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Regional inequalities in cervical cancer survival in Minas Gerais State, Brazil

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ABSTRACT

Background: Cervical cancer survival is marked by socioeconomic and demographic inequalities. We investigated differences in survival across health regions in Minas Gerais, Brazil, in cervical cancer patients who underwent treatment in the Brazilian Public Health System.
Methods: From a database developed through probabilistic and deterministic linkage of data from information systems of the Brazilian Public Health System, we identified cervical cancer cases, diagnosed between 2002 and 2010, who underwent radiation and/or chemotherapy and lived in Minas Gerais, Brazil. Five-year overall and cause-specific survivals were estimated by the Kaplan–Meier method and compared using the log-rank test. We used extended Cox models to assess the relationship between the health region of residence and the overall and cause-specific death risk, adjusting for relevant variables.
Results: We included 5613 patients with a median age of 55.0 years. Median follow-up time was 70.0 months. Five-year overall and cause-specific survivals were 56.3 % and 63.6 %, respectively. Across the 13 health regions, 5-year survival ranged from 46.6%–64.2% ($p < 0.001$) in the overall analysis and from 52.0% to 72.0% ($p < 0.001$) in the cause-specific analysis. Multivariate models revealed a significantly higher death risk for most health regions in comparison to the reference health region (Norte). Adjustment by age, tumor stage, comorbidity, treatment, travel time, and year of diagnosis had little effect on the association.
Conclusion: We found regional disparities in cervical cancer survival that persisted after relevant adjustments. Uneven regional provision of health services might be implicated in these disparities, affecting timely access to treatment for cervical cancer patients.

1. Introduction

Cancer survival is potentially influenced by place of residence, which may reflect regional differences in prognostic factors such as tumor, patient, and healthcare characteristics [1–6]. Recognizing the impact of these factors is crucial for the development of strategies to mitigate regional inequalities.

Socioeconomic and demographic inequities are well-known cervical cancer survival determinants [7–11]. The influence of place of residence in the survival of cervical cancer patients has been investigated in different geographical settings [3,5,8,12,13]. In England, regional disparities in 1-year cervical cancer relative survival were found among the 28 cancer networks [5]. Analyses including cancer in various sites pointed to a north–south divide in the country, with geographical clustering of lower survival in the north [5]. Researchers in Australia found a variation of 40.9–78.8 % in 5-year cervical cancer relative survival among the 17 health service regions in New South Wales [3]. After adjustments, the differences in the excess risk of death were explained by age, years since diagnosis, and spread of disease [3]. These studies took place in high-income countries where access to health is universal.

In Brazil, an upper-middle-income country with a public health system based on decentralized universal access (Sistema Único de Saúde, SUS), cervical cancer is the third commonest cancer in women (estimated age-standardized incidence 12.6 per 100,000 women) [14]. Incidence and mortality vary widely among the Brazilian regions

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[14–17], but evidence on cervical cancer survival disparities in the country is sparse, and most available studies were conducted in single health units [12,18–20], thus presenting an important limitation on representativeness. To our knowledge, no investigations conducted in a Brazilian setting have specifically investigated the influence of place of residence on cervical cancer survival.

Our study was carried out using health data from Minas Gerais, a state in southeastern Brazil ranked as the second most populous and the fourth largest in the country. Quite similarly to Brazil overall, Minas Gerais is marked by strong socioeconomic inequalities [21]. Following a strategy of health networks, cancer care in the state is organized in health regions (or macroregions) [22]. These health regions are marked by important contrasts. For instance, Jequitinhonha has a human development index (HDI) of 0.65 and has no qualified cancer care facilities, while Centro has an HDI of 0.76 and 15 accreditations for cancer care (Supplemental Tables 1 and 2). Given their role in cancer management, health regions are appropriate units for the analysis of regional variation in cancer survival. This study investigated the association between health region of residence and survival in women diagnosed with cervical cancer who underwent radiation and/or chemotherapy as part of their cancer treatment by the SUS in Minas Gerais, Brazil. Furthermore, we examined the influence of age, tumor stage, comorbidity, type of treatment, and place of treatment-related variables on this association.

2. Methods

2.1. Data source and study population

We conducted a non-concurrent prospective cohort study. For the data source, we used the National Database in Oncology: a subset from the National Database of Health centered on the individual, developed through probabilistic and deterministic record linkage of data from SUS information systems: (a) the Hospital Information System (SIH), an administrative database that contains information about hospitalizations financed by the SUS; (b) the Ambulatory Information System (SIA), an administrative database that stores data of high-cost/complexity outpatient procedures covered by the SUS; and (c) the Mortality Information System (SIM), an epidemiological database that provides processed information from death certificates [23]. In the strategy to build the database, kappa statistics and administrative review were used to guarantee the quality of the linkage, and the graph algorithm and in-depth research were used to generate unique and anonymous identifiers [23]. The integrated database provides health data for over 15 years (2000–2015), preserving patient privacy [23].

Eligible cases were women diagnosed with invasive cervical cancer (ICD-10 codes C53) between January 1 st, 2002 and June 30th, 2010 who met the following criteria: (a) were aged 18 or above, (b) had undergone radiation and/or chemotherapy as part of their cancer treatment, and (c) had resided in Minas Gerais state at the date of their first cancer treatment. A total of 5613 patients met the inclusion criteria and made up our study population. A minimum of 5 years follow-up time was assured for all participants as vital status information was available until June 30th, 2015. We intentionally did not include patients treated with surgery only (n = 8928) as relevant variables for survival analyses—date of diagnosis and tumor stage—were not available for them, given the availability of this information in the database from which their variables are obtained (SIH).

2.2. Study variables

The health region of residence was the central exposure variable investigated in our study. It was assessed at the registry of the patient's first cancer treatment and classified according to the regionalization planning instrument for health regions in Minas Gerais [22]. In Supplemental Tables 1 and 2 we show selected population, cancer care, demographic, and socioeconomic characteristics of the health regions.

The study outcome was survival time, defined as the time interval (in months) between the date of diagnosis and the date of death or end of the follow-up period (June 30th, 2015), whichever came first. For overall survival analysis, all deaths, regardless of their causes, were considered as events, and patients with no registry of death by June 30th, 2015, were considered censored observations.

We also estimated net survival using the framework of cause-specific survival, for which we adopted a broader modified definition that considers as cause-specific deaths all those attributed to neoplasms (ICD-10, Chapter 2), including but not limited to cervical cancer [24,25]. These deaths were considered as events in the cause-specific survival analysis. Deaths attributed to other causes, with no information on cause of death (n = 13), and patients with no record of death by June 30th, 2015 were censored.

The following covariables were included in the study: (a) age at diagnosis, as a continuous variable and categorized (19–49, 50–59, 60–69, 70–79, ≥80); (b) tumor stage, reported according to the TNM classification of malignant tumors of the Union for International Cancer Control (I, II, III, IV) [26]; (c) comorbidity (0, 1, ≥2), measured by the Elixhauser score [27], designed for administrative data and expressed as an unweighted count of conditions retrospectively found in the National Database of Health within a 1-year look-back period from the date of cancer treatment initiation; therefore, all patients had at least 1 complete year as look-back period to register comorbidities; (d) treatment, classified according to all records identified in our database during all study periods (surgery with radiation/chemotherapy/both, radiation only, radiation with chemotherapy, chemotherapy only); (e) municipality type (urban, intermediate, rural), adapted from a classification used by the Brazilian Institute of Geography and Statistics [28]; (f) correspondence between residence region and treatment health region (yes/no); (g) travel time, estimated from the best viable road route between the municipality of residence and the municipality where the first cancer treatment occurred, in minutes (0–29, 30–59, 60–89, ≥80) (OpenStreetMap contributors, https://www.openstreetmap.org); and (h) year of diagnosis (2002–2004, 2005–2007, 2008–2010). Most variables used in our study had excellent completeness as a result of their mandatory presence in the databases for reimbursement.

2.3. Data analysis

We present descriptive statistics for all participants' characteristics. Additionally, distribution of variables according to the health region of residence is shown in Supplemental Table 3. The Kaplan–Meier method and the log-rank test were used to estimate and compare 5-year survival probabilities according to each study variable.

To assess differences in survival among the 13 health regions, we examined the association between the health region of residence and survival (death risk) fitting extended Cox regression models. This analysis strategy accounted for the time-varying effect of covariates by including interactions with time functions. Cox proportional hazard models were not employed due to violation of the proportional hazard assumption evidenced by Schoenfeld residuals. First, we calculated association between each covariable and survival time (Supplemental Table 4). Then we examined the effect of tumor stage, comorbidity, treatment, and correspondence between residence region and treatment health region on the association between health region of residence and survival using age-adjusted models (Supplemental Tables 5 and 6). This analysis was conducted for each of those variables separately, aiming to evidence their particular impact on the regional variation in survival. For the cause-specific analyses, the effect of travel time was also investigated (Supplemental Table 6).

In the final extended Cox models assessing the association between health region and survival, we estimated hazard ratios (HRs) and 95 % confidence intervals (95 %CIs) adjusting for the covariables significantly associated with survival in our univariate analysis (age, tumor stage,

comorbidity, treatment, and—only in the cause-specific analyses–travel time). Additionally, those analyses were adjusted for year of diagnosis and correspondence between residence region and treatment health region. Year of diagnosis was included to account for temporal changes such as modifications in clinical practices and treatment protocols that occurred along the study period, even though this variable did not show statistically significant association with survival in the univariate analysis. Adjustment for correspondence between residence region and treatment health region aimed to account for the effect of patients who received treatment outside their health region of residence. Because we wanted to examine the impact of residing in each health region on survival, and because the provision and effectiveness of health services in each health region might play an important role in this outcome, controlling for this effect was considered adequate for our analyses.

We conducted the described analyses for both overall and cause-specific survival. The health region Norte was the reference category because it had the largest population among the three health regions with the highest overall survival rates. We conducted statistical analyses in R software version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org), considering a level of significance of 5%.

2.4. Ethical aspects

The Research Ethics Committee of the Universidade Federal de Minas Gerais granted ethical approval to the research project of which this study is a part (CAAE:00211718.1.0000.5149).

3. Results

The median age of participants was 55.0 years (IQR: 22.0) and for most of them (90.2 %) no records of comorbidity were found in the year before treatment initiation (Table 1). Over half of the patients were diagnosed with tumor stage III or IV (56.7 %), and the most common treatment was radiation with chemotherapy (36.7 %). The majority of participants (82.9 %) started their treatment in the same health region in which they resided, and 78.3 % lived in urban municipalities. Travel time to the municipality of treatment was less than 30 min for nearly half of the patients (45.5 %) (Table 1).

The median follow-up time was 70.0 months (IQR: 89.0). Over half of the patients (2891, 51.0 %) died during the study period, and 2187 (76.4 %) of these deaths were due to cervical cancer or cancer in other sites (cause-specific deaths). Overall and cause-specific 5-year survivals were 56.3 % (95 %CI: 55.0; 57.6) and 63.6 % (95 %CI: 62.3; 64.9), respectively (Table 2). Kaplan–Meier analyses showed a statistically significant association between the health region of residence and overall and cause-specific survival ($p < 0.001$). Triângulo do Sul was the health region with the lowest overall (46.6 %) and cause-specific 5-year survival rate (52.0 %), whereas Centro Sul and Norte presented the highest 5-year overall (64.2 %) and cause-specific (72.0 %) survival (Table 2). Fig. 1 show 5-year overall survival rates estimated for each health region in a map representation of health regions' boundaries. Advanced age at diagnosis, late tumor stage, and presence of comorbidity were each associated with lower rates of 5-year overall and cause-specific survival in the Kaplan–Meier analyses. Treatment was also associated with both overall and cause-specific 5-year survival rates. Longer travel time was associated with higher 5-year cause-specific survival, and municipality type was not associated with overall or cause-specific survival (Table 2). Cox univariate analyses showed patterns similar to the associations found in the Kaplan–Meier analyses (Supplemental Table 4). In the Supplemental Tables 5 and 6, we observe modest effect in the association of health region and death risk for most covariables included in the final models.

In our adjusted analyses using extended Cox regression, seven health regions presented a higher overall death risk in comparison to the health region Norte (Table 3). The magnitude of the association was higher in Jequitinhonha (HR: 1.97, 95 %CI: 1.33; 2.93), Triângulo do Sul (HR: 1.61, 95 %CI: 1.26; 2.06) and Leste do Sul (HR: 1.60, 95 %CI: 1.18; 2.17) (Table 3). Differences were more prominent in the cause-specific analysis, in which nine health regions showed statistically significant higher death risk (Table 3). Cause-specific death risk was nearly doubled in Jequitinhonha, Triângulo do Sul, and Oeste in comparison to the reference category (Table 3). In general, the magnitude of the HR increased in the adjusted models in comparison to the crude models. Moreover, adjustment by age, tumor stage, comorbidity, treatment, travel time, correspondence between residence region and treatment health region, and year of diagnosis did not noticeably change the number of health regions with significantly higher death risk (Table 3).

Table 1
Characteristics of cervical cancer patients who underwent radiation and/or chemotherapy as part of their treatment in the Brazilian Public Health System, in Minas Gerais state, Brazil, 2002 – 2010.

	n (%)
All participants	5613 (100.0)
Health region	
Centro	1884 (33.6)
Centro Sul	187 (3.3)
Jequitinhonha	62 (1.1)
Leste	490 (8.7)
Leste do Sul	179 (3.2)
Nordeste	235 (4.2)
Noroeste	111 (2.0)
Norte	597 (10.6)
Oeste	330 (5.9)
Sudeste	532 (9.5)
Sul	484 (8.6)
Triângulo do Norte	376 (6.7)
Triângulo do Sul	146 (2.6)
Age (years), median (IQR)	55.0 (22.0)
Age (years)	
19 - 49	2054 (36.6)
50 - 59	1370 (24.4)
60 - 69	1177 (21.0)
70 - 79	731 (13.0)
≥ 80	281 (5.0)
Tumor stage	
I	835 (14.9)
II	1596 (28.4)
III	2660 (47.4)
IV	522 (9.3)
Comorbidity (Elixhauser score)	
0	5065 (90.2)
1	493 (8.8)
≥ 2	55 (1.0)
Treatment	
Surgery with radiation/chemotherapy/both	1535 (27.3)
Radiation only	1815 (32.3)
Radiation with chemotherapy	2062 (36.7)
Chemotherapy only	201 (3.6)
Correspondence between residence region and treatment health region, n (%)	
Yes	4660 (83.0)
No	953 (17.0)
Municipality type	
Urban	4393 (78.3)
Intermediate	374 (6.7)
Rural	846 (15.1)
Travel time (minutes)	
< 30	2552 (45.5)
30 - 120	1630 (29.0)
> 120	1431 (25.5)
Year of diagnosis, n (%)	
2002 - 2004	2399 (42.7)
2005 - 2007	1506 (26.8)
2008 - 2010	1708 (30.4)

Abbreviations: IQR = interquartile range.

Table 2
Five-year survival estimates[a] according to the health region of residence and other characteristics for cervical cancer patients who underwent radiation and/or chemotherapy as part of their treatment in the Brazilian Public Health System, in Minas Gerais state, Brazil, 2002 – 2010.

	5-year overall survival, % (95 %CI)	p-value[b]	5-year cause-specific survival, % (95 %CI)	p-value[b]
All participants	56.3 (55.0; 57.6)		63.6 (62.3; 64.9)	
Health region				
Centro	55.4 (53.2; 57.7)	**< 0.001**	61.3 (59.1; 63.6)	**< 0.001**
Centro Sul	64.2 (57.7; 71.4)		70.9 (64.6; 77.9)	
Jequitinhonha	53.2 (42.2; 67.2)		62.9 (51.6; 76.6)	
Leste	54.3 (50.1; 58.9)		63.1 (58.8; 67.7)	
Leste do Sul	49.7 (42.9; 57.6)		59.1 (52.1; 67.1)	
Nordeste	54.9 (48.9; 61.6)		66.8 (60.8; 73.4)	
Noroeste	55.0 (46.4; 65.0)		63.7 (55.2; 73.5)	
Norte	62.1 (58.4; 66.2)		72.0 (68.4; 75.8)	
Oeste	51.5 (46.4; 57.2)		57.0 (51.8; 62.8)	
Sudeste	54.5 (50.4; 58.9)		62.1 (58.0; 66.4)	
Sul	58.1 (53.8; 62.6)		65.2 (61.0; 69.7)	
Triângulo do Norte	63.6 (58.9; 68.6)		69.1 (64.5; 74.0)	
Triângulo do Sul	46.6 (39.2; 55.4)		52.0 (44.3; 61.0)	
Age (years)				
19 - 49	59.8 (57.8; 62.0)	**< 0.001**	64.4 (62.4; 66.6)	**< 0.001**
50 - 59	59.9 (57.4; 62.6)		65.9 (63.4; 68.5)	
60 - 69	55.6 (52.8; 58.5)		63.8 (61.0; 66.7)	
70 - 79	48.2 (44.7; 51.9)		60.6 (57.0; 64.5)	
≥ 80	37.0 (31.8; 43.1)		51.5 (45.5; 58.2)	
Tumor stage				
I	74.9 (72.0; 77.9)	**< 0.001**	81.8 (79.2; 84.5)	**< 0.001**
II	63.1 (60.8; 65.5)		70.4 (68.1; 72.7)	
III	49.9 (48.0; 51.8)		57.3 (55.3; 59.2)	
IV	38.5 (34.6; 42.9)		44.8 (40.6; 49.4)	
Comorbidity (Elixhauser score)				
0	58.2 (56.9; 59.6)	**< 0.001**	65.3 (64.0; 66.7)	**< 0.001**
1	38.7 (34.7; 43.3)		47.8 (43.4; 52.6)	
≥ 2	36.4 (25.6; 51.6)		41.5 (29.9; 57.6)	
Treatment				
Surgery with radiation/ chemotherapy/both	60.1 (57.7; 62.6)	**0.017**	66.9 (64.6; 69.4)	**< 0.001**
Radiation only	56.6 (54.3; 58.9)		65.3 (63.0; 67.6)	
Radiation with chemotherapy	53.4 (51.3; 55.6)		60.2 (58.1; 62.4)	
Chemotherapy only	54.2 (47.8; 61.6)		57.9 (61.4; 65.3)	
Correspondence between residence region and treatment health region, n (%)				
Yes	56.1 (54.7; 57.5)	0.95	63.0 (61.6; 64.5)	0.3
No	57.3 (54.2; 60.5)		66.3 (63.3; 69.5)	
Municipality type				
Urban	56.4 (54.9; 57.9)	0.28	63.1 (61.6; 64.5)	0.28
Intermediate	53.7 (48.9; 59.0)		63.7 (58.9; 69.0)	
Rural	57.0 (53.7; 60.4)		66.4 (63.1; 69.7)	
Travel time (minutes)				
< 30	54.7 (52.8; 56.7)	0.27	60.8 (58.9; 62.8)	**0.002**
30 - 120	57.3 (55.0; 59.8)		64.4 (62.1; 66.8)	
> 120	58.0 (55.5; 60.6)		67.7 (65.2; 70.2)	
Year of diagnosis, n (%)				
2002 - 2004	57.5 (55.6; 59.5)	0.45	65.1 (63.2; 67.1)	0.091
2005 - 2007	54.9 (52.5; 57.5)		62.4 (59.9; 64.9)	
2008 - 2010	55.8 (53.5; 58.2)		62.5 (60.2; 64.9)	

Abbreviations: CI = confidence interval.
p-values in bold are statistically significant (< 0.05).
Notes:
[a] Five-year survival was estimated using the Kaplan-Meier method.
[b] p-values are from log-rank test.

4. Discussion

We found disparities in overall and cause-specific survival for cervical cancer patients across the health regions of Minas Gerais state, Brazil. Common prognostic factors for survival (such as age, tumor stage, comorbidity, and treatment) did not explain these disparities, and nor did other variables explored in our study (such as municipality type, travel time, and year of diagnosis).

Factors related to cancer care, such as access and quality, might be implicated in the evidenced disparities in survival. In Minas Gerais, the noticeable socioeconomic inequalities [22,29,30] still reflect on health care. Despite the health networks strategy, there is a large concentration of services, equipment, and specialized human resources in the central and southern regions of the state [22,31]. Nineteen out of the 31 accredited hospitals for specialized cancer care in 2015 were concentrated in only three of the 13 health regions of the state (nine in Centro, five in Sudeste, and five in Sul) [31]. Further information regarding the distribution of accredited facilities is found in Supplemental Table 1.

It is essential to identify and address the factors influencing regional disparities in survival. Tumor stage, a recognized predictor in cervical cancer survival [7,32], did not have a substantial effect on the death risk differences across the health regions. Studies in which the role of tumor stage on cancer survival was investigated showed different results according to the cancer site [1,2,4]. Minas Gerais experienced a considerable yet uneven expansion of cervical cancer screening coverage from 2000 to 2010, as shown in Supplemental Table 1 [33]. Because of this, we expected a larger influence of tumor stage on survival differences. We may have had limitations in detecting these differences due to the absence in our study of patients treated exclusively with surgery, since they were probably diagnosed in the early stages of cervical cancer. These patients are likely to be the main beneficiaries of the expansion of cervical cancer screening coverage. Increased comorbidity was

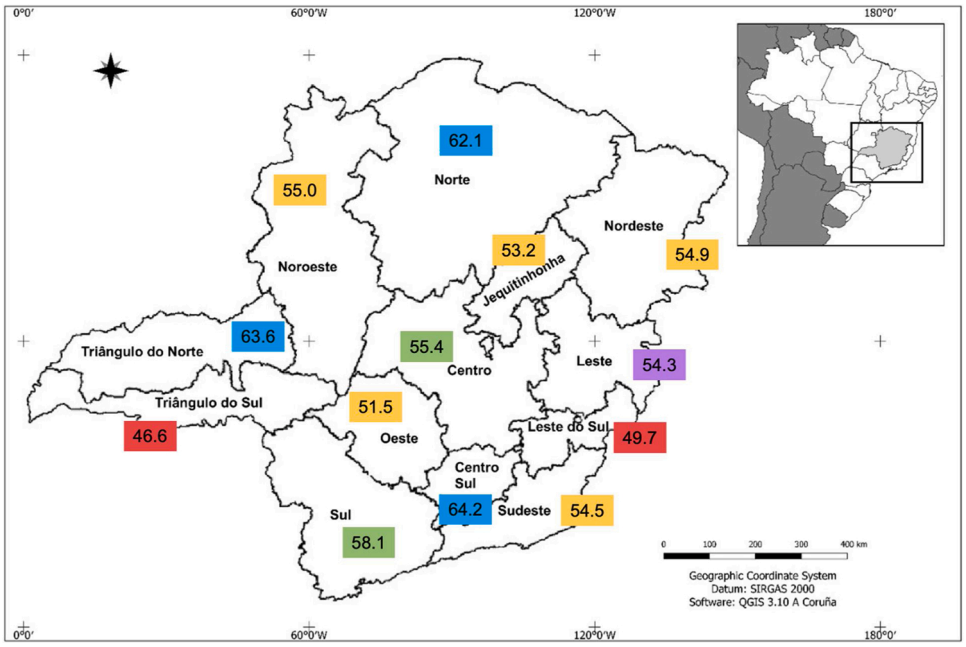

Fig. 1. Health regions boundaries in Minas Gerais state, Brazil, according to the Master of Plan of Regionalization of Minas Gerais, 2011 [22], and five-year overall survival rates (%) estimated for each health region.

associated with reduced cervical cancer survival in our analyses, which was also observed in findings from New Zealand and Australia [34,35], but not in a Danish study [9]. Our findings suggest little effect of comorbidity on regional disparities in survival, as observed by Skyrud et al. for cancer in other sites [1].

Regional disparities not explained by age, tumor stage, comorbidity, and treatment might be related to factors such as access to cancer care in the different health regions and the quality of these services. Timely access to cancer treatment in the state of Minas Gerais can be affected by the deficit and the uneven distribution of units accredited for cancer treatment, especially radiation therapy [22,36,37]. Health regions like Norte, Nordeste, Noroeste, Triângulo do Norte, Triângulo do Sul and Oeste have shown difficulties in decentralizing complex health services, whereas health regions Sul and Sudeste, which are among those with the highest survival rates in our study, had a better spatial distribution of cancer treatment facilities [37,38].

An important indicator of healthcare networks' effectiveness evaluates whether the population has access to medical procedures in their health region. In 2010, the component of cancer treatment and cancer surgery of this indicator presented high heterogeneity among the health regions [39], in agreement with that observed in our study with the variable 'correspondence between residence region and treatment health region'. We did find that health regions in which most cervical cancer patients had their treatment in another health region are the same ones with poorer results for this indicator. Moreover, health regions figuring among those with the highest survival rates in our study, such as Sul and Sudeste, had better results in the abovementioned indicator in recent surveys, that is, they had a higher proportion of the population having access to medical procedures in their own health region of residence [37].

In addition to issues related to cancer care, demographic and socioeconomic characteristics might be implicated in the observed regional differences in survival. Race/skin color and socioeconomic status are among those characteristics, as they are potentially associated with cervical cancer survival [8,10,40] and have heterogeneous distribution among the health regions of Minas Gerais [41,42]. According to the 2010 census, health regions with lower survival rates in our study (Nordeste and Jequitinhonha) had a lower average household income *per capita*, higher rates of illiteracy, and lower education rates among women, in contrast to health regions such as Centro, Triângulo do Norte and Triângulo do Sul [41,42]. Nordeste and Jequitinhonha also had the highest proportions of black women among those aged ≥15 [41,42]. It is worth mentioning, however, that our analyses were adjusted by tumor stage, one of the main factors by which sociodemographic and economic determinants operate in cancer survival [7,11,43].

This study has some limitations. Working with health regions implied the existence of categories with a small number of cases and events, thus reducing the precision of estimates and our ability to detect statistically significant differences. Still, notable disparities in survival were evidenced. The use of administrative data may also have limited our ability to explain the regional differences, especially because of potential unmeasured confounders. Race/skin color, for example, was not included in our analyses due to low completeness (67.9 %) in our database. Furthermore, the absence of direct variables reflecting socioeconomic and healthcare characteristics prevented us from drawing conclusions on the mechanisms of survival disparities across the health regions. In this regard, we could only provide hypotheses in the light of the literature.

In terms of representativeness, our study included only patients who underwent treatment in the Brazilian Public Health System. It is estimated that in 2015 around 25 % of the population in Minas Gerais was covered by private health insurance, but it should be noted that part of those still accesses the public health system, especially for highly complex interventions such as cancer treatment [44]. In comparison with population-based data from Brazilian cervical cancer patients in the same period, our study population had a higher median age (55 versus 52 years) and a larger proportion of patients diagnosed in stages III and IV (56.7 % versus 46.4 %) [45], likely reflecting our non-inclusion of patients treated exclusively with surgery.

As suitable life tables were not available for estimation of relative survival, we estimated cause-specific survival as a measure of net survival. Misclassification of the cause of death is a common concern for cause-specific survival, as these causes rely on death certificates [24]. For instance, the cause of death may be attributed to cancer at the site of metastasis, instead of cancer at the primary site. In our cohort, 33 % of the observed deaths were attributed to neoplasms (ICD-10, Chapter 2) other than cervical cancer (C53). This is the reason why we considered cause-specific deaths as all those attributed to neoplasms (ICD-10,

Table 3
Death risk[a] according to health region in cervical cancer patients who underwent radiation and/or chemotherapy as part of their treatment in the Brazilian Public Health System in Minas Gerais state, Brazil, 2002-2010.

Health region	Overall death risk, HR (95 % CI)		Cause-specific death risk, HR (95 %CI)	
	Crude	Adjusted[b]	Crude	Adjusted[c]
Norte	Ref.	Ref.	Ref.	Ref.
Centro	**1.21 (1.06; 1.38)****	**1.19 (1.04; 1.37)***	**1.44 (1.22; 1.69)*****	**1.40 (1.18; 1.65)*****
Centro Sul	0.97 (0.76; 1.24)	1.16 (0.86; 1.56)	1.06 (0.79; 1.42)	1.26 (0.88; 1.81)
Jequitinhonha	**1.49 (1.06; 2.10)***	**1.97 (1.33; 2.93)*****	**1.63 (1.10; 2.43)***	**2.24 (1.41; 3.55)*****
Leste	**1.25 (1.06; 1.48)****	1.09 (0.92; 1.29)	**1.40 (1.14; 1.71)****	1.18 (0.96; 1.46)
Leste do Sul	**1.42 (1.13; 1.79)****	**1.60 (1.18; 2.17)****	**1.59 (1.21; 2.07)*****	**1.86 (1.31; 2.65)*****
Nordeste	**1.27 (1.02; 1.57)***	**1.42 (1.06; 1.91)***	1.28 (0.99; 1.66)	**1.48 (1.05; 2.08)***
Noroeste	1.23 (0.92; 1.63)	**1.55 (1.11; 2.18)***	1.39 (1.00; 1.94)	**1.76 (1.19; 2.60)****
Oeste	**1.38 (1.15; 1.67)*****	**1.56 (1.28; 1.90)*****	**1.68 (1.36; 2.09)*****	**1.94 (1.54; 2.46)*****
Sudeste	**1.29 (1.09; 1.52)****	1.17 (0.99; 1.38)	**1.44 (1.18; 1.76)*****	**1.32 (1.08; 1.63)****
Sul	1.14 (0.96; 1.36)	1.13 (0.95; 1.35)	**1.30 (1.05; 1.59)***	**1.29 (1.04; 1.60)***
Triângulo do Norte	0.92 (0.76; 1.12)	0.91 (0.75; 1.11)	1.10 (0.88; 1.38)	1.05 (0.83; 1.32)
Triângulo do Sul	**1.56 (1.23; 2.00)*****	**1.61 (1.26; 2.06)*****	**1.94 (1.47; 2.55)*****	**1.91 (1.44; 2.53)*****

Abbreviations: HR = Hazard ratio; CI = confidence interval; Ref. = reference. Values in bold are statistically significant ($p < 0.05$).
Notes:
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[a] Estimated using extended Cox models.
[b] Adjusted by age + tumor stage + comorbidity (Elixhauser score) + treatment + correspondence between residence region and treatment health region + year of diagnosis.
[c] Adjusted by age + tumor stage + comorbidity (Elixhauser score) + treatment + travel time + correspondence between residence region and treatment health region + year of diagnosis.

Chapter 2), including, but not limited to cervical cancer [24,25].

Nonetheless, the record linkage strategy of the SUS information systems is a strong feature of our study as it allowed us to build a cohort including all patients treated in the Brazilian Public Health System. This strategy also enabled our analyses to be adjusted for well-known essential variables in cancer survival analyses, such as age, year of diagnosis, treatment, comorbidities, and tumor stage.

Our findings point out significant regional disparities in survival among cervical cancer patients treated by radiation and/or chemotherapy and covered by the Brazilian Public Health System in Minas Gerais state, Brazil, regardless of major potential confounders (age, comorbidities, cancer and treatment characteristics). Although the underlying mechanisms of these inequalities are likely to be complex, efforts to identify them are crucial to better suggest and implement interventions. The improvement of information systems and cancer registries in Brazil is an important step to allow future research to examine to what extent different factors explain regional variation in survival. After critically analyzing data about health networks in Minas Gerais, we suppose that disparities in the quality of cancer care might be implicated in the regional variations in survival, as well as differences in socioeconomic and demographic characteristics. In this sense, aiming for a more equitable distribution of treatment centers, and assuring timely and adequate treatment for patients, might help to reduce cervical cancer survival inequalities.

Author contributions

NPC, FBP and MLC conceived and designed the study. MLC acquired the data. NPC performed the analysis and drafted the manuscript. NPC, FBP and MLC revised the manuscript. All authors read and approved the final version.

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CRediT authorship contribution statement

Nathália Pacífico de Carvalho: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft. **Flávia Bulegon Pilecco:** Conceptualization, Methodology, Writing - review & editing, Supervision, Funding acquisition. **Mariângela Leal Cherchiglia:** Conceptualization, Methodology, Data curation, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2021.101899.

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