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Secular trend of cervical cancer mortality in Brazil and regions

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Abstract *The scope of this study was to describe the secular trend of cervical cancer mortality in Brazil and its various regions from 1980 to 2021. It involved a populational and ecological study, based on data available at the Department of Informatics of the Unified Health System, using codes 180 and C53. Crude rates, age-specific rates, and age-standardized rates were calculated for the Brazilian and world population. The Average Annual Percent Change (AAPC) was obtained by trend analysis using the Joinpoint Regression Program, with a significance level of 0.05 and 95% confidence intervals (95%CI). There were 171,793 deaths from cervical cancer. In Brazil (AAPC -0.3; CI95%-1.0; 0.4), North (AAPC 0.6; 95%CI -0.1; 1.3) and South (AAPC 0.0; 95%CI -0.5; 0.5) the trends were stationary, increasing in the Northeast (AAPC 0.6; 95%CI 0.3; 0.8) and in the Midwest (AAPC -1.3; 95%CI -1.5; -1.1), and decreasing in the Southeast (AAPC -0.9; 95%CI -1.4; -0.5). Regional differences indicate that public policies need to be improved regarding women's access to a health system that offers adequate prevention, screening and treatment through management strategies that include the most vulnerable population.*
Key words *Time series studies, Mortality, Uterine cervical neoplasms*

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Introduction

The epidemiological transition of cancer in high-income countries is characterised by a decrease in the number of cases from infectious agents and an increase in those related to the lifestyle habits in the globalised world. However, low- and medium-income countries still present serious problems related to cancers with highly infectious aspects, such as cervical cancer[1,2]. Age-standardized rates for cervical cancer incidence and mortality in countries with a high human development index (HDI) are 11.3 and 5.2 per 100,000 women, respectively, while, in countries with medium and low HDI, they reach 18.8 and 12.4[3].

Cervical cancer occupies 4th place in the ranking of the diseases with the highest incidence in the female population in the world, lies in 3rd place in Brazil. For all types of cancer in women, it is the 4th cause of death in the world and third in Brazil[3,4]. The distribution of this neoplasm is heterogeneous in this country's regions: the 2nd most predominant in the North and Northeast, 3rd in the Midwest, 4th in the South, and 5th in the Southeast. Whereas in the northern region, for every 100,000 women, 20.5 are affected by the disease, in the Southeast, the incidence drops to 12.9[5].

The actions of cervical cancer prevention and tracking are organised and planned by public policies so that they are standardised throughout the country, thus reducing social iniquities. Until the mid-1970s these public policies occurred only in specific cities. The first national action took place through the National Cancer Control Program between 1972 and 1975. With the permanence of high mortality from the disease, in 1998, the Program was implemented, and, in the same year, the National Program to Combat Cervical Cancer was launched. In 2011, the Brazilian guidelines for the tracking of cervical cancer were launched, updated in 2016, and, in 2014, the quadrivalent vaccine against Human Papillomavirus (HPV) was made available by the Unified Health System (SUS)[6].

Integration of cervical cancer-related actions is important to improve adherence to the methods available for disease prevention and control[7]. However, despite current scientific knowledge about this cancer, it still causes significant harm to the health of the female population, and it leads to the death of thousands of women every year, especially in low- and medium-income countries, where about 90% of the deaths occur[8].

The study aims to identify the panorama of cervical cancer deaths in Brazil as a whole and in the regions, since this indicator reflects deficiencies in the process across the range from primary prevention to effective treatment, above all when considering the pathophysiological process of the illness. From this perspective, the mortality trend study can provide important information on the conditions of tracking and treatment of cervical cancer in each region, as mortality rates reveal the fragility of the health system to aid women in the higher risk age group. Thus, it is expected to contribute to the improvement of public policies, seeking that soon this disease will no longer be considered a public health problem in the country. Therefore, the goal was to describe the secular trend of cervical cancer mortality in Brazil and regions from 1980 to 2021.

Materials and methods

A population and ecological study of temporal series was conducted. The cases of cervical cancer deaths from 1980 to 2021 were analysed in all age groups in Brazil as a whole and in the regions (North, Northeast, Midwest, Southeast and South). The data were collected in the Departamento de Informática do Sistema Único de Saúde (DATASUS) [SUS I.T. Dept.], which uses information from the Mortality Information System (SIM). For data related to the period from 1980 to 1995, code 180 (malignant cervical neoplasm) was used for International Disease Classification (IDC)[9]. From 1996 to 2021, the research was via code C 53 (malignant cervical neoplasm) according to the IDC-10. Age-specific rates were calculated through census and intercensal populations, estimated for each year of the study and by age group according to the Instituto Brasileiro de Geografia e Estatística (IBGE) [Brazilian Geography and Statistics Institute][9] and standard age rates for the world population in order to make comparisons with other countries[10,11].

Death data were collected by five-year age groups, and, to evaluate the results, the phases of life were used, namely: young adults (20-44), middle-aged adults (45-64) and the elderly (≥ 65). The ≤ 19 age group was not included in the specific analysis for age groups as it represented only 0.3% of the total cases.

To identify the temporal trend of mortality due to ill-defined causes, an indicator that can impact other causes of death, the data were col-

lected via codes 780-799 for IDC-9 (1980-1995) and R00-R99 for IDC-10 (1996-2021).

Mortality trends were calculated by age-standardized rates through the Joinpoint Regression Program, version 4.9.1.0, National Cancer Institute, USA. The program uses a junction points regression model to identify the indicator trend in the study period (increasing, decreasing or stationary). Two metrics are provided, the Annual Percent Change (APC), related to segments that present junction points, and Average Annual Percent Change (AAPC), referring to the annual mean. The significance level adopted was 0.05 and the confidence interval 95% (CI95%). The Monte Carlo Permutation Test[12]. The null hypothesis was represented by the absence of an observable trend (stationary).

The research project was submitted to the Research Ethics Committee (REC) of the Sergipe Federal University (UFS) and approved under Opinion No. 4.490.285. All the guidelines and rules of Resolution No. 466 of December 12, 2012[13], which deal with research involving human beings, were fulfilled in the construction of the work. It was not necessary to use the free, clarified consent term because it was a population-based study through unidentified databases.

Results

171,793 cervical cancer deaths were registered in Brazil from 1980 to 2021. In absolute figures, the Southeast region had more deaths (38.5%) and the Midwest less (7.6 %). In the AAPC evaluation, Brazil as a whole, the North and South presented stationary trends, the Midwest and the Southeast, decreasing, and, in the Northeast, growing. Ill-defined causes showed a decreasing trend (Table 1, Figure 1).

The age group 45 to 64, comprising middle-aged adults, accounted for 44.7% of cervical cancer deaths in Brazil, representing the hardest hit in all regions. Deaths with the age ignored and the age range 0 to 19 were not described because combined, they represented only 0.3% (Figure 2).

Analysis of the age mortality according to AAPC evidenced the following significant trends: decreasing in the 45 to 64 group in Brazil overall; decreasing in the age groups 45 to 64 and 65 or older in the Midwest; increasing in the range 65 or more in the Northeast; decreasing for 45 to 64 and 65 or older in the Southeast; and growing in the South for the group 20 to 44. The North did not have any significant trend (Table 2).

Discussion

Brazil showed a stationary trend in the cervical cancer mortality from 1980 to 2021. The APC evaluation identified that the 1980s and 90s were marked by a stationary trend too. From 2002 to 2014, a significant decrease in deaths was observed, while the subsequent period was marked by a new stationary trend. The decreasing trend can be explained by the implementation of public policies, especially the Women's Health Care Program in 1984, the National Cervical Cancer Control Program – Viva Mulher in 1998, and the Action Plan for Reduction of the Incidence and Mortality from Cervical Cancer in 2010[6]. These resulted in better tracking through cytopathological examination[14]. However, the lack of resources for proper treatment of women diagnosed with precursor lesion or cervical cancer caused the mortality from the disease to behave divergently in the regions, even after the national implementation of the aforementioned public policies, thus justifying the overall results found in the country[14].

The stationary mortality trend in 2014 can be attributed to population growth and ageing[15], regional disparities in access to prevention, tracking and treatment[16], and the decreasing trend to perform cytopathological examinations from 2006 to 2014[17]. Furthermore, improvement in registering death, along with decreased deaths from ill-defined causes, as evidenced in this study, may explain this trend of stability after the period of decline.

The political and economic crisis that occurred in Brazil in 2015 triggered fiscal austerity measures, leading to a consequent reduction in investment in health, a fact that directly impacted the activities of prevention, tracking and treatment of disease in general, as well as the investment via the public policies already instituted, which might cause regression in the health of the whole country[18], especially in places that already had a fragile structure[19]. Thus, stationary trends, after a period of decline, identified for both cervical cancer and ill-defined causes, may also have been related to this occurrence.

Another point that should be highlighted is the COVID-19 pandemic as of 2020, in which the health services had to adapt to patient care for those affected, considerably reducing or even interrupting tracking cancer care and

Table 1. Description of cervical cancer mortality trends in Brazil as a whole and its regions, 1980-2021.

Location	N (%)	JP	APC	95% CI	AAPC	95% CI
Brazil	171,793 (100%)	1980-1996	-0.1	-0.4; 0.1	-0.3	-1.0; 0.4
		1996-1999	2.5	-4.3; 9.9		
		1999-2002	-3.1	-9.2; 3.5		
		2002-2014	**-0.8***	-1.1; -0.5		
		2014-2018	1.9	0.5; 4.4		
		2018-2021	-1.8	-4.1; 0.5		
Midwest	13,045 (7.6%)	1980-2021	**-1.3***	-1.5; -1.1	**-1.3***	-1.5; -1.1
Northeast	47,479 (27.6%)	1980-1996	**-0.7***	-1.0; -0.3	**0.6***	0.3; 0.8
		1996-2006	**3.0***	2.3; 3.7		
		2006-2021	**0.3***	0.1; 0.5		
North	17,538 (10.2%)	1980-1986	2.2	-1.1; 5.6	0.6	-0.1; 1.3
		1986-1993	-2.6	-5.5; 0.3		
		1993-2017	**2.0***	1.7; 2.2		
		2017-2021	**-4.1***	-6.5; -1.6		
Southeast	66,052 (38.5%)	1980-2000	-0.2	-0.5; 0.1	**-0.9***	-1.4; -0.5
		2000-2005	**-4.0***	-6.7; -1.3		
		2005-2014	**-2.1***	-3.0; -1.2		
		2014-2021	0.7	-0.3; 1.8		
South	27,679 (16.1%)	1980-1998	**2.0***	1.3; 2.7	0.0	-0.5; 0.5
		1998-2010	**-4.2***	-5.5; -3.0		
		2010-2021	**1.6***	0.6; 2.6		
Ill-defined causes	2,215,327 (100%)	1980-2003	**-3.7***	-4.1; -3.3	**-4.7***	-5.8; -3.6
		2003-2007	**-18.1***	-24.8; -10.8		
		2007-2018	**-4.7***	-6.5; -2.9		
			7.2	-2.6; 18.0		

N = population. JP = joinpoint. * Values with statistical significance.

Source: Authors.

treatment[20]. Thus, both diagnosis and treatment delays may have impacted cervical cancer, especially the former required in a timely manner. In addition, the vulnerability of cancer patients to Covid-19 infection may have caused death by the disease of many individuals in advance, thus reducing the cancer mortality in the pandemic period due to change in the basic cause of death[21].

Countries with lower HDI concentrate high mortality rates from cervical cancer. In the world, by 2020, approximately 342,000 women had died from this neoplasm, which determined the age-standardized rate at 7.3 per 100,000 women. Analysis by country showed, for example, mortality rates of 1.6 in Australia and New Zealand, 2.1 in North America, 2.0 in Western Europe, and 2.3 in Western Asia, a reality that contrasts with the rate of 28.6 identified in East Africa, 16.6 in West Africa, 10.0 in Southeast Asia, and 7.8 in South America[3]. In Brazil, in 2021, the age-standardized rate was 4.5 deaths per 100,000 women. The discrepancy among these rates characterises cervical cancer as one of those presenting the most differences worldwide[3], and is still a public health problem in low- and medium-income countries[8]. Inequalities found in access to health services that provide tracking and treatment of the disease justify this reality[22], since the low effectiveness of prevention and tracking programs results in difficulty in providing care, the late diagnosis leading higher mortality[23]. In addition, other factors, such as lack of information, low socio-economic level[24] and exposure to risk factors, may influence the panorama of cervical neoplasm[25].

Cervical cancer is a disease marked by regional differences in Brazil[16]. In this study, according to the AAPC, the Northeast presented a growing trend of mortality, the Midwest and the Southeast a decreasing trend, and the North and the South a stationary trend. However, at

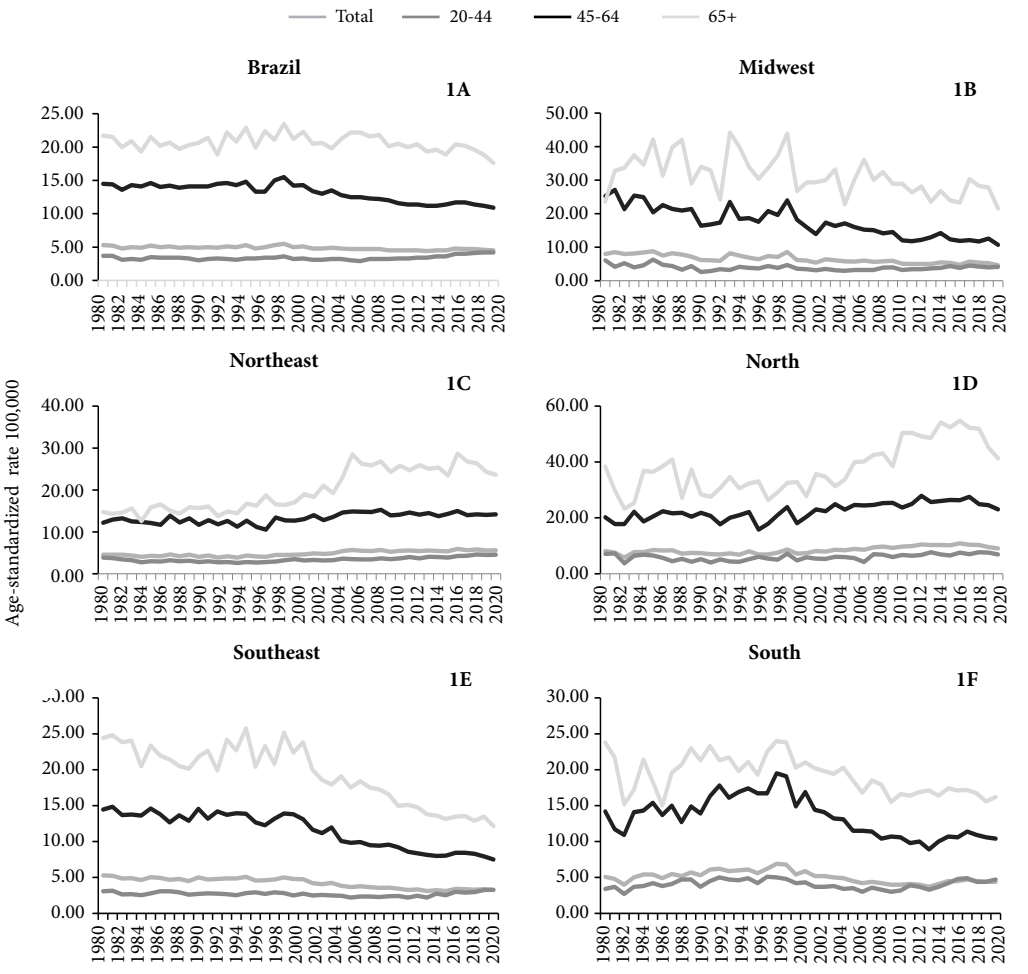


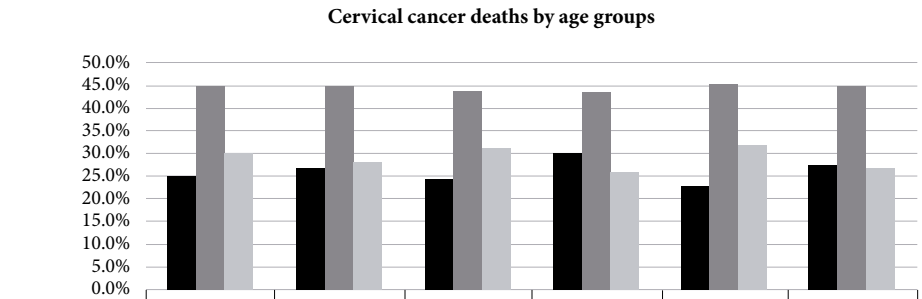
Figure 1. Cervical cancer mortality trends in all age ranges in Brazil (1A), Midwest (1B), Northeast (1C), North (1D), Southeast (1E) and South (1F), 1980-2021.

Source: Authors.

standard age mortality rates, an increase in the North and Northeast was seen, and a reduction in other regions. In terms of mortality, cervical neoplasm is lies in first place in the North, third in the Northeast and Midwest, fifth in the South, and, in the Southeast is not among the five main cancers that lead to death in the female population[26].

Regional disparity was also evidenced in the United States, where women in the southern region, considered to have greater poverty, showed a higher incidence and mortality by cervical cancer[27]. Improvement in the registration of deaths from ill-defined causes may have been responsible for the increased mortality in the North[28]. However, differences between regions related to tracking and treatment cannot be discarded, and strategies should be devised, as women who have not been properly accompanied throughout their lives have a greater tendency to present the disease in more advanced stages[29].

Projections till 2030 indicate that mortality trends will continue decreasing in the most advanced regions of the country (South and Southeast), while the others may have an increase in mortality[30]. It is noteworthy that a reduction in cervical cancer deaths is expected in Brazil due to the introduction in 2014 of the HPV[31] vaccine. However, low vaccination coverage has been observed in recent years, a fact that compromises the reduction of both HPV infection and cervical cancer[32].



	Brazil	Midwest	Northeast	North	Southeast	South
20-44 years	25.0%	26.5%	24.4%	30.2%	22.7%	27.8%
45-64 years	44.7%	44.9%	43.9%	43.7%	45.3%	44.9%
65+ years	30.0%	28.1%	31.3%	25.8%	31.8%	27.1%

Figure 2. Description of cervical cancer deaths by age groups in Brazil and regions, 1980-2021.

Source: Authors.

In this study, in absolute figures, the age group 45 to 64 was the most afflicted by cervical cancer mortality. In 2018, the global mean age for the incidence of this cancer was 53, reaching its greatest peak at 40 in countries with the best resources, and 55 to 69 in those with limited resources; For mortality, the global mean age was 59, with a range from 45 to 76. It is observed that women of productive age, both in personal and social aspects, are affected by cervical cancer, which can damage their activities and lead to loss of productive years[33].

Young adult women (20-44) had a growing trend in mortality in the southern region alone, and the other places maintained stationary trends. Risk factors related to the development of cervical cancer include precocious initiation of sexual activity and multiplicity of partners, both of which favour HPV[34] infection. As evidenced by Roteli-Martins et al., the earlier sexual activity begins, the greater the positivity for HPV[35]. Countries with greater resource availability for tracking have not increased the incidence from the age of 40, which may reflect avoidance by appropriate screening, which shows the importance of related actions to control this cancer[33].

In middle-aged adults (45 - 64) a decreasing trend was observed in Brazil as a whole, in the Midwest and Southeast, and stationary trend in the Northeast, North and South. Studies that evaluated cervical cancer mortality in Brazil, 2006 to 2014 and from 2012 to 2016, showed that the age group most affected was 50 to 54[16,17]. The time between HPV infection and the evolution of cervical cancer is estimated to be 15 years[36], which suggests persistent infection at an early age, and development of disease complications at the age identified in this work. The decreasing and stationary trends observed in the study can be attributed to the improvement in tracking due to the public policies implemented[37], especially for this age group. However, it is important to intensify health campaigns, as this group is still the most prone to mortality due to this cancer, especially in the North where there has been an increase in deaths.

In the elderly (≥ 65), there was an increase in mortality in the Northeast, reduction in the Midwest and Southeast and stability in Brazil, North and South. The cervical cancer tracking policy in Brazil recommends that cytopathological examination be performed up to age 64, and, after this period, if the woman has two consecutive negative tests within five years, the screening can be finalised[6]. An ageing population brought by demographic transition has collaborated toward increasing sexual activity in old age, a fact that contributes to the risk of sexually transmitted infections in the elderly[38]. Therefore, it should be noted that cultural factors involving taboos and prejudice can become even more striking in this section of the population, which makes it necessary to have a specific approach to this age group aimed at fulfilling recommendations for tracking the disease, as well as providing guidance regarding safe sexual practices[38,39].

Faced with the cultural, social and economic complexity of cervical cancer, as well as the existence of health systems marked by social dis-

Table 2. Description of cervical cancer mortality trends by age groups in the whole of Brazil and its regions, 1980-2021.

Location	Age groups	JP	APC	95% CI	AAPC	95% CI
Brazil	20-44	1980-1982	-8.0	-20.2; 6.1	0.3	-0.5; 1.0
		1982-1999	0.2	-0.2; 0.6		
		1999-2007	**-1.5***	-2.7; -0.2		
		2007-2021	**2.6***	2.2; 2.9		
	45-64	1980-1999	0.1	-0.1; 0.4	**-0.5***	-0.8; -0.3
		1999-2012	**-1.8***	-2.2; -1.3		
		2012-2021	-0.2	-0.8; 0.4		
	≥ 65	1980-2000	**0.4***	0.2; 0.7	-0.3	-1.4; 0.8
		2000-2004	-1.9	-6.2; 2.6		
		2004-2007	3.2	-7.4; 15.0		
		2007-2015	**-1.9***	-2.7; -1.0		
		2015-2018	2.3	-6.8; 12.3		
		2018-2021	**-4.5***	-7.9; -1.0		
Midwest	20-44	1980-1986	0.5	-4.7; 6.0	-0.3	-3.6; 3.0
		1986-1990	-12.0	-26.5; 5.3		
		1990-1999	**4.3***	1.0; 7.7		
		1999-2002	-11.8	-39.6; 28.8		
		2002-2021	**1.8***	1.2; 2.4		
	45-64	1980-1991	**-3.3***	-5.1; -1.6	**-2.0***	-4.0; -0.0
		1991-1999	1.8	-1.4; 5.0		
		1999-2002	-8.1	-29.7; 20.0		
		2002-2021	**-1.9***	-2.4; -1.4		
	≥ 65	1980-2021	**-1.0***	-1.3; -0.7	**-1.0***	-1.3; -0.7
Northeast	20-44	1980-1984	**-8.0***	-11.9; -4.0	0.3	-1.4; 2.1
		1984-1987	2.8	-13.9; 22.8		
		1987-1996	**-1.8***	-3.1; -0.5		
		1996-1999	6.8	-9.3; 25.8		
		1999-2010	**1.0***	0.3; 1.7		
		2010-2021	**2.3***	1.8; 2.8		
	45-64	1980-1997	**-0.5***	-0.8; -0.1	0.2	-0.0; 0.5
		1997-2006	**2.4***	1.5; 3.3		
		2006-2021	**-0.3***	-0.6; 0.0		
	≥ 65	1980-2002	**1.1***	0.7; 1.5	**1.2***	0.1; 2.4
		2002-2006	**10.6***	3.3; 18.4		
		2006-2015	-0.8	-1.9; 0.3		
		2015-2018	3.8	-8.1; 17.4		
		2018-2021	**-5.5***	-10.2; -0.6		
North	20-44	1980-1990	**-3.8***	-6.7; -0.7	0.2	-0.6; 1.0
		1990-2021	**1.5***	1.2; 1.9		
	45-64	1980-2018	**1.0***	0.8; 1.2	0.6	-0.0; 1.1
		2018-2021	-5.0	-11.9; 2.5		
	≥ 65	1980-1982	-21.3	-55.3; 38.3	0.3	-4.1; 4.8
		1982-1985	16.2	-29.9; 92.4		
		1985-1998	**-1.9***	-3.5; -0.3		
		1998-2017	**3.6***	3.1; 4.2		
		2017-2021	**-6.8***	-10.8; -2.6		

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Table 2. Description of cervical cancer mortality trends by age groups in the whole of Brazil and its regions, 1980-2021.

Location	Age groups	JP	APC	95% CI	AAPC	95% CI
Southeast	20-44	1980-1983	-7.4	-15.4; 1.4	0.1	-1.6; 1.8
		1983-1987	4.8	-3.5; 13.8		
		1987-1990	-5.1	-21; 14.1		
		1990-1996	1.1	-1.9; 4.2		
		1996-2012	**-1.4***	-1.9; -1.0		
		2012-2021	**4.6***	3.6; 5.6		
	45-64	1980-2000	-0.3	-0.7; 0.1	**-1.5***	-1.9; -1.0
		2000-2007	**-4.5***	-6.5; -2.6		
		2007-2021	**-1.6***	-2.1; -1		
	≥ 65	1980-1988	**-2.1***	-3.5; -0.6	**-1.6***	-2.8; -0.3
		1988-2000	**1.1***	0.3; 1.8		
		2000-2003	-7.8	-21.2; 7.8		
		2003-2008	-1.0	-4.3; 2.5		
		2008-2014	**-4.1***	-6.2; -2.0		
		2014-2021	-1.1	-2.3; 0.2		
South	20-44	1980-1997	**2.2***	1.2; 3.2	**0.9***	0.2; 1.6
		1997-2009	**-4.1***	-5.5; -2.6		
		2009-2021	**4.2***	2.9; 5.5		
	45-64	1980-1998	**2.2***	1.5; 2.8	-0.4	-0.9; 0.2
		1998-2010	**-4.9***	-6.0; -3.8		
		2010-2021	0.7	-0.4; 1.8		
	≥ 65	1980-1982	-13.7	-35.6; 15.7	-0.9	-2.4; 0.5
		1982-1998	**1.5***	0.6; 2.4		
		1998-2010	**-2.5***	-3.6; -1.5		
			-0.1	-1.1; 0.8		

JP = joinpoint. * Values with statistical significance.

Source: Authors.

crepancies, the World Health Organization instituted a global strategy to eliminate the disease as a public health problem. Goals include HPV vaccination in 90% of girls up to 15, tracking 70% of women from 35 to 45 with a high-performance test, and access to proper treatment for 90% of women. The goal is to reduce the incidence and mortality caused by this cancer, especially in low- and medium-income countries, where about nine in every ten cases of the disease[8] are concentrated. Achieving the goals could reduce the mortality to 0.2 per 100,000 women by 2120, which means 98.6% of deaths, equivalent to 62.6 million lives[40].

The strong points of the work include analysis of a long period (1980-2021) showing cervical cancer behaviour in the country, stratification by region and age group, and the use of the joinpoint regression model for temporal trend analysis. The limitations refer to the high death rate due to ill-defined causes in the initial years of the study, but which have reduced the time in the temporal series, the divergences that can be found in the analysis of secondary data due to the structure available to record information in each place, and non-redistribution of deaths registered in IDC-10 C55, which is the malignant neoplasm of the unspecified portion of the uterus, as the work specifically aimed to verify the C53 code.

Regional differences identified in mortality trends show that public policies need to be improved in terms of women's access to a proper prevention, tracking and treatment, taking into account the social, cultural, economic and educational diversity in Brazil. For this, important administrative strategies are required to reach the more vulnerable populations, mainly through investment in primary health care actions seeking to effectively boost the reduction in cervical cancer mortality rates in the whole country.

Collaborations

YAC Ferrari and CA Lima contributed to the design of the project, the analysis and interpretation of data, the writing of the article and critical review of the content and the approval of the final version. CVF Jesus, JFC Batista and BEB Silva contributed to the analysis and interpretation of data, critical review of content and approval of the final version. AB Cavalcante contributed to the analysis and interpretation of data, writing of the article and critical review of the content and approval of the final version.

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