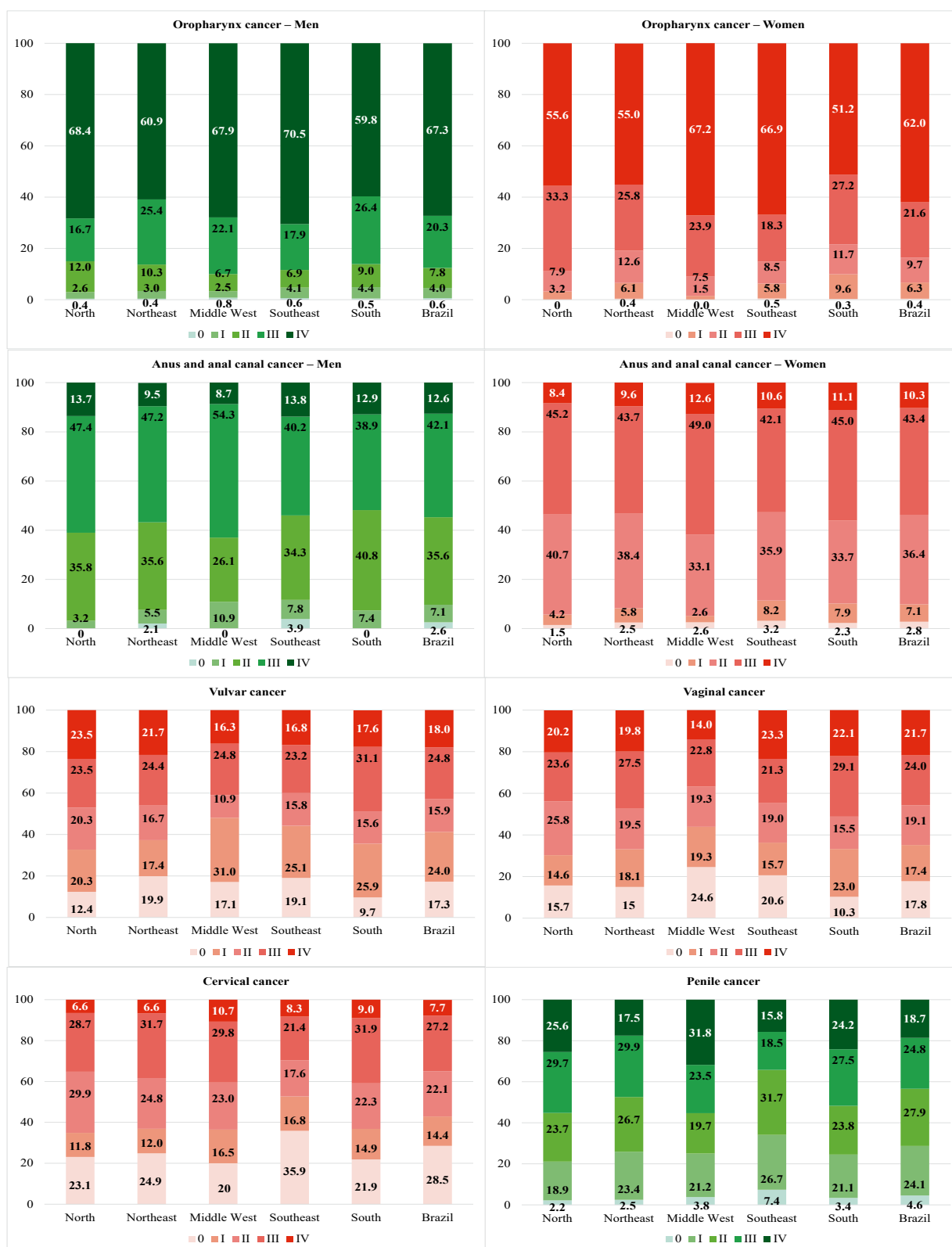
Figure 2. Percentage of clinical staging, according to HPV-related types of cancer, Brazil and Regions, 2006 to 2020
Source: Based on PNI[19] data.

of 3.9% per year in men and 2.0% in women. For anal and anal canal cancer, there was an average increase of 7.1% per year among men and 4.4% among women.

The North had the highest increase in mortality among men (11.5% per year), while the Northeast presented the highest increase among women (7% per year).

In penile cancer, an average increase of 1% per year was observed in Brazil, with significant increases in the North (2.5%) and Northeast (3.2%) regions, while the other regions remained stable. The mortality rates from vulvar cancer showed stability, with the Southeast Region showing a significant drop of -1% per year. For vaginal cancer, a downward trend was observed throughout the country, with the Middle West being the region with the highest decrease, of -4.4% per year. In cervical cancer, rates showed a slight drop of -0.3% per year, with increases in the North and Northeast regions of 1.2% per year (Table 2).

DISCUSSION

Studies on the impact of HPV on cancers beyond the cervix are still limited, although the virus is an important

Table 2. Age-adjusted mortality rates1 trend of the different types of HPV-related cancer, both sexes, Brazil and Regions, 2000 to 2022

Type of cancer	Regions	Men			Women		
		Period	APC (95%CI)	AAPC (95%CI)	Period	APC (95%CI)	AAPC (95%CI)
Oropharyngeal	North	2000-2007	-4.95(-27.37; 60.39)	1.15(-1.50; 7.18)	2000-2022	2.09(-0.62; 5.35)	2.09(-0.62; 5.35)
		2007-2022	4.13(-29.59; 19.86)				
	Northeast	2000-2007	7.42*(3.74; 29.46)	3.9*(2.7; 5.77)	2000-2022	2.01*(0.79; 3.37)	2.01*(0.79; 3.37)
		2007-2022	2.3(-0.03; 3.01)				
	Middle West	2000-2022	2.59*(1.7; 3.64)	2.59*(1.70; 3.64)	2000-2022	0.29(-2; 2.74)	0.29(-2; 2.74)
	Southeast	2000-2022	-1.07*(-1.63; -0.56)	-1.07*(-1.63; -0.56)	2000-2022	-0.52(-1.43; 0.36)	-0.52(-1.43; 0.36)
	South	2000-2022	-0.35(-0.99; 0.28)	-0.35(-0.99; 0.28)	2000-2022	0.16(-1.34; 1.65)	0.16(-1.34; 1.65)
	Brazil	2000-2022	0.1(-0.31; 0.5)	0.10(-0.31; 0.50)	2000-2011	-0.41(-3.26; 0.52)	0.35(-0.45; 1.16)
					2011-2014	5.92*(1.54; 8.27)	
					2014-2022	-2.48*(-5.31; -1.3)	
Anal and anal canal	North	2000-2022	11.53*(9.61; 15.8)	11.53*(9.61; 15.8)	2000-2016	2.08*(0.53; 5.4)	5.84*(4.22; 8.19)
					2016-2020	19*(0.76; 28.17)	
	Northeast	2000-2017	3.62*(0.14; 7.87)	8.22*(6.63; 11.18)	2000-2016	4.73(-9.47; 184.57)	6.91*(4.22; 18.03)
		2017-2020	48.97*(27.43; 63.41)		2016-2022	12.94*(6.06; 32.89)	
		2020-2022	-3.09(-15.68; 14.48)				
	Middle West	2000-2017	1.67(-2.45; 5.43)	5.27*(3.38; 7.99)	2000-2022	5.49*(3.43; 8.47)	5.49*(3.43; 8.47)
		2017-2020	46.11*(22.88; 62.83)				
		2020-2022	-13.44(-27.78; 6.85)				
	Southeast	2000-2016	3.36(-0.42; 6.8)	7.76*(6.2; 10.06)	2000-2011	-1.79(-6.14; 1.3)	2.95*(1.89; 4.32)
		2016-2022	20.42*(13.75; 36.97)		2011-2022	7.93*(5.95; 12.1)	
	South	2000-2016	0.31(-4.14; 13.65)	7.03*(5.34; 10.99)	2000-2017	1.55(-0.48; 3.72)	4.21*(2.82; 5.88)
		2016-2019	48.22(-2.71; 65.45)		2017-2020	36.29*(19.98; 46.1)	
		2019-2022	9.23(-5.74; 23.58)		2020-2022	-13.17(-25.81; 3.37)	
	Brazil	2000-2016	2.39*(0.35; 5.01)	7.15*(6.17; 8.79)	2000-2016	2.08*(0.53; 5.4)	4.43*(3.5; 6.07)
		2016-2020	32.66*(24.54; 47.78)		2016-2020	19*(0.76; 28.17)	
		2020-2022	0.51(-8.78; 12.72)		2020-2022	-3.48(-14.17; 11.87)	
Penile	North	2000-2016	5.92*(4.37; 10.65)	2.49*(0.68; 5.02)			
		2016-2022	-6.11(-21.47; 0.23)				
	Northeast	2000-2008	8.78*(5.23; 19.4)	3.23*(2.05; 5.31)			
		2008-2022	0.19(-1.59; 1.2)				
	Middle West	2000-2022	0.28(-1.66; 2.25)	0.28(-1.66; 2.25)			
	Southeast	2000-2022	-0.71*(-1.29; -0.14)	-0.71*(-1.29; -0.14)			
	South	2000-2022	0.19(-1.04; 1.43)	0.19(-1.04; 1.43)			
	Brazil	2000-2010	2.15*(1.14; 10.38)	1.07*(0.3; 1.98)			
		2010-2022	0.17(-4; 0.84)				

Table 2. continuation

Type of cancer	Regions	Men			Women		
		Period	APC (95%CI)	AAPC (95%CI)	Period	APC (95%CI)	AAPC (95%CI)
Vulvar	North				2000-2022	1.99(-0.96; 6.03)	1.99(-0.96; 6.03)
	Northeast				2000-2022	1.01(-0.51; 2.62)	1.01(-0.51; 2.62)
	Middle West				2000-2022	-0.25(-1.97; 1.46)	-0.25(-1.97; 1.46)
	Southeast				2000-2011	-1.61*(-4.02; -0.42)	-0.99*(-1.89; -0.38)
					2011-2014	8.12*(1.91; 11.55)	
					2014-2022	-3.38*(-9.08; -1.63)	
	South				2000-2022	0.07(-1.08; 1.25)	0.07(-1.08; 1.25)
	Brazil				2000-2011	-0.41(-3.26; 0.52)	-0.33(-1.02; 0.12)
					2011-2014	5.92*(1.54; 8.27)	
					2014-2022	-2.48*(-5.31; -1.3)	
Vaginal	North				2000-2022	-0.36(-4; 3.43)	-0.36(-4; 3.43)
	Northeast				2000-2022	0.25(-2.32; 2.72)	0.25(-2.32; 2.72)
	Middle West				2000-2022	-4.38*(-9.08; -1.23)	-4.38*(-9.08; -1.23)
	Southeast				2000-2022	-1.51*(-2.77; -0.36)	-1.51*(-2.77; -0.36)
	South				2000-2022	-1.32(-3.69; 0.84)	-1.32(-3.69; 0.84)
	Brazil				2000-2022	-0.93(-2; 0.07)	-0.93(-2; 0.07)
Cervical	North				2000-2014	2.44*(1.92; 3.67)	1.22*(0.63; 1.81)
					2014-2022	-0.9(-3.54; 0.33)	
	Northeast				2000-2006	3.49*(1.27; 13.52)	1.16*(0.45; 2.16)
					2006-2022	0.3(-1.13; 0.68)	
	Middle West				2000-2022	-0.99*(-1.66; -0.36)	-0.99*(-1.66; -0.36)
	Southeast				2000-2003	-5.45*(-9.2; -2.26)	-1.56*(-2; -1.06)
					2003-2014	-2.21(-3.88; 2.18)	
					2014-2022	0.86(-2.94; 5.38)	
	South				2000-2010	-3.62*(-5.36; -2.46)	-0.93*(-1.44; -0.44)
					2010-2022	1.37*(0.34; 2.8)	
	Brazil				2000-2014	-0.88(-1.6; 0.6)	-0.31*(-0.55; -0.04)
					2014-2017	2.12(-1.73; 3.02)	
					2017-2022	-0.15(-2.8; 0.97)	

Source: Based on SIM[23] data.

Captions: AAPC = Average Annual Percentage Change; APC = Annual Percentage Change; *statistically significant (p<0.05); 95%CI = 95% Confidence interval; [1]World Standard Population, 1960/100 thousand people.

risk factor for tumors in places such as oral cavity, anus, vagina, vulva and penis. Understanding the profile of patients and the extent of these diseases is essential for effective prevention strategies[27].

Although the HPV vaccine is highly effective in preventing various types of cancer, adherence to vaccination varies between Regions. The WHO recommends vaccination coverage of at least 90% to eliminate cervical cancer. In 2019, more than 65% of girls vaccinated globally were in low- and medium-income countries. More than 85% of high-income countries have comprehensive vaccination programs, which significantly reduces HPV infection rates. However, in 2020, less than 25% of low-income countries and less than 30% of low-medium-income countries had incorporated the HPV vaccine into their national immunization schedules[7].

In Brazil, in 2019, 87.08% of Brazilian girls aged between 9 and 14 received the first dose of the vaccine. In 2022, coverage fell to 75.81%. Among boys, the figures are also worrying. Vaccination coverage fell from 61.55% in 2019 to 52.16% in 2022, insufficient to maximize the expected preventive impact[28]. If Brazil reached a 90% HPV vaccine coverage rate, there would be a significant reduction in HPV cases and cancer precursor lesions[29]. Strategies to improve this coverage could include broader educational campaigns, greater involvement of schools, and the fight against vaccine misinformation, which are key factors for the overall benefits of the HPV vaccination program to be reflected in the health of the Brazilian population.

Some international studies corroborate the effectiveness of HPV vaccination in reducing the incidence of cervical cancer and precursor lesions. In Australia, the introduction of the vaccination program in 2007 resulted in a decrease of almost 50% in high-grade cervical lesions among young women, evidencing the effectiveness of the vaccination strategy[30]. Similarly, in Scotland, vaccination has shown a reduction of up to 90% in precancerous cervical lesions in vaccinated women compared to unvaccinated women[31]. In Sweden, a national cohort study revealed an 88% decrease in the incidence of invasive cervical cancer among young people who received the vaccine before the age of 17[29]. These findings highlight the importance of HPV vaccination as an effective preventive measure and highlight the need for robust immunization programs in young populations to ensure a significant reduction in the burden of HPV-related diseases.

The present study points out that, in Brazil, there is a need to increase adherence to vaccination coverage to tackle the incidence and mortality of HPV-related cancers, especially in the North Region. The heterogeneity in vaccination coverage, with some regions presenting lower rates, reflects socioeconomic disparities and the need for adapted strategies to improve adherence to vaccination. Important decisions have been made to expand the age range of HPV vaccination in some countries. Low vaccination coverage in male adolescents is an obstacle to reducing the burden of the disease, reflecting economic, logistical, and cultural challenges that limit the full potential of this prevention[3,4].

The information on the profile of hospital morbidity in this study was extracted from the National Cancer Institute (INCA) RHC Integrator, an official repository of RHC in Brazil. This database allows us to outline the profile of care provided to oncological patients. According to a Ministry of Health/SAS Ordinance no. 1,399, of December 17, 2019, all SUS health facilities qualified in high complexity must implement and maintain an RHC continuously[32].

Among cancers common to both sexes, oral cavity cancer presented the highest percentage of cases in men (85.2%), while anal and anal canal cancer was more frequent in women (72.4%), corroborating the literature[33,34]. Regarding age group, oropharyngeal, anal, anal canal, vulvar, vaginal, and penile cancers predominated in the adult population aged 45 years and over. However, cervical cancer showed a higher incidence in women aged 25 to 45 years, also in line with the literature[34].

The variables race/skin color and education level were considered socioeconomic level *proxies*. The distribution of cancer cases was similar between whites and blacks (brown and black), and about 40% of the patients analyzed did not complete elementary school. However, the high proportion of ignored data requires caution in results interpretation. It is important to note that the race/color variable is self-declared, reflecting the perception of the individual and not necessarily the genotype. The disparity in access to healthcare is often cited as a factor contributing to high incidence and diagnosis in advanced stages of cancer in Brazil[35-41].

The information analyzed brings important reflections on the arrival of patients to health units, which directly impacts the reduction of preventable deaths from the disease. This study observed that, even with more than 30% of cases lacking staging information, most patients with oropharyngeal, anal, anal canal, vulvar, vaginal, and penile cancer reach health units in advanced stages of the disease (stages III and IV), representing more than 40% of cases. For cervical cancer, although 43% of patients are diagnosed at early stages (0 and I), a significant number of women (35%) are still diagnosed in late stages. This data is alarming, considering Brazil has a well-established early detection and screening program, with clear guidelines from the Ministry of Health. The National Program of Uterine Cervical Cancer Control, established in 1998, has been instrumental in formulating policies for disease control in states and municipalities[36].

Another critical aspect is the interval between diagnosis and treatment initiation. Although Law 12.732/12 establishes that treatment should begin within 60 days after diagnosis, compliance with the regulations is still a challenge in Brazil[42]. This study data shows that a significant portion of patients begin treatment after the established deadline, with worse scenarios for those who already arrive at the health unit with a confirmed diagnosis. This scenario highlights the inefficiency of the health system in streamlining treatment, often due to the delay in referral to specialized care. Thus, optimizing this path is critical to ensure treatment starts faster and more effectively.

Knowledge about cancer mortality trends in a country allows health professionals and managers to plan and implement new strategies for their prevention and control[43]. This is particularly relevant in the context of HPV-related cancer, which still represents a difficulty for public health, especially in low- and middle-income countries, where vaccination coverage is still insufficient.

Therefore, when discussing HPV-related cancer mortality trends, it is essential to consider not only epidemiological data but also the factors that influence the implementation of vaccination programs. Improving HPV vaccine coverage in low- and middle-income countries is an urgent priority to reduce the burden of cancer and achieve global health goals.

The main results indicate that the trends in mortality rates due to oropharyngeal cancer in Brazil remained relatively stable for both sexes from 2000 to 2002. However, there was an increase in this mortality among men in the Northeast and Middle West regions. Among women, mortality rates remained generally stable, except in the Northeast Region, where there was a significant increase of 2% per year. These findings are consistent with international literature. For example, a study conducted in Uruguay showed a decreasing trend in mortality from oropharyngeal cancer among men (p=0.048), while in women the rates remained stable (p=0.544) from 1997 to 2014[44]. Similarly, a study conducted in Brazil from 1979 to 2002 revealed a statistically significant reduction in mortality from tonsil cancer, but an increase in mortality rates from oropharyngeal cancer in both sexes[45].

It is important to mention that the improvement in oropharyngeal cancer mortality observed in some countries may be associated with a reduction in tobacco use and alcohol consumption, recognized risk factors for this type of cancer. In addition, the impact of public policies aimed at cancer prevention and early detection, combined with education programs for dental professionals, may also have contributed to the reduction of mortality related to this type of cancer[46]. These factors highlight the importance of integrated and long-term strategies for the control of oropharyngeal cancer, adapted to the epidemiological characteristics of each Region.

The mortality trend analysis of this study followed an average annual increase for the whole country, in both sexes, ranging from 3% in women in the Southeast Region and 12% in men in the North Region from 2000 to 2022. These findings are corroborated by a study conducted in southern Spain, which showed an increase of about 7% per year for both sexes, from 1985 to 2017[12].

A recent study by Mignozzi et al.[47] analyzed the trend of anal cancer mortality in different countries, for the 1994 to 2020 period. Mortality rates showed an annual increase ranging from 1% in Japan and the United Kingdom and 5% in Portugal, in males. Among women, an average annual increase of 2% was observed in Switzerland and 3% in Canada and the United States of America[47].

In Brazil, mortality trends for vulvar and vaginal cancers remained stable, except in the Southeast, where there was an annual reduction of 1% between 2000 and 2022. Between 2011 and 2014, vulvar cancer mortality increased by 8% per year, followed by a 3% drop per year from 2014 to 2022, a period possibly impacted by the COVID-19 pandemic.

Regarding vaginal cancer, the mortality trend in Brazil remained relatively stable, with a not statistically significant AAPC (-0.93%; confidence interval – 95%CI: -2; 0.07). However, the Southeast and Middle West Regions showed significant annual reductions of 1.5% and 4.4%, respectively, during the 2000-2022 period. Again, it is essential to consider the possible impact of the COVID-19 pandemic on the observed decrease in these rates.

In comparison, a Spanish study conducted in Granada identified a significant increase in mortality rates from vulvar and vaginal cancer between 1985 and 2017, with a 1% AAPC for vulvar cancer and 5% for vaginal cancer[12].

These findings highlight the importance of considering regional and temporal variations, as well as external factors such as the pandemic, in the analysis of mortality trends.

There was a slight decline in cervical cancer mortality rates in Brazil (AAPC: -0.31%) as a whole and in the South (AAPC: -0.93%), Middle West (AAPC: -0.99%) and Southeast (AAPC: -1.56%) Regions. This phenomenon can be attributed to the implementation and effectiveness of cervical cancer screening programs in these Regions. However, a growing trend in cervical cancer mortality was also identified in the North and Northeast regions of Brazil (AAPC: 1.2%). A possible explanation for this difference may be the absence or insufficiency of effective screening programs in these Regions, resulting in diagnoses at more advanced stages of the disease.

Bosetti et al.[48] reported that the reduction in cervical cancer mortality is one of the main factors for reducing overall cancer mortality in Europe, corroborating these findings. A recent study with data from Global Cancer Statistics 2018 (Globocan) indicated that, of the 31 countries analyzed, 30 showed stable or decreasing trends in cervical cancer mortality over the past 10 years, especially where effective screening programs exist[48,49].

Mortality from penile cancer showed a consistent increase during the study period in Brazil, with an average growth of approximately 1% per year. This trend was observed in almost all Regions of the country, with the Northeast region highlighting the higher increase in

mortality rate (AAPC: 3.23%). On the other hand, the Southeast Region was the only one to show a modest decline in mortality (AAPC: -0.71%), a statistically significant decrease.

The findings of this study are in line with international studies. Hansen et al. observed a slight increase in penile cancer mortality in Norway (AAPC: 0.47%, 1956-2015), while in Saxony, Germany, there was a significant drop (Annual Percent Change – APC: -3.46%, 1990-2012). In Granada, Spain, there was an increase in mortality between 1985 and 2017 (APC: 2.45%)[7,50,51].

CONCLUSION

Although the HPV vaccine is available free of charge through SUS, the challenges to achieving optimal vaccination coverage persist. The control of HPV-related cancers in Brazil depends on vaccination awareness and the reduction of access barriers. It is essential to ensure adequate care from diagnosis to treatment in health units, expanding the prevention of HPV beyond cervical cancer and the female population. This study reinforces the importance of specific public policies, encouraging managers to plan effective strategies for their Regions.

CONTRIBUTIONS

Fernanda Cristina da Silva de Lima and Rejane de Souza Reis contributed to the study design, planning, data acquisition, analysis and interpretation, wording, and critical review. Darlan Henrique Nascimento da Silva and Juan Pablo Ferreira Cavalcante contributed substantially to data acquisition, analysis, and interpretation, and in critical review. Flavia de Miranda Correa and Alfredo José Monteiro Scaff contributed substantially to data analysis and interpretation, wording and critical review. Yammê Ramos Portella Santos has substantially contributed to the study design and planning; data acquisition, analysis and interpretation; and critical review. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

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