Factors associated with delay in specialized treatment after diagnosis of cervical cancer in Bahia State, Brazil

Fatores associados ao início do tratamento especializado em tempo inoportuno após diagnóstico do câncer do colo do útero no Estado da Bahia, Brasil

Factores asociados con el inicio del tratamiento especializado en tiempo inadecuado tras un diagnóstico de cáncer de cuello de útero en el estado de Bahía, Brasil

Dândara Santos Silva [1]
Mônica Conceição Pinto [1]
Maria Aparecida Araújo Figueiredo [1]

Abstract

This study aimed to analyze factors associated with delay in specialized treatment after diagnosis of cervical cancer in the State of Bahia, Brazil. This was a cross-sectional hospital-based study of women treated in accredited units in the Hospital-Based Cancer Registry (HBCR) system in the State of Bahia from 2008 to 2017. A descriptive analysis and logistic regression were performed with backward stepwise modeling to estimate crude and adjusted prevalence ratios (PR), defining statistical significance as $p \leq 0.05$ in Pearson's chi-square test. We analyzed 9,184 cases, and 65% had delayed treatment (time between diagnosis and first treatment > 60 days). Delayed treatment was more prevalent among women 65 years or older (PR = 1.30; 95%CI: 1.21-1.39), with no schooling (PR = 1.24; 95%CI: 1.15-1.33), and in advanced stages (PR = 1.17; 95%CI: 1.13-1.21). Most of the cases analyzed had delayed treatment, more prevalent among older women, with less schooling, and advanced tumor stages, highlighting the need to expand access to cancer treatment services in Bahia state, especially for these groups in worse conditions.

Uterine Cervical Neoplasm; Time-to-Treatment; Women's Health; Hospital Records; Medical Oncology

Correspondence
D. S. Silva
Universidade do Estado da Bahia.
Rua Silveira Martins 2555, Salvador, BA 41150-000, Brasil.

[1] Universidade do Estado da Bahia, Salvador, Brasil.

Introduction

Cervical cancer occurs due to persistent lesions from cervical infection caused by oncogenic subtypes of the human papillomavirus (HPV) [1,2]. Even when such lesions are asymptomatic, they can be identified by cytopathological examination during the precursor stage of cancer, which increases the likelihood of cure if treatment is begun early [3]. Based on this evidence, since 1984 Brazil has adopted the prevention strategy of cytopathology screening in women 25 to 64 years of age who are already sexually active [4].

Among the most important neoplasms in the world in women, cervical cancer has the fourth highest incidence and is the fourth leading cause of death. The rates are even higher in less developed countries, since the disease is intrinsically linked to unfavorable living and health conditions [5,6,7].

In Brazil, cervical cancer shows intermediate incidence and mortality rates when compared to the global scenario, as the third leading cause of cancer in women (except nonmelanoma skin cancer) and the fourth most lethal cause [8,9]. The mortality rate in Brazil in 2019 (adjusted for age and the world population), was 5.33 deaths per 100,000 women, and estimated incidence in 2020 was 12.60 cases per 100,000 women [8,10].

Comparing Brazil's five major geographic regions, the rates were highest in the North and Northeast, with 26.24 and 16.10 cases of cervical cancer per 100,000 women, respectively. In Bahia, the largest state in Northeast Brazil, cervical cancer was the second most common cancer in women (12.51 new cases per 100,000 women) [10].

Although data from the World Health Organization (WHO) point to a reduction in the incidence of this neoplasm in Brazil, the rates are still far from reaching the levels in developed countries [9,11].

Given the issue's social relevance, the Brazilian Congress passed *Federal Law n. 12,732* in 2012 [12], also known as the "60 Days Law", which determines that all persons diagnosed with cancer should receive the first treatment within 60 days after the confirmed diagnosis. However, since there are still no mechanisms to ensure the law's enforcement, persons with cancer, users of the Brazilian Unified National Health System (SUS), report long and difficult efforts to access timely oncological treatment [13].

The current study thus aims to analyze factors associated with delay in specialized treatment after cervical cancer diagnosis in women recorded in the Hospital-Based Cancer Registry (HBCR) in Bahia State.

Methods

This retrospective cross-sectional observational hospital-based epidemiological study used the public domain secondary database of the HBCR in the State of Bahia [14].

Study subjects were women diagnosed with cervical cancer that received the first treatment in specialized cancer care centers accredited in the SUS and recorded in the HBCR in the state of Bahia, from 2008 to 2017 (Figure 1). The sample included all women with the primary tumor in the uterine cervix and classified in the system as "analytical cases" (n = 10,627), since "nonanalytical cases" refer to single consultations performed to complement follow-up already underway in other institutions (i.e., inclusion of these cases could generate duplicate information). Exclusion criteria were: (a) observations in persons less than 10 years old (n = 6); (b) cases in which it was not possible to determine whether the woman's place of residence was in the State of Bahia (n = 11) and/or those belonging to other states (n = 182); (c) observations that were missing the date of diagnosis and/or date of start of first treatment for the cervical cancer (n = 763), since the absence of either would prevent the determination of the outcome variable (time-to-treatment); and (d) cases in which date of start of treatment preceded date of diagnosis (n = 481), since it was not possible to confirm whether the treatment was performed before the histopathological diagnosis or if it was a keying-in error. After application of these criteria (Figure 2), a dataset was obtained with 9,184 observations, exported to an Excel (https://products.office.com/) spreadsheet and categorized as dichotomous or polytomous variables. The included and excluded individuals' basic characteristics were analyzed, and no major differences were observed between the groups.

Figure 1

Number of specialized cancer care establishments accredited in the Hospital-Based Cancer Registry and percentage of women diagnosed with cervical cancer with delayed first treatment. Bahia State, Brazil, 2008-2017.
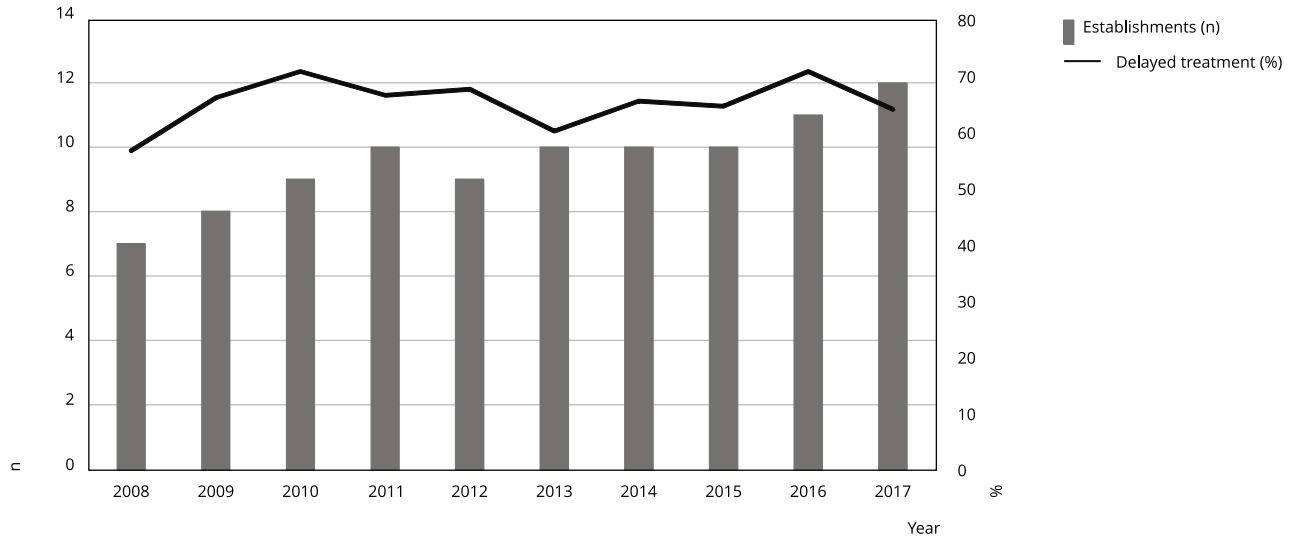
The outcome variable was defined as delayed treatment, dichotomized as "yes" (> 60 days) and "no" (≤ 60 days). Independent variables were: age group (10-24, 25-34, 35-44, 45-54, 55-64, and 65 years or older); schooling (university, secondary, primary, none); race/skin color (nonblack versus black, the former consisting of white, Asian-descendant, and indigenous and the latter of black and brown); marital status (married versus unmarried, the first consisting of married or living with partner and the second single, widow, and separate); tumor stage (early versus advanced, the latter defined as cases with classification ≥ IIb); year of inclusion in the HBCR (variable dichotomized as 2008-2012 and 2013-2017, based on the 60-day parameter set by *Federal Law n. 12,732/2012* [12]). Among these variables, some data were excluded because they were classified as "missing" or "not applicable", namely: race/skin color (6.4%), schooling (13.7%), marital status (6.9%), and tumor stage (13%).
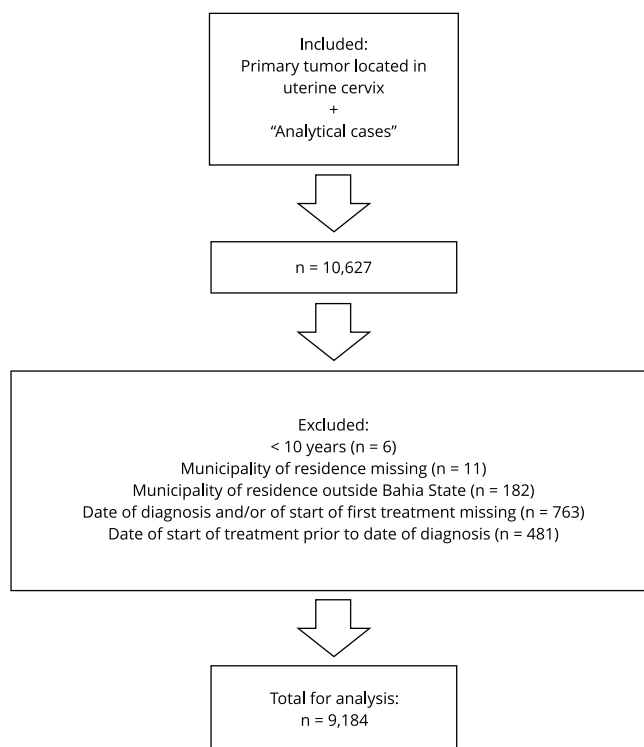
Descriptive analysis identified absolute and relative frequencies for each of the variables. Bivariate analysis showed crude association between each of the independent variables and the outcome variable, using as measure of association the prevalence ratio (PR) in each stratum with the respective 95% confidence intervals (95%CI). Statistical significance was assessed with Pearson's chi-square test, setting significance at $p ≤ 0.05$.

Multivariate analysis was performed using backward stepwise logistic regression and verification of likelihood ratio. Based on the saturated model, variables without statistical significance were removed from the final model. The final model's goodness-of-fit was assessed with the Hosmer-Lemeshow test. Since this was a prevalence study, the odds ratios (OR) were converted to PR, using logistic regression for correction to PR as proposed by Norton et al. [15], a procedure to control the associations' overestimation. All analyses were performed in Stata version 16.0 (https://www.stata.com).

The study was submitted to the State University of Bahia (UNEB) Institutional Review Board (CAAE n. 26815519.2.0000.0057), in compliance with *Resolutions n. 466/2012* and *n. 510/2016*, and was approved under review (n. 3.786.718) on December 20, 2019.

Figure 2

Flowchart of application of inclusion and exclusion criteria.

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┌─────────────────────────────┐
│        Included:            │
│  Primary tumor located in   │
│      uterine cervix         │
│            +                │
│     "Analytical cases"      │
└─────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐
│        n = 10,627           │
└─────────────────────────────┘
              │
              ▼
┌──────────────────────────────────────────────────────────────┐
│                         Excluded:                              │
│                    < 10 years (n = 6)                          │
│          Municipality of residence missing (n = 11)            │
│      Municipality of residence outside Bahia State (n = 182)   │
│  Date of diagnosis and/or of start of first treatment missing  │
│                        (n = 763)                               │
│  Date of start of treatment prior to date of diagnosis (n = 481)│
└──────────────────────────────────────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐
│      Total for analysis:    │
│          n = 9,184          │
└─────────────────────────────┘
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Results

The 9,184 women with cervical cancer in the sample had the following characteristics: delayed treatment (65.1%), age 35 to 44 years (25.5%), primary schooling (53.1%), black race/skin color (87.4%), unmarried (67.4%), early-stage tumor (48.8%), and first specialized consultation from 2008 to 2012 (50.5%) (Table 1).

As for the relationship between accreditation of healthcare establishments and the percentage of delayed treatment, except for the year 2012, although accreditation of hospitals in the State of Bahia was increasing, the data showed no major change in the proportion of delayed treatment (Figure 1).

Bivariate analysis (Table 2) showed an increase in the prevalence of delayed treatment between age groups, with a gradual elevation of the prevalence ratio from 8% (95%CI: 0.99-1.17) in women 25-34 years of age to 19% (95%CI: 1.11-1.28) in those 35-44 years, 29% (95%CI: 1.21-1.38) from 45-54 years, 30% (95%CI: 1.22-1.38) from 55-64 years, and 31% (95%CI: 1.24-1.39) in women 65 or older, compared to females 10-24 years of age. Education showed an inverse association between more schooling (university level) and delayed treatment, or 13% (95%CI: 1.04-1.22) for women with secondary schooling, 28% (95%CI: 1.16-1.40) for primary, and 34% (95%CI: 1.26-1.42) for no schooling. As for marital status, unmarried women had 4% (95%CI: 1.01-1.08) higher prevalence of delayed treatment compared to married women. For staging, there was a 20% higher prevalence of delayed treatment (95%CI: 1.16-1.24) among women with advanced-stage tumor diagnosis, compared to early-stage diagnosis. The variables race/skin color and year of first consultation did not show statistically significant differences in the bivariate analysis, but we opted to include the variable "year

Table 1

Characteristics of women with cervical cancer included in the study according to Hospital-Based Cancer Registry. Bahia State, Brazil, 2008-2017.

Characteristics	n	%
Sociodemographic		
Age group (years)		
10-24	242	2.6
25-34	1,885	20.5
35-44	2,338	25.5
45-54	1,902	20.7
55-64	1,391	15.2
≥ 65	1,426	15.5
Race/Skin color		
Nonblack	578	6.3
Black	8,023	87.4
Missing	583	6.4
Schooling		
University	251	2.7
Secondary	1,640	17.9
Primary	4,877	53.1
None	1,162	12.7
Missing	1,254	13.7
Marital status		
Married/Living with partner	2,362	25.7
Unmarried	6,189	67.4
Missing	633	6.9
Clinical		
Stage		
Early	4,483	48.8
Advanced	3,509	38.2
Missing	1,192	13.0
Year of first treatment		
2008-2012	4,639	50.5
2013-2017	4,545	49.5
Delayed treatment		
Yes	5,977	65.1
No	3,207	34.9

of first consultation" in the adjusted model, considering its explanatory importance for the outcome (delayed treatment) following passage of the "60 Days Law" [12].

The final model (Table 2) elaborated in the multivariate analysis showed the following prevalence rates for delayed treatment according to age group: 25-34, 35-44 years, 45-54, 55-64, and 65 years or older, respectively, 12% (95%CI: 1.02-1.22), 22% (95%CI: 1.13-1.38), 28% (95%CI: 1.18-1.38), 28% (95%CI: 1.19-1.38), and 30% (95%CI: 1.21-1.39) higher than females in the 10-24-year group, thus with a dose-response effect. The same effect was seen in schooling, as shown by confirmation of a direct association between delayed treatment and low schooling, with increases of 12% (95%CI: 1.03-1.22), 18% (95%CI: 1.07-1.30), and 24% (95%CI: 1.15-1.33) in women with secondary, primary, and no schooling, respectively, compared to those with university education. As for cancer staging, the prevalence of delayed treatment was 17% higher (95%CI: 1.13-1.21) among cases diagnosed in advanced stages compared to those diagnosed in early stages. As for marital status, unmarried women showed

Table 2

Association between characteristics of women with cervical cancer and delayed treatment. Bahia State, Brazil 2008-2017.

Characteristics	Crude analysis		Adjusted analysis	
	PR (95%CI)	p-value	PR (95%CI)	p-value
Age group (years)				
10-24	1.00		1.00	
25-34	1.08 (0.99-1.17)	0.016	1.12 (1.02-1.22)	0.014
35-44	1.19 (1.11-1.28)	< 0.001	1.22 (1.13-1.33)	< 0.001
45-54	1.29 (1.21-1.38)	< 0.001	1.28 (1.18-1.38)	< 0.001
55-64	1.30 (1.22-1.38)	< 0.001	1.28 (1.19-1.38)	< 0.001
≥ 65	1.31 (1.24-1.39)	< 0.001	1.30 (1.21-1.39)	< 0.001
Schooling				
University	1.00		1.00	
Secondary	1.13 (1.04-1.22)	0.004	1.12 (1.03-1.22)	0.007
Primary	1.28 (1.16-1.40)	< 0.001	1.18 (1.07-1.30)	< 0.001
None	1.34 (1.26-1.42)	< 0.001	1.24 (1.15-1.33)	< 0.001
Stage				
Early	1.00		1.00	
Advanced	1.20 (1.16-1.24)	< 0.001	1.17 (1.13-1.21)	< 0.001
Year of first consultation				
2008-2012	1.00		1.00	
2013-2017	1.00 (0.97-1.03)	0.830	0.99 (0.96-1.03)	0.589
Marital status				
Married/Living with partner	1.00			
Unmarried	1.04 (1.01-1.08)	0.013	1.04 (1.00-1.08)	0.051
Race/Skin color			*	
Nonblack	1.00			
Black	1.03 (0.96-1.09)	0.410		

95%CI: 95% confidence interval; PR: prevalence ratio.

Note: model's goodness-of-fit verified with the Hosmer-Lemeshow test (p = 0.372).

* Ethnic variable excluded from the final model.

4% higher prevalence of delayed treatment compared to married women. However, no statistically significant association was seen between this variable and delayed treatment after converting the measure of association from OR to PR. Although it was not possible to reach conclusions concerning this variable in the current study, we opted to maintain it in the adjusted analysis, since it improved the final model's goodness-of-fit.

Discussion

This study showed that 65% of women in the sample began their cervical cancer treatment with delay. Prompt specialized treatment is considered a determinant factor for survival of cervical cancer patients, but there is no standardized international definition of "delayed treatment" [16,17], which hinders the comparison of studies, especially in different countries. Most studies in Brazil use the 60-day parameter between diagnosis and treatment as the cutoff to assess results, which allows comparison of their findings with the current study [18,19,20,21,22]. Previous studies have found that time between diagnosis and first treatment of cervical cancer exceeded 60 days in most patients, corroborating our findings [18,20,21,22].

Another study on time trend and factors associated with advanced-stage diagnosis of cervical cancer showed that delayed treatment is a persistent problem throughout Brazil, since this unfavorable outcome was observed in roughly half of the cases analyzed [19]. Other authors also reported that delay in diagnosis and treatment of cervical cancer is a reality for users of the SUS, due to weaknesses in the cancer care network, a fact directly associated with higher case-fatality in this disease [18,20].

According to a meta-analysis with data from 34 articles (n = 1,272,681 patients), assessing the scenario for the world's seven most prevalent types of cancer, including cervical cancer, for every four weeks of delay between diagnosis and first treatment, or between the conclusion of one treatment and the start of the next, there is a 6-8% increase in the odds of death, while a delay of eight or 12 weeks represented increases in case-fatality of 17% and 26%, respectively, thus having greater impact on the population [23].

The current study's results also showed that young women have lower prevalence of delayed treatment when compared to older women, with an upward trend according to increasing age. Still, in the adjusted analysis, the rates were slightly stationary among women over 45 years. In agreement with these findings, a study in Taiwan (China) and another in California (United States) found that older women had longer delays in accessing treatment for cervical cancer [24,25].

In Brazil, other studies have already reported an association between advanced age and late diagnosis and advanced clinical stages [18,19,26]. These findings may be related to the low coverage of cervical cancer screening among older women, as indicated in previous studies [27,28], culminating in diagnosis in more advanced stages and thus in delays in initiating treatment.

The analysis according to tumor stage showed that in Bahia state, the detection of cervical cancer was late in the period from 2008 to 2017, when approximately 38% of cases recorded in the HBCR were in advanced stages at diagnosis. The scenario was even more critical, since among these cases there was a higher prevalence of delayed treatment compared to those detected in the early stage. Other authors have reported similar results, for example in a hospital-based study in 2018 with 65,843 Brazilian women, showing that the proportion of advanced-stage diagnoses increased from 46.80% in 2000 to 53.53% in 2012 [19]. Another study reported that 44% of women were diagnosed in stage III, followed by 31.4% in stage II [29]. Consistent with these studies, Nascimento & Silva [20] emphasize that the risk of death increases more than threefold in advanced stages with indication of palliative radiotherapy [23].

Although the subjective reasons for the high prevalence of delayed cervical cancer treatment and advanced stages of the disease were not the object of this study, one can assume a relationship between access to diagnosis and available treatment services in the state healthcare network, especially for women living in rural areas. However, further studies are necessary to elucidate this phenomenon.

Women with less schooling were more prone to delayed treatment when compared to those with more schooling. Other authors had already associated low schooling with advanced stages of cervical cancer [19,26,30]. However, our study also evidenced a dose-response effect between schooling and time from cancer diagnosis to first treatment, where the lower the schooling, the longer the time elapsed. This finding may be related to more proactive selfcare in persons with more schooling, better understanding of the health-disease process, knowledge of and access to the healthcare network, and better socioeconomic status, but other study designs are needed to explore and test these assumptions.

According to the WHO, HPV vaccination, screening, and management of care for the disease can help eliminate cervical cancer when applied strategically, but such strategic actions have not been implemented comprehensively, especially in low and middle-income countries. WHO thus launched a global strategy in 2020 to accelerate the elimination of cervical cancer as a public health problem, calling on nations to meet the 90-70-90 targets by the year 2030, according to which, 90% of girls vaccinated against HPV by 15 years of age, 70% of women screened by 35 years and again at 45 years, and treatment of 90% of women diagnosed with cervical cancer or precursor lesions [31]. However, in addition to the importance of reaching the proposed 90% treatment target for women diagnosed with cervical cancer, our results point to the need to ensure access to timely first treatment, since 65% of the women in our sample began treatment late. Corroborating this need, the delay in initiating treatment has been identified as a determinant factor in increased cancer mortality [23].

In addition, our study found no statistically significant difference in the association between delayed treatment for cervical cancer when comparing the period prior to (2008-2012) and follow-

ing (2013-2017) passage of the "60 Days Law" [12], possibly because there was not enough time for any change to be observed. Since the analysis was performed since the first year after passage of the law, which limits the identification of its impact for reducing the time to access treatment, one can assume that the current study is not only pioneering but may serve as a reference for future analyses of the trend in delayed treatment in the State of Bahia. New studies are thus needed in subsequent periods to assess the adequacy of the healthcare network for cancer patients and possible impacts on access to first treatment after cervical cancer diagnosis.

The possibility of selection bias in this study needs to be addressed, since the dataset was from hospitals in the SUS, which are predominantly public units with a minimal share of private institutions (which complement the public system through public contracts or agreements with the SUS). Thus, the sample may not include an important share of high-income persons, who generally rely on private health services. Still, we believe that the study portrays the reality of the great majority of the female population in the state, since evidence shows that in Northeast Brazil, where the State of Bahia is located, 83.4% of the population lacks access to private care and only uses the SUS [32].

Since the study used a secondary database, it also had limitations related to incompleteness of data with random distribution among the variables, namely: race/skin color 6%; marital status 7%; schooling 14%; and tumor stage 13%. We opted to keep these variables in the study (especially schooling and staging, with incompleteness exceeding 10%) based on their importance for explaining the outcome variable. Considering that data in the HBCR are obtained from records of care in each accredited healthcare unit, we emphasize the importance of record completeness, not only for clinical practice, but also for developing research and public policies based on each location's specificities.

Finally, we reiterate that treatment delays in cervical cancer are still a public health problem in the Bahia state, requiring increasing and on-going preventive measures and intensification of screening, as well as the supply of timely treatment, especially among women with low schooling, diagnosed in advanced stages of the disease, and with increasing age. We thus recommend the implementation of policies to ensure early treatment of the disease, in compliance with the Brazilian legislation.

Contributors

D. S. Silva contributed to the theoretical model's conception, data collection, preparation, analysis, and interpretation, writing and critical revision of the manuscript. M. C. Pinto contributed to the theoretical model's conception, data collection and preparation, writing and critical revision of the manuscript. M. A. A. Figueiredo contributed to the theoretical model's conception, data analysis and interpretation, writing and critical revision of the manuscript. All the outhors approvedal of the final version, sharing the responsibility for all aspects of the work, including the guarantee of its precision and integrity.

Additional informations

ORCID: Dândara Santos Silva (0000-0002-1176-5370); Mônica Conceição Pinto (0000-0001-7390-7293); Maria Aparecida Araújo Figueiredo (0000-0002-2613-1194).

Acknowledgments

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Resumo

Este estudo teve o objetivo de analisar os fatores associados ao tratamento especializado em tempo inoportuno após diagnóstico do câncer do colo do útero no Estado da Bahia, Brasil. Trata-se de um estudo de base hospitalar, de corte transversal, realizado com mulheres tratadas em unidades credenciadas ao sistema de Registro Hospitalar de Câncer (RHC) do Estado da Bahia, no período de 2008 a 2017. Foi realizada análise descritiva e regressão logística, construída na modelagem stepwise backward, *para estimar as razões de prevalência (RP) bruta e ajustada, sendo consideradas estatisticamente significantes aquelas com o valor de p ≤ 0,05 pelo teste qui-quadrado de Pearson. Foram analisados 9.184 casos, destes, 65% tiveram tratamento em tempo inoportuno (tempo transcorrido entre o diagnóstico e o primeiro tratamento > 60 dias). A prevalência de tratamento em tempo inoportuno apresentou valores mais elevados entre mulheres com 65 anos ou mais (RP = 1,30; IC95%: 1,21-1,39), nenhuma escolaridade (RP = 1,24; IC95%: 1,15-1,33) e estadiamento avançado (RP = 1,17; IC95%: 1,13-1,21). Na maioria dos casos analisados, houve tratamento em tempo inoportuno, com maior prevalência entre as mulheres com mais idade, menor escolaridade e estadiamento clínico do tumor avançado, evidenciando a necessidade de ampliação do acesso aos serviços de tratamento oncológico no Estado da Bahia, em especial para estes grupos que apresentaram pior situação.*

Neoplasias do Colo do Útero; Tempo para o Tratamento; Saúde da Mulher; Registros Hospitalares; Oncologia

Resumen

El objetivo de este estudio fue analizar los factores asociados al tratamiento especializado en un tiempo inadecuado, tras el diagnóstico del cáncer de cuello de útero en el estado de Bahía, Brasil. Se trata de un estudio con base hospitalaria, de corte transversal, realizado con mujeres tratadas en unidades acreditadas en el sistema de Registro Hospitalario de Cáncer (RHC) del estado de Bahía, en el período de 2008 a 2017. Se realizó un análisis descriptivo y regresión logística, construida en el modelado stepwise backward, *para estimar las razones de prevalencia (RP) bruta y ajustada, siendo consideradas estadísticamente significativas aquellas con el valor de p ≤ 0,05, mediante el test chi-cuadrado de Pearson. Todos los análisis fueron procesados en el programa Stata versión 16.0. Se analizaron 9.184 casos, de estos, un 65% tuvieron tratamiento en un tiempo inadecuado (tiempo transcurrido entre el diagnóstico y el primer tratamiento > 60 días). La prevalencia de tratamiento en tiempo inoportuno presentó valores más elevados entre mujeres con 65 años o más (RP = 1,30; IC95%: 1,21-1,39), ninguna escolaridad (RP = 1,24; IC95%: 1,15-1,33) y estadio avanzado (RP = 1,17; IC95%: 1,13-1,21). En la mayoría de los casos analizados, hubo tratamiento en un tiempo inadecuado, con mayor prevalencia entre las mujeres con más edad, menor escolaridad y estadio clínico del tumor avanzado, evidenciando la necesidad de una ampliación del acceso a los servicios de tratamiento oncológico en el estado de Bahía, en especial para estos grupos que presentaron peor situación.*

Neoplasias del Cuello Uterino; Tiempo de Tratamiento; Salud de la Mujer; Registros de Hospitales; Oncología Médica