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IMPACT OF SCREENING, DIAGNOSIS AND TREATMENT ON CERVICAL CANCER MORTALITY IN BRAZIL

IMPACTO DO RASTREIO, DIAGNÓSTICO E TRATAMENTO NA MORTALIDADE POR CÂNCER DE COLO DE ÚTERO NO BRASIL

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ABSTRACT: Objective: to analyze the impact of screening, diagnosis, and treatment on cervical cancer mortality in Brazil from 2009 to 2019. Method: The dependent variable was the cervical cancer mortality rate, and the independent variables were cytopathological examination coverage, proportion of late diagnoses, and time between diagnosis and treatment. A panel data model was used considering the 27 Brazilian federation units and the year as a time variable. Results: the cervical cancer mortality rate varied from 8.57 deaths per 100,000 women in 2009 to 7.93 deaths per 100,000 women in 2019, and this subtle reduction did not present a statistically significant relationship with the independent variables. Conclusion: the indicators related to screening, diagnosis, and treatment did not impact cervical cancer mortality rates.

KEYWORDS: Access to health services. Cervical cancer. Mortality.

RESUMO: Objetivo: analisar o impacto do rastreio, diagnóstico e tratamento na mortalidade por câncer de colo de útero no Brasil nos anos de 2009 e 2019. Método: A variável dependente foi a taxa de mortalidade por câncer de colo de útero, e as variáveis independentes foram a cobertura do exame citopatológico, proporção de diagnósticos tardios e o tempo entre diagnóstico e tratamento. Utilizou-se do modelo de dados em painel considerando as 27 unidades da federação do Brasil e o ano como variável de tempo. Resultados: a taxa de mortalidade por câncer de colo de útero variou de 8,57 óbitos a cada 100 mil mulheres em 2009 para 7,93 óbitos a cada 100 mil mulheres em 2019 e essa redução sutil não apresentou relação estatisticamente significativa com as variáveis independentes. Conclusão: os indicadores relativos ao rastreio, diagnóstico e tratamento não impactaram nas taxas de mortalidade por câncer de colo de útero.

PALAVRAS-CHAVE: Acesso aos serviços de saúde. Câncer de colo de útero. Mortalidade.

INTRODUCTION

Cervical cancer is a major cause of morbidity and mortality among women worldwide, ranking fourth in incidence and mortality according to data from the Global Cancer Observatory[1]. In Brazil, it is the second most common cancer among women in the North, Northeast, and Central-West regions, and in the South and Southeast regions, it ranks fourth and fifth, respectively[2]. The main causative agent of cervical cancer is infection by the Human Papillomavirus (HPV), transmitted by direct contact with infected skin or mucosa[3]. Other risk factors for cervical cancer documented experimentally are related to immunological factors, such as Acquired Immune Deficiency Syndrome (AIDS), genetic factors such as p53 protein polymorphism, social factors such as smoking, and prolonged use of oral contraceptives[4,5]. In addition, other factors stand out, such as early onset of sexual activity, multiparity, low education and income, multiple partners, and clinical history of Sexually Transmitted Infections. (STIs)[6].

Cervical cancer can be detected early through a cytopathological test, popularly known as a Pap smear or preventive test. This test is the most effective and common screening method for detecting cervical diseases, and should be performed in a timely manner[7].

In Brazil, the Ministry of Health recommends that preventive tests be performed on women between the ages of 25 and 64 years, every three years, if they have two negative tests performed one year apart[8]. Although this test is targeted at women who are sexually active, virgins, women who have undergone hysterectomy, pregnant women and women in menopause can take the test[9].

According to the protocols recommended worldwide for combating cervical cancer, countries must meet goals such as: achieving 90% HPV vaccination coverage in girls up to 15 years old; 70% screening coverage and 90% treatment of pre-cancerous lesions[10].

In Brazil, there have been government actions to encourage the control of cervical cancer since the 1980s. The creation of the Comprehensive Women's Health Care Program in 1984 made preventive examinations a routine part of gynecological consultations. The Oncology Program, in 1986, which created the Cervical Cancer Prevention and Control Expansion Project, aimed to improve the coordination of services. However, it was only in 1990, with the consolidation of the Unified Health System (SUS), that it actually began to encourage public health policies focused on prevention, diagnosis and treatment[11].

Nevertheless, these policies still have weaknesses that impact cancer mortality rates, showing that there are inequalities in the supply and access to health services for the diagnosis and treatment of cancer in Brazil.

Cervical cancer staging is based on the degree of spread of the disease, ranging from 0 to IV. In which the initial stage is 0 and I indicates that the tumor is only in the cells of the cervix. Stage II: the cancer extends beyond the cervix, reaching nearby structures, such as the upper part of the vagina, but without invading the pelvic wall. The advanced stage is III and IV, characterized by the cancer already spreading to other adjacent organs, such as the ovaries and bladder. Early diagnosis allows the identification of cancer in its early stages, which significantly increases the chances of therapeutic success. On the other hand, the lack of timely intervention can result in the progression of the tumor to more advanced stages, where the risk of metastasis is evident and can substantially contribute to the reduction in survival rates[12]. Therefore, treatment should be initiated in a timely manner, as recommended by Law 12,732/12, which establishes a maximum time of 60 days between diagnosis and the start of treatment, ensuring that the cancer is curable[13].

Identifying the behavior of cervical cancer mortality over time and identifying factors associated with its decline or progression can provide support for a better strategy to address the problem in Brazil.

In this sense, the objective of this study is to analyze the impact of screening, diagnosis and treatment strategies on cervical cancer mortality in Brazil from 2009 to 2019.

METHODOLOGY

This is an ecological study, whose aggregation unit was the 27 states of the Brazilian federation. The dependent variable of the study was the standardized mortality rate for cervical cancer, for the period from 2009 to 2019, by place of residence.

Information on deaths was obtained from the Mortality Information System (MIS), and the codes for cervical cancer (C53) and unspecified uterine cancer (C55) were considered.

Deaths from unspecified uterine cancer were distributed proportionally in deaths from cervical and corpus uteri cancer, according to the methodology of the World Health Organization[14]. The second process of correction of the number of deaths considered the distribution of ill-defined deaths by age groups, following the method of Santos & Souza[15].

The crude and adjusted mortality rates (per 100,000 women) were calculated according to the standard world population using the direct standardization method. Deaths without data on residence and age group were excluded. Demographic information was obtained from the Brazilian Institute of Geography and Statistics (IBGE).

The temporal trend of cervical cancer mortality in the federative units of Brazil for the period from 2009 to 2019 was analyzed. To analyze mortality trends, Joinpoint regression analysis was performed using the Joinpoint Regression Program Software (National Cancer Institute, Bethesda, Maryland, USA), Version 4.9.1.0., from April 2022. The objective of the analysis was to identify the occurrence of possible join points, the point at which a significant change in the trend has occurred.

The method applied identified join points based on the model with a maximum of 3 change points. The final model selected was the best-fit model, with the Annual Percentage Change (APC) based on the trend of each segment, estimating whether these values are statistically significant at an alpha of 0.05. The significance tests used are based on the Monte Carlo permutation method and the calculation of the annual percentage change in the ratio, using the logarithm of the ratio[16].

To quantify the summary measure of the trend over the predetermined fixed period, the Average Annual Percentage Change (AAPC) was calculated. The AAPC is calculated based on the weighted average of the angular coefficients of the regression line with weights equal to the length of each segment over the interval.

When the trend was not significant, it was considered stationary or stable, that is, it did not demonstrate statistically significant growth or reduction in its time series. An upward trend indicated a significant increase in rates over the historical series; and a downward trend indicated a significant reduction in rates.

With the hypothesis that the cervical cancer mortality rate is related to the provision of health services and the quality of care in these services, indicators related to the coverage of cytopathological examinations, late diagnosis and the time elapsed between the date of diagnosis and the start of treatment were collected.

The ratio of cervical cytopathological examinations was calculated by the quotient between the number of cervical cytopathological examinations (codes 02.03.01.001-9 and 02.03.01.008-6) performed on women resident in the age group of 25 to 64 years during the period and 1/3 of the

estimated female population in the same year, same age group and same geographic area[17]. The data were obtained from the SUS Outpatient Information System (SIA/SUS).

The proportion of late diagnoses of cervical cancer was extracted from the Integrator of the Hospital Cancer Registry (IRHC). This registry groups standardized data collected by Hospital Cancer Registries, located in general or specialized cancer hospitals (public, private or philanthropic).

Data on cervical cancer staging at the time of diagnosis were collected from the IRHC for women aged 25 years or older, diagnosed in 2009-2019. Cases without data on the TNM staging of the tumor, cases of carcinoma in situ (TNM 0) and those without information on age and residence at the time of diagnosis were excluded.

Clinical staging of the tumor used the TNM (Tumor-Nodes-Metastasis) Classification of Malignant Tumors[18], dichotomized into late stage (TNM III and IV) and early stage (TNM I and II). The proportion of late stage diagnosis of cervical cancer was calculated by the ratio between the number of cases in TNM stages III and IV by the total number of cases with TNM classification I to IV.

Using data from the IRHC, the median of the time interval (in days) elapsed between the first diagnosis and the start of treatment was identified, by year of the first consultation. For the calculation of the times, the records of analytical, coherent and validated cases were included. All records without previous treatment were considered, that is, those without diagnosis and without treatment and those with diagnosis and without treatment; only records whose treatment was after the diagnosis were included and records with dates considered invalid, such as 99/99/9999 and 88/88/8888, and those with formats other than dd/mm/yyyy, were excluded.

All variables included in the model are continuous in nature, and therefore, a linear regression model for panel data (panel data analysis) was chosen, considering the 27 states of the federation as the unit of analysis and year as the time variable. The Hausman test was applied to define whether the model had fixed or random effects. The fixed effects model was chosen because it is the most appropriate for the characteristics of the data in this study.

This research used secondary data extracted from official websites open to public consultation. Therefore, there was no need for assessment by the Ethics and Research Committee (ERC) as recommended by Resolution number 466/2012 of the National Health Council (NHC).

RESULTS

During the period 2009-2019, cervical cancer mortality rates showed significant reductions in the states of Amazonas, Ceará, Maranhão, Piauí, Rio de Janeiro, Mato Grosso and the Federal District. Meanwhile, Rio Grande do Sul was the only state to record a significant increase in rates during the period (Table 1).

Table 1: Annual variation in cervical cancer mortality rates in Brazilian states, 2009-2019.

FEDERATIVE UNIT	Period	AAPC	95%CI	Analysis
Acre	2009-2019	2.5	[-5.3; 10.9]	STABILITY
Amapá	2009-2019	-0.1	[-7.5; 7.8]	STABILITY
Rondônia	2009-2019	0.1	[-2.3; 2.5]	STABILITY
Roraima	2009-2019	2.5	[-4.8; 10.4]	STABILITY
Pará	2009-2019	-1.6	[-3.4; 0.3]	STABILITY
Amazonas	2009-2019	-2.8*	[-4.8; -0.8]	REDUCTION
Tocantins	2009-2019	-2.7	[-5.5; 0.2]	STABILITY
Alagoas	2009-2019	-0.6	[-2.1; 1.0]	STABILITY
Sergipe	2009-2019	-1.5	[-3.3; 0.3]	STABILITY
Rio Grande do Norte	2009-2019	-1.1	[-3.9; 1.9]	STABILITY
Pernambuco	2009-2019	-0.9	[-2.7; 0.8]	STABILITY
Bahia	2009-2019	-0.9	[-2.4; 0.6]	STABILITY
Ceará	2009-2019	-1.7*	[-3.0; -0.3]	REDUCTION
Maranhão	2009-2019	-2.2*	[-3.7; -0.7]	REDUCTION
Paraíba	2009-2019	1.4	[-1.2; 4.0]	STABILITY
Piauí	2000-2019	-3.2*	[-4.6; -1.8]	REDUCTION
São Paulo	2009-2019	-1.3	[-2.6; 0.1]	STABILITY
Rio de Janeiro	2009-2019	-1.0*	[-1.8; -0.2]	REDUCTION
Minas Gerais	2009-2019	-0.5	[-1.4; 0.4]	STABILITY
Espírito Santo	2009-2019	0.2	[-2.3; 2.8]	STABILITY
Rio Grande do Sul	2009-2019	1.2*	[0.0; 2.5]	INCREASE
Paraná	2009-2019	-0.2	[-1.7; 1.3]	STABILITY
Santa Catarina	2009-2019	0.9	[-1.1; 2.9]	STABILITY
Mato Grosso	2009-2019	-2.5*	[-4.3; -0.6]	REDUCTION
Mato Grosso do Sul	2009-2019	-2.4	[-5.8; 1.2]	STABILITY
Distrito Federal	2009-2019	-3.1*	[-5.0; -1.1]	REDUCTION
Goiás	2009-2019	0.2	[-1.9; 2.3]	STABILITY

AAPC: Average Annual Percentage of Change; 95%CI: 95% confidence interval; *: results with p-value <0.05
Source: prepared by the authors

Figure 1 shows that over the 11 years analyzed there was a subtle reduction in the mean cervical cancer mortality rate, but with a tendency towards stability (Figure 1).

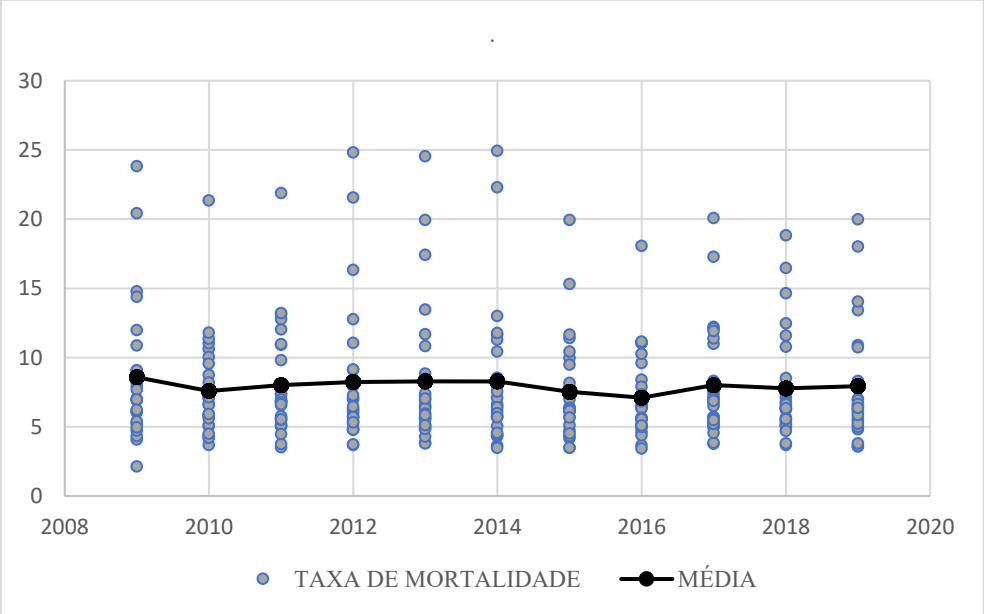

Figure 01: Standardized Mortality Rate for Cervical Cancer in the Federative Units of Brazil from 2009 to 2019.

The mortality rate for cervical cancer varied from 8.57 deaths per 100,000 women in 2009 to 7.93 deaths per 100,000 women in 2019. The analysis of the Compound annual rate showed that there was a reduction in the number of cytopathological tests performed in Brazil (reduction of -3.8% per year), and there was a trend towards an increase in late-stage diagnosis (increase of 3.08% per year) and in the time interval between diagnosis and treatment (increase of 8.69% per year) (Table 2).

Table 2: Mean and 95% confidence interval of the dependent and independent variables for the first and last years of the study and the percentage of annual variation.

Variable	Mean 2009 (95%CI)	Mean 2019 (95%CI)	Compound Annual Rate (%)
Cervical cancer mortality rate	8.57 (6.71-10.43)	7.93 (6.36-9.49)	-0.04
Cytopathological rate	0.58 (0.53-0.64)	0.34 (0.30-0.37)	-3.08
Proportion of late-stage cervical cancer diagnosis	50.61 (46.79-54.42)	51.04 (47.94-54.13)	3.08
Time interval between first diagnosis and start of treatment	65.68 (53.14-78.22)	90.64 (75.45-105.83)	8.69

The analysis of the Compound Annual Rate for the period 2009-2019 for the federative units showed that, with the exception of Amapá and Piauí, for all other Brazilian federative units there was a reduction in the number of cytopathological tests performed. There was an increase in the proportion of diagnoses in advanced stages in 17 federative units and an increase in the time between diagnosis and treatment in 20 federative units. Also noteworthy is the state of Amazonas, which had a 12.15% increase in the proportion of diagnoses in late stages, and the state of Rondônia with a 67.66% increase in the time interval between diagnosis and treatment (Table 3).

Table 3: Compound Annual Rate (%) of the independent variables of the study for the period 2009-2019 according to the federative units.

Federative unit	Cytopathological ratio	Proportion of late diagnosis	Time interval between diagnosis and treatment
Rondônia	-1.77%	11.83%	67.66%
Acre	-4.19%	6.78%	27.25%
Amazonas	-6.23%	12.15%	5.61%
Roraima	-7.00%	9.67%	32.18%
Pará	-7.46%	-1.63%	-7.00%
Amapá	51.43%	-6.36%	-12.60%
Tocantins	-14.73%	5.77%	22.37%
Maranhão	-6.83%	6.10%	20.90%
Piauí	3.00%	2.65%	41.38%
Ceará	-5.55%	-1.37%	3.70%
Rio Grande do Norte	-5.60%	0.19%	-3.98%
Paraíba	-2.74%	-1.15%	7.42%
Pernambuco	-3.90%	7.06%	5.16%
Alagoas	-8.04%	1.46%	4.80%
Sergipe	-0.12%	8.51%	7.21%
Bahia	-5.49%	-1.66%	-0.98%
Minas Gerais	-4.84%	-2.65%	4.75%
Espírito Santo	-7.31%	-6.78%	-1.37%
Rio de Janeiro	-3.53%	4.21%	5.28%
São Paulo	-3.09%	1.85%	0.89%
Paraná	-1.95%	0.96%	-0.53%
Santa Catarina	-9.12%	-1.63%	1.33%
Rio Grande do Sul	-3.38%	-2.00%	5.95%
Mato Grosso do Sul	-8.19%	11.34%	13.73%
Mato Grosso	-6.44%	11.78%	10.51%
Goiás	-6.62%	10.86%	-44.60%
Distrito Federal	-3.37%	-4.60%	17.58%

Table 4 shows the results of the panel analysis. In the bivariate analysis, the independent variables did not present a statistically significant relationship with the outcome, and therefore, it was decided not to perform the multivariate analysis.

Table 4: Panel Data Regression in a fixed effects model for cervical cancer mortality rate in Brazil by federative units in the period from 2009 to 2019.

Variable	Bivariate analysis				Parameters		
	β	95%CI		p-value	R^2 (within)	R^2 (between)	Intraclass Correlation (rho)
Cytopathological ratio	0.832	-0.992	2.65	0.37	0.003	0.004	0.829
Ratio of late stage diagnosis of cervical cancer	0.0002	-0.031	0.03	0.98	0.000	0.039	0.828
Time interval between first diagnosis and start of treatment	-0.004	-0.013	0.005	0.39	0.002	0.173	0.831

Source: prepared by the Authors
95%CI: confidence interval. Breusch and Pagan Lagrangian test (p-value < 0.005); Number of observations: 251; Number of groups: 27

DISCUSSION

The results of this study showed that cervical cancer mortality rates in the period between 2009 and 2019 showed a small reduction for Brazil, but that this reduction varied between the federative units. Furthermore, it was demonstrated that this small reduction was not related to the effect of cytopathological exam coverage, time between diagnosis and treatment, and advanced staging at the time of diagnosis.

An analysis of the magnitude and variation of the cervical cancer mortality burden from 1980 to 2019, carried out by Meira et al.[19], showed that the states in the most developed regions (South and Southeast) showed a reduction in the risk of death in the period.

Furthermore, Barbosa et al.[20], in their study, highlight a projection of a reduction in the cervical cancer mortality rate by 2030, although this reduction is unevenly distributed among the different regions of Brazil. These regional differences were also observed in our study, with higher mortality in the state of Rio Grande do Sul, while in Piauí it continues to decrease. These notable geographic contrasts reflect differences in exposure to risk factors, such as socioeconomic aspects and individual behaviors, and in access to adequate screening in cancer treatment.

The present study found that the cervical cancer mortality rate for the year 2019 is 7.93 deaths per 100,000 women, representing a value slightly above the global rate, which is 7.3 deaths per 100,000 women[21].

Another data found in this study reflects how much the time interval between the first diagnosis and the start of treatment is increasing. This can be explained by the difficulty women face in accessing treatment services, for example, the large chemotherapy and radiotherapy centers are located in large urban areas and cannot meet all the demand requested[22].

The ratio of cytopathological exams, which reflects the supply of preventive exams for the female population, reached values far from the analysis parameter of the Ministry of Health[17], indicating a deficit in the supply of preventive exams throughout Brazil. It is also worth noting that Primary Health

Care (PHC), responsible for most cytopathological exams, is not being effective in offering the exam or seeking out eligible/targeted women. The role of PHC in preventing cervical cancer is essential, whether in educational or care actions[23].

A study conducted with data from 2006-2014 on women aged 25-64 years in Brazil observed a decrease in the number of preventive exams performed and, consequently, a decrease in screening coverage[24].

In addition, another important point found in this study is the proportion of cases diagnosed in advanced stages. In Brazil, more than half of the cases of cervical cancer that reach institutions have the disease in advanced stages[25]. In developed countries, such as England, it can be observed that only 23.8% of registered cases are detected in late stages (III and IV)[26]. Furthermore, the percentage increase in advanced stages is related to socioeconomic issues[27].

Despite Brazil's health policies, significant barriers still limit women's access to prevention, diagnosis and treatment services. Geographical distance, economic costs, lack of information, institutional bias, inadequate schedules and precarious infrastructure and human resources reveal structural flaws that perpetuate inequalities. These issues highlight the urgency of more inclusive and effective policies to ensure an equitable and accessible health system for all women. The role of PHC in implementing measures to prevent cervical cancer is also noteworthy, such as vaccination against HPV in girls aged 9 to 14 years[28].

In addition to vaccination, which is the best cost-effective strategy to combat this cancer, it is important to implement sex education programs to raise awareness about sexually transmitted infections, which encourage delay in sexual initiation, reduce high-risk behaviors and promote the use of condoms in order to reduce HPV infection rates[29].

As a limitation of this study, we should note the use of secondary data that may contain possible biases due to underreporting. However, the DATASUS database is a national registry of the Ministry of Health in Brazil, and therefore provides population-based data, which in recent years has been gaining notable quality. In addition, it is suggested that other studies could include variables that have not been tested, such as HPV vaccination coverage. The results of this study have important practical implications for public health policy in Brazil, especially with regard to reducing mortality from cervical cancer. The finding of regional inequalities in access to diagnostic and treatment services highlights the need for a more targeted approach for the most affected areas. Improving the provision of cytopathological exams and expanding access to specialized treatments in the most deprived regions are essential actions to achieve a more equitable reduction in mortality rates. In addition, expanding the training of health professionals and strengthening PHC are fundamental measures to ensure that more women receive adequate care and early diagnosis.

Another relevant point for practice is the implementation of effective health education programs, aimed at raising awareness about cervical cancer prevention, with an emphasis on vaccination against HPV and the promotion of preventive behaviors, such as condom use and delaying sexual initiation. These actions can significantly reduce the incidence of cervical cancer, especially in the most vulnerable populations.

Finally, the study also suggests the need to further investigate the socioeconomic and regional factors that influence late staging and mortality, so that more efficient public policies can be developed. Improving the collection and quality of health data is crucial to developing more accurate and effective strategies.

CONCLUSION

A better understanding of the situation of cervical cancer in Brazil, broken down into geographic regions and different annual periods, allows health managers to gain more information about the disease and its epidemiology.

The results of this study show that there has been a substantial deterioration in the screening, diagnosis and treatment services for cervical cancer in Brazil, which may reflect in the future in a change in the trend of mortality from this cancer. Therefore, it is necessary to develop strategies to increase the coverage of screening programs, investments in primary and secondary prevention, early detection and timely treatment, producing positive results in health indicators.

In addition, the data and the method adopted do not allow us to exclude the hypothesis that the mortality rate from cervical cancer is not associated with indicators of prevention, initial diagnosis and immediate treatment. Studies to measure the age-period-cohort effect and a longer monitoring period are suggested.

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