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Time trends and age-period-cohort analysis of cervical cancer mortality rate in Brazil

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ABSTRACT

Background: Cervical cancer (CC) is a common preventable and curable disease that may lead to death. Our aim was to describe the patterns of time trends in CC mortality rates among women in Brazil from 1980 to 2017, and identify the influence of age, period and birth cohort (APC) stratified by region (North NR, Northeast NER, Southeast SER, South SR, Center-Western region CWR).

Methods: We performed a time-series analysis using secondary data bases. Crude (MR) and WHO age-standardized CC mortality rates (aMR) were estimated per 100,000 women. We evaluated time trends using permutation joinpoint regression models (JP) and APC models to estimate the effect of APC on MR.

Results: The JP analysis showed a temporal decrease in all regions, except the NR, which had an annual percentage increase of 0.44 (95%CI 0.2 - 0.7). MR in the NR was 2 to 4 times higher than in the other regions. We observed steady increases in MR with age in the NR and NER. A plateau after age 40 was observed in SER, SR, and CWR. The NR and NER MR ratio stabilized around the year 2000. Birth cohort effect showed decreasing MR ratio from 1900 to 1970 for all regions, except the NR, which showed increasing MR rate from older to more recent cohorts.

Conclusion: We showed relevant differences in cervical MR by region, which may reflect inequality in access to primary and secondary prevention as well as treatment, particularly in the NR.

1. Background

Precancerous cervical lesions may progress to invasive cervical cancer over a period of 10–20 years [1,2]. These lesions can be detected by screening and treated effectively with a high potential for cure in the initial stages. In Brazil, cervical cancer control has been defined by the official agenda as a public health priority. Quality analysis of cervical cancer public health interventions has shown that the implementation of screening campaigns has been heterogeneous in time comparing different regions across the country [3].

Cervical cancer is the third most frequent cancer among women with the third cancer-related mortality in Brazil [4,5]. Incidence and mortality are related to both social inequalities and socio-economic development, Brazil has five regions that show great heterogeneity in these aspects [5]. The incidence and mortality from cervical cancer are 2 times higher among women in the Northern region (in the Amazon area) when compared to the Southeastern region of Brazil [3]. Cervical cancer-related mortality reflects the effect of effective primary and secondary prevention strategies (screening of pre-malignant lesions or asymptomatic cervical cancer) as well as cancer treatment access (tertiary prevention) [5–7]. Variation across countries and within countries between geographic areas may highlight inequalities in access to health care [2]. The analysis of this heterogeneity among regions is extremely important to develop tailored public health interventions considering each region context.

Temporal trends in mortality are an important component of surveillance and, thus, allocation of resources. The aim of the present study was to describe trends in cervical cancer mortality rates among women in Brazil from 1980 to 2017, identifying the influences of age, period and birth cohort effects stratified by region to explore and evaluate the

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inequalities to health care [8].

2. Methods

We performed a time-series analysis to evaluate temporal trends in cervical cancer mortality rates in Brazil by using the geopolitical division in macroregions: North, Northeast, Southeast, South, and Central-West [9] (see Table S0 of the supplementary material).

2.1. Data sources

The number of cervical cancer deaths was obtained from the Mortality Information System of the Brazilian Ministry of Health [10]. This database compiles information from death causes identified and codified routinely in death certificates for vital statistics purposes. The term "cervical cancer" was used to identify cervical malignant neoplasm using the classification codes from the 9th and 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD). Due to changes in ICD, we identified the deaths using code 180 through 1995 (ICD-9), and code C53 (ICD-10) from 1996 through 2017 [11,12].

The population denominator from 1980 to 2017 was estimated using the information collected in 1980, 1991, 2000 and 2010 censuses conducted by the Brazilian Institute of Geography and Statistics [13]. For the other years, we used inter-censal estimates of the female population for each age and region.

Ill-defined causes of death are those whose cause is unknown and represents a quality indicator of the death registration system [14,15]. An important consideration is that the proportion of ill-defined death hanged over time and across regions during the study period, ranging from 22% in 1980 to 6% in 2017 for the whole country, with a higher variation for specific regions [16]. The proportional redistribution of these ill-defined deaths is a well-established acceptable methodology to deal with this problem [17–19]. We proportionally redistributed deaths from ill-defined causes for each year and five-year age group, using the following formula [20]:

$$Redistributed\ CCD_{age\ group,\ year} = CCD_{age\ group,\ year} + IDD_{age\ group,\ year} * \left(\frac{CCD_{age\ group,\ year}}{TD_{age\ group,\ year} - IDD_{age\ group,\ year}} \right),$$

where CCD is the total number of cervical cancer deaths and, for the female population only, IDD is the number of ill-defined deaths, and TD is the total number of deaths.

From 1980–1995 the codes used in the classification of ill-defined causes of deaths were 780–799 (symptoms, signs, and ill-defined conditions). From 1996 on the codes were: I46 cardiac arrest, I95-I99 other and unspecified disorders of the circulatory system, J96 respiratory failure, not elsewhere classified, P28 other respiratory conditions originating in the perinatal period, all codes corresponding to the R symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified category [21].

Cervical cancer deaths, the total number of deaths, ill-defined causes of death and the denominator estimates were obtained from public data available at www.datasus.gov.br website [22].

2.2. Data analysis

Crude and age-standardized mortality rates for cervical cancer were calculated per 100,000 women for each year. Mortality rates were age-standardized based on the standard population proposed by the WHO in 2001 [23].

We evaluated time trends of annual age-standardized cervical cancer mortality rates using a permutation joinpoint regression model analysis [24,25]. This regression model fits joined straight lines on a logarithmic scale to the observed annual age-standardized rates. We considered as "joinpoint" the significant changes in time-related trend tendencies [24]. We estimated the annual percentage change (A%C) for each segment. The terms "increase" or "decrease" were used when the slope indicated an A%C different from ± 0.5 % and a significant p-value; otherwise, trends were considered stable over time [26,27]. For this analysis, the joinpoint software settings were: a maximum of 5 joinpoints were allowed; the minimum number of data points allowed between joinpoints was 4; and joinpoints were not allowed within 4 data points of the beginning or end of the series [28]. We used the JoinPoint Regression Program 4.7.0.0 [24,29].

Mortality from cervical cancer for a given region is a function of differences in age, period and birth cohort effects. These components may correspond to different factors affecting the distribution of cervical cancer, e.g. its diagnosis, its treatment and response to treatment. The incorporation of these three components related to time simultaneously in a model is called the non-identifiability problem [8]. Considering this problem, we chose APC models using Poisson regression for event counts to estimate the effect of each of these components on cervical cancer mortality. The log-linear regression model we used is described as follows:

$$log\ (r_{ijk}) = log\ (\frac{d_{ijk}}{n_{ijk}}) = \tau + \alpha_i + \beta_j + \gamma_k\ ,$$

where r_{ijk} is the expected mortality rate at age i, period j, and cohort k; d_{ijk} is the expected number of deaths assumed to follow a Poisson distribution; n_{ijk} is the population at risk of death (the $\log(n_{ijk})$ is the offset term or the log-linear adjustment term for contingency tables); τ represents the intercept or mean adjusted rate; α_i represents the ith row age effect for i = 1,…, α age groups; β_j represents the jth column period effect for j = 1,…, p periods; and α_k represents the kth diagonal cohort effect for k = 1,…, (α + p − 1) cohorts [8,30].

APC models were fitted using the command apcfit STATA version 15.1. It models age, period, and cohort effects by fitting cubic splines and overcomes the non-identifiability problem arising from the linear relations of the three time-related factors [31]. Since apcfit models time related variables as continuous, we used period and mortality rates estimated for each year. As age was obtained for five-year intervals, we used the age in the middle of each interval. We calculated the birth cohort by subtracting this age from the year of death. Due to the low mortality under age 20 years, we fitted APC models including only age groups of 20 years and older at death. In order to allow comparisons between the models for each regions, we selected 1943 as the fixed reference birth cohort and 2001 as the fixed reference for the period's effects in all models based on the median number of cases. The age effect is presented as mortality rates, while the period and cohort effect curves are presented as relative risks (RR) on the log-scale. We presented the full APC model in all cases in order to estimate the adjusted effects of age period and cohort on cervical cancer mortality.

The contributions of period and birth cohort effects were assessed by comparing the complete model including age, period and birth cohort (APC), with the reduced models with only age and period (AP) or age and birth cohort (AC). The adjusted effects were evaluated by the likelihood ratio test, which compares the nested models' goodness-of-fit using the deviance and degrees of freedom and the Akaike Information Criterion (AIC). Results with $p \leq 0.05$ were considered statistically significant.

3. Results

A total of 145,147 women died from cervical cancer in the entire country during the 38-years study period. Considering the ill-defined

Table 1
Crude and WHO age-standardized Cervical Cancer mortality rates per 100,000 women. Brazil 1980–2017.

Year	Cervical Cancer Deaths	Population	Crude Cervical Cancer mortality rate	WHO Age-Standardized Cervical Cancer mortality rate
1980	2,616	59,812,019	4.37 (95 %CI 4.21–4.54)	7.08 (95 %CI 6.87–7.3)
1981	2,679	60,977,862	4.39 (95 %CI 4.23–4.56)	7.01 (95 %CI 6.81–7.23)
1982	2,551	62,341,214	4.09 (95 %CI 3.94–4.25)	6.46 (95 %CI 6.27– 6.66)
1983	2,809	63,709,877	4.41 (95 %CI 4.25–4.58)	6.84 (95 %CI 6.64–7.05)
1984	2,829	65,075,010	4.35 (95 %CI 4.19–4.51)	6.65 (95 %CI 6.46–6.85)
1985	3,117	66,435,198	4.69 (95 %CI 4.53–4.86)	7.08 (95 %CI 6.88–7.28)
1986	3,055	67,783,436	4.51 (95 %CI 4.35–4.67)	6.7 (95 %CI 6.5–6.89)
1987	3,198	69,111,839	4.63 (95 %CI 4.47–4.79)	6.79 (95 %CI 6.6–6.99)
1988	3,178	70,413,062	4.51 (95 %CI 4.36–4.67)	6.53 (95 %CI 6.35–6.73)
1989	3,265	71,680,346	4.55 (95 %CI 4.4–4.71)	6.56 (95 %CI 6.37–6.75)
1990	3,306	72,916,980	4.53 (95 %CI 4.38–4.69)	6.5 (95 %CI 6.32–6.69)
1991	3,484	74,340,353	4.69 (95 %CI 4.53–4.84)	6.64 (95 %CI 6.46–6.83)
1992	3,572	75,311,650	4.74 (95 %CI 4.59–4.9)	6.5 (95 %CI 6.32–6.69)
1993	3,659	76,493,348	4.78 (95 %CI 4.63–4.94)	6.81 (95 %CI 6.63–7)
1994	3,578	77,581,633	4.61 (95 %CI 4.46–4.77)	6.56 (95 %CI 6.38–6.74)
1995	3,812	78,633,511	4.85 (95 %CI 4.7–5)	6.91 (95 %CI 6.73–7.1)
1996	3,837	79,416,982	4.83 (95 %CI 4.68–4.99)	6.26 (95 %CI 6.08–6.43)
1997	4,040	80,708,834	5.01 (95 %CI 4.85–5.16)	6.51 (95 %CI 6.33–6.69)
1998	4,286	81,795,453	5.24 (95 %CI 5.09–5.4)	6.83 (95 %CI 6.65–7.01)
1999	4,580	82,881,478	5.53 (95 %CI 5.37–5.69)	7.21 (95 %CI 7.03–7.4)
2000	4,623	86,223,155	5.36 (95 %CI 5.21–5.52)	6.48 (95 %CI 6.31–6.65)
2001	4,919	87,531,932	5.62 (95 %CI 5.46–5.78)	6.79 (95 %CI 6.62–6.97)
2002	4,743	88,672,139	5.35 (95 %CI 5.2–5.5)	6.48 (95 %CI 6.32–6.65)
2003	4,842	89,807,838	5.39 (95 %CI 5.24– 5.55)	6.53 (95 %CI 6.37–6.7)
2004	5,010	90,939,676	5.51 (95 %CI 5.36–5.66)	6.69 (95 %CI 6.52–6.86)
2005	5,025	93,513,055	5.37 (95 %CI 5.23–5.52)	6.55 (95 %CI 6.38–6.71)
2006	5,003	94,824,221	5.28 (95 %CI 5.13–5.42)	6.45 (95 %CI 6.29–6.61)
2007	5,073	96,293,080	5.27 (95 %CI 5.13–5.42)	5.65 (95 %CI 5.5–5.8)
2008	5,241	96,453,502	5.43 (95 %CI 5.29–5.58)	5.69 (95 %CI 5.54–5.84)
2009	5,429	97,430,444	5.57 (95 %CI 5.43–5.72)	5.72 (95 %CI 5.58–5.88)
2010	5,342	97,348,809	5.49 (95 %CI 5.34–.64)	5.4 (95 %CI 5.25–5.55)
2011	5,511	98,175,155	5.61 (95 %CI 5.47–5.76)	5.52 (95 %CI 5.38–5.67)
2012	5,600	98,983,648	5.66 (95 %CI 5.51–5.81)	5.57 (95 %CI 5.43–5.72)
2013	5,748	101,695,856	5.65 (95 %CI 5.51–5.8)	5.44 (95 %CI 5.3–5.59)
2014	5,760	102,609,055	5.61 (95 %CI 5.47–5.76)	5.3 (95 %CI 5.16–5.44)
2015	6,050	103,495,127	5.85 (95 %CI 5.7–5.99)	5.42 (95 %CI 5.28–5.56)
2016	6,187	104,355,330	5.93 (95 %CI 5.78–6.08)	5.39 (95 %CI 5.26–5.54)
2017	6,733	105,189,655	6.4 (95 %CI 6.25–6.56)	5.71 (95 %CI 5.57–5.86)

causes, the total estimated redistributed number of deaths was 164,243. The number of the total population used as denominator ranged from 59,812,019 in 1980 to 105,189,655 in 2017. The rates for the entire period show a decline that is presented in Table 1 and Fig. 1a.

The different patterns for age-standardized cervical cancer mortality rates by region are shown in Fig. 1b. Table S1 presents adjusted cervical cancer mortality rates for all regions. Figs. S1a and S1b show the changes in the denominator between regions from the beginning to the end of the analysed period.

3.1. Time trend analysis

The age-standardized mortality rate for the Northern region is higher for every year than the mortality in the other regions. In 1980, the cervical cancer mortality rate for the Northern region was more than twice the mortality rate in the Southeastern region. This difference increased to more than 3 times in 2017. This shows not only that the time pattern is different for the Northern region, but also that the magnitude of the difference in mortality rate between these two regions has increased during the period covered in our study.

Descending pattern and a marked decrease since around 2000 were shown in the Southeastern, Southern, and Center-Western regions. The joinpoint regression analysis is consistent with the inspection of the adjusted mortality rates, showing an increase in the age-standardized mortality rate in the Northern region. In the Northeastern region, cervical cancer mortality remained relatively constant. A similar pattern of decline since 1999 and 2001 was shown in the South and Southeast, respectively. Mortality in the Center-Western region declined consistently throughout the period, without any joinpoint.

All joinpoint regression modeled mortality rates for Brazil and for each region are shown in Table 2, and Fig. 2a and b respectively.

3.2. Age period cohort analysis

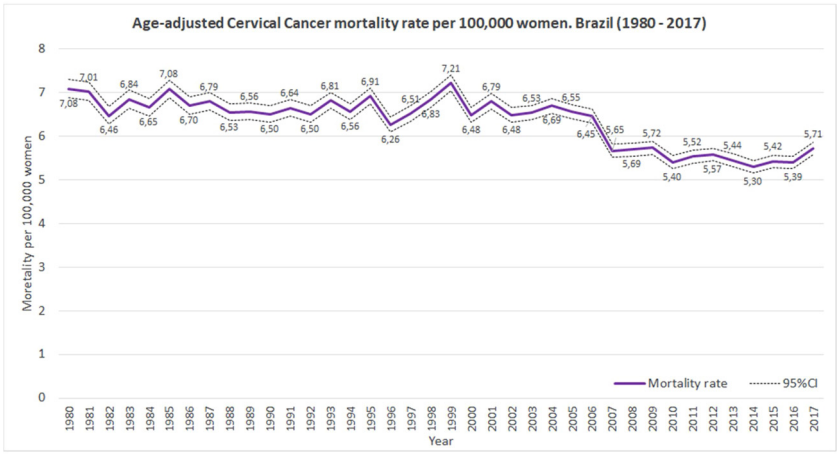
The complete APC models with age, period and cohort components were significantly better than the model with only two factors, age and period ($p < 0.0001$) or age and cohort ($p < 0.0001$), with the only exception being the Southeastern region. In this last region, the effect of birth cohort on mortality is not statistically significant since the fit of the complete APC model is better than the AC model without period ($p < 0.001$) and also the complete APC model does not have a better fit than the AP model without birth cohort (p 0.1616). AIC and BIC consistently support this. The comparisons between the full APC models with the reduced models including AP or AC are shown in Table 3.

Fig. 3a integrates the plots of the point estimates for the effects on cervical cancer mortality of the three time-related factors studied for the period 1980 to 2017. The adjusted effects of age, period and birth cohort for all regions are presented in Fig. 3b–d respectively.

3.2.1. Age effect

All mortality rates increase continuously with age. The lower rate is found at age 20 years for the period analyzed, with the older ages, as expected, having higher mortality rates. This was consistent in all regions but there were differences in magnitude and pattern. The Northern region had between 2 to 4 times higher rates for each age group than the other regions. There was a steady increase in the Northern and Northeastern regions that is more pronounced for the former, reaching almost 80 per 100,000. The other 3 regions

a



b

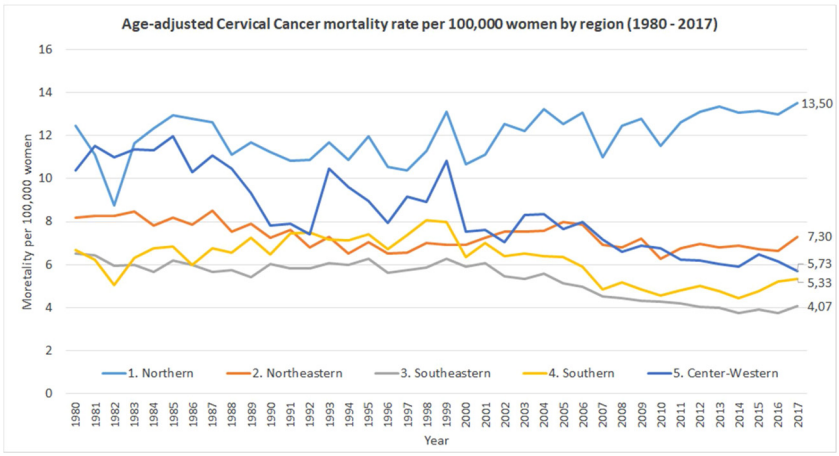


Fig. 1. a and b) Age-standardized cervical cancer mortality rates per 100,000 women with 95 % confidence intervals for Brazil (1a) and by region (1b), 1. North, 2. Northeast, 3. Southeast, 4. South, 5. Center-Western region.1980–2017.

Table 2
Calendar year periods with distinct cervical cancer trends as defined by joinpoint analyses by region. Brazil.1980–2017.

Region	Joinpoint (95%CI)	Period	A%C (95 %CI)	p
Brazil	–	1980–2004	−0.1 (−0.3 to 0.1)	0.3
	2004 (2001 - 2006)	2004–2010	−3.3 (−5.3 to −1.2)	< 0.01
	2010 (2007 - 2013)	2010–2017	−0.26 (−1 to 1.6)	0.7
1. North	no joinpoint	1980–2017	0.44 (0.2 to 0.7)	< 0.01
2. Northeast	–	1980–1997	−1.53 (−2 to −1.1)	< 0.01
	1997 (1994 - 2001)	1997–2005	2.12 (0.6 to 3.7)	< 0.01
	2005 (2002 - 2007)	2005–2010	−3.58 (−6.7 to 0.3)	< 0.01
	2010 (2008 - 2013)	2010–2017	1.03 (−0.4 to 2.5)	0.2
3. Southeast	–	1980–2001	−0.11 (−0.4 to 0.2)	0.5
	2001 (1984 - 2005)	2001–2013	−3.51 (−4.3 to −2.7)	< 0.01
	2013 (1998 - 2013)	2013–2017	0.71 (−3.6 to 5.3)	0.7
4. South	–	1980–1999	1.18 (0.6 to 1.8)	< 0.01
	1999 (1996 - 2001)	1999–2010	−4.39 (−5.8 to −3)	< 0.01
	2010 (2006 - 2013)	2010–2017	1.33 (−1.4 to 4.1)	0.3
5. Center-West	no joinpoint	1980–2017	−1.79 (−2.1 to −1.5)	< 0.01

A%C, estimated the annual percentage change

(Southeast, South, and Center-west), present a distinct pattern with a plateau beginning at around 40 years, and a slight increase from ages 40 to ≥80 years. The higher mortality rate for these 3 regions is around 25 per 100,000.

3.2.2. Period effect

All regions show a statistically significant period effect on cervical cancer mortality. However, different patterns were observed. In the Northern and Northeastern regions, we observed fluctuations in mortality rate ratio, that stabilize around 2000. In the Southern and Center-western region, the highest peak is around 2000, followed by a decrease in rate ratio that is more prominent in the South.

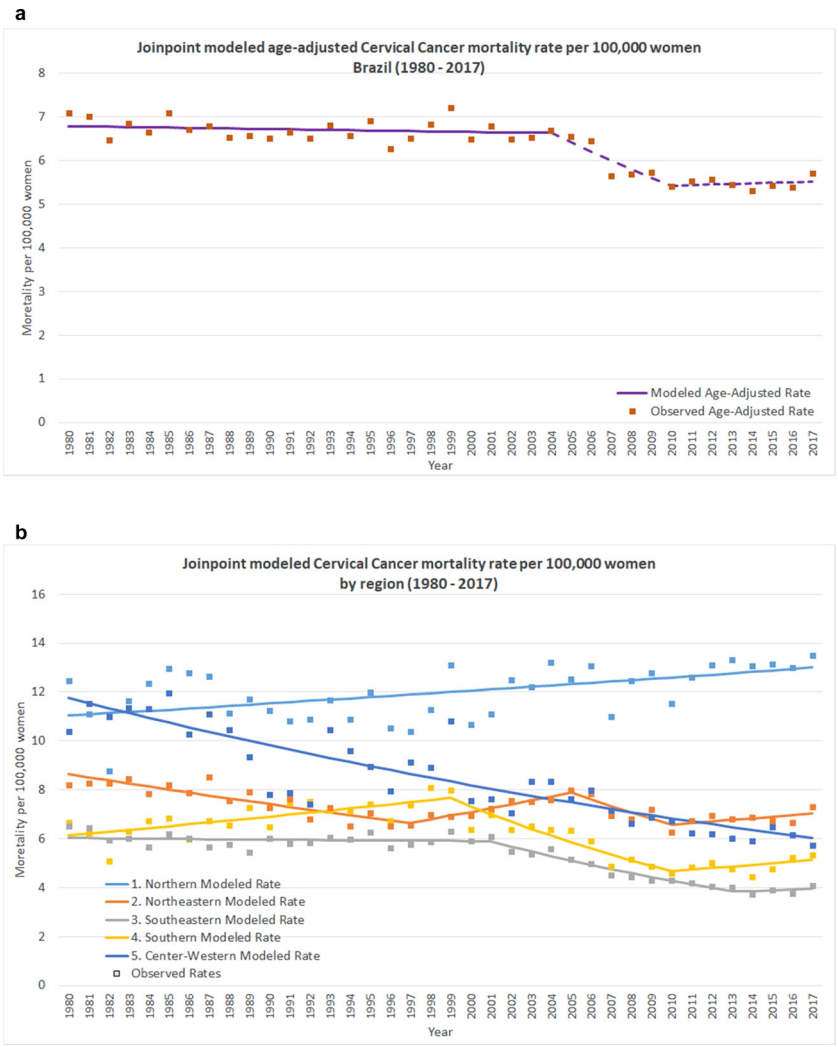


Fig. 2. a and b) Observed and joinpoint modeled age-standardized cervical cancer mortality rates per 100,000 women for Brazil (2a) and by region (2b), 1. North, 2. Northeast, 3. Southeast, 4. South, 5. Center-Western region.1980–2017.

3.2.3. Birth cohort effect

We show a decreasing rate ratio from 1900 to 1970 for all regions but the Northern. The Southeastern, Southern and Center-Western regions decline from a rate ratio of 2. The Northeastern region has a less marked slope that changes at around 1940. The last segment from this region is characterized by a greater negative slope. The Northern region exhibited a different behavior, with an increase in rate ratios until around the 1950 birth cohort. From 1950 on, the birth cohort effect seemed to be stabilized.

4. Discussion

In this study, we explored the effects of age, period and birth cohort on cervical cancer mortality by region in Brazil. We observed an overall decrease in cervical cancer mortality for the whole country and significant effects of age, period and birth cohort. In concordance with previous studies, age, period and birth cohort effects varied by region [32–35].

Considering the effect of age on mortality, we described a plateau that began at around ages 40–50 years, with a very mild increase in older ages in the Southeastern, Southern and Center-Western regions. This pattern could indicate greater effectiveness in early detection campaigns in the early stages of cervical cancer with a consistent greater probability of surviving the disease in the older ages.

Considering the observed period effect, until the 1980s, cervical cancer control actions carried out in Brazil were limited to isolated initiatives by municipalities or institutions, especially in the Southeastern region. Since this decade, guidelines and a nationwide program have been defined to expand early detection of cervical cancer. Parallel to this, the country also began to change its health care model, with the implementation of a public and universal health system - the Unified Health System (SUS), strengthening the organization and decentralization of actions to municipalities [36]. In the following decade, the Viva Mulher cervical cancer control program was implemented, which substantially expanded the coverage of the Pap smear in all regions of Brazil, with two campaigns conducted between 1998 and 2002, in addition to the implementation of the use of High-Frequency Surgery or LLETZ (Large Loop Excision of the Transformation Zone) in the treatment of cervical cancer precursor lesion [32,37]. This led to a substantial increase in coverage of the Papanicolaou test in all regions of Brazil, which could explain, at least partly, the stabilization of the mortality rate and the pattern of the mortality rate by age.

However, given the different levels of organization of the healthcare network in the country's regions, the actions were not implemented uniformly. Regional differences in the structure of health care may justify a possible delay in the impact of screening on mortality. Such a context may explain the variations observed between regions in mortality rate and the pattern of mortality rate by age. The increase in coverage did not reflect in the same proportion in the provision of timely treatment, especially in the states of the least developed regions,

Table 3
Adjustments to the models of age-period-cohort effects, for cervical cancer mortality rates for Brazil and by region, from 1980 to 2017. All p values test the null hypothesis of equal goodness of fit between each model compared with the APC complete model.

Models by region	Akaike Information Criterion	Bayesian Information Criterion	Degrees of freedom	log-likelihood	p (> |Chi2|)
Brazil					
Age Period Cohort model	4044.2	4104.8	15	−2007.1089	ref
Age Period model	4168.5	4213	11	−2073.275	< 0.001
Age Cohort model	4426.9	4471.4	11	−2202.473	< 0.001
1. North					
Age Period Cohort model	2775.6	2836.2	15	−1372.795	ref
Age Period model	2819.1	2863.6	11	−1398.577	< 0.001
Age Cohort model	2783.8	2828.2	11	−1380.912	0.0027
2. Northeast					
Age Period Cohort model	3483.2	3543.7	15	−1726.586	ref
Age Period model	3536.1	3580.6	11	−1757.075	< 0.001
Age Cohort model	3557.0	3601.4	11	−1767.519	< 0.001
3. Southeast					
Age Period Cohort model	3414.0	3474.6	15	−1691.998	ref
Age Period model	3412.5	3457.0	11	−1695.274	0.1616
Age Cohort model	3913.2	3957.6	11	−1945.615	< 0.001
4. South					
Age Period Cohort model	2972.5	3033.0	15	−1471.229	ref
Age Period model	3020.5	3064.9	11	−1499.237	< 0.001
Age Cohort model	3322.3	3366.7	11	−1650.15	< 0.001
5. Center-West					
Age Period Cohort model	2587.4	2647.9	15	−1278.69	ref
Age Period model	2595.2	2639.6	11	−1286.595	0.0033
Age Cohort model	2601.3	2645.7	11	−1289.662	0.002

where they also needed to organize their services for the treatment of the precursor injury.

The Northern region has a lower amount of cases and populations with consistent broader confidence intervals. The effect of birth cohort on mortality in this region may suggest misdiagnosis in the older birth cohorts, that could be related to differences in adherence and availability to screening by birth cohort and region. The increment in the access to screening cancer programs described by Costa y col. may be responsible in part for the decrease in cervical cancer mortality rate in the more developed Southeast, South, and Center-Western regions [38]. Inequality in Pap smear coverage among Brazilian regions has more pronounced when it is found that the highest percentages of women who have never tested, or who have taken the test irregularly, were recorded in the Northern and Northeastern states of Brazil [39], highlighting the greater vulnerability of women living in these regions.

Meira and col. studied age, period and birth cohort effects on mortality from cervical cancer in two municipalities from the Southeastern region: Rio de Janeiro and São Paulo [33]. They used similar methods to evaluate mortality between 1980 to 2009. Their findings are similar to ours in this region. We observed the same birth cohort and period effect on cervical cancer mortality patterns. The age effect in Meira's study does not show the plateau we consistently observed in our curves for the Southeast, South, and Center-Western regions. These differences may be due to the period, region and population size differences between both studies.

All these differences in the observed patterns may represent inequalities in access to screening and early treatment of cervical cancer between regions. The Northeastern region has the lowest socio-economic indicators of the country and had the highest illiteracy rate in Brazil in 2010 (17.6 % of people 10 years or older) [40]. Similarly, the Northern region had a clearly different mortality pattern, thus, suggesting inequity in access to health services. The Northeastern region behaves in an intermediate fashion between the Northern region and the rest of the country. Previous studies showed a relationship between cervical cancer mortality and poorer socioeconomic indicators [41]. Costa and col. studied quality indicators for the cervical cancer screening program by region from 2006 to 2013 and showed that the Northern and Northeastern regions had the worst performance, i.e. a low positivity index and high-grade squamous intraepithelial lesion percentage. The poor performance in these regions may impact cervical cancer mortality [3].

In addition to the coverage of the Pap smear and the quality of the cytology tests, it is necessary to consider the access of women with altered results to diagnostic confirmation, as well as to the treatment of precursor lesions and cancer cases. Such actions, due to the complexity of care, are performed in specialized services and usually occur in larger municipalities with more assistance structure. When analyzing data from the outpatient information systems of the Unified Health System, there was a dispersion of health services for the diagnostic investigation and treatment of precursor injury [42], leading to the displacement of women to other municipalities and covering greater distances, especially in the northern states, whose services are usually concentrated in the capitals. This difficulty in accessing diagnostic and treatment services for the population residing outside large urban centers was pointed as one of the factors that could explain the stabilization and absence of a reduction in cervical cancer mortality rates observed within the states when compared to the capital cities [43].

The study of Giarinelli and col. suggest that these time-related tendencies could be different between capital cities and municipalities, particularly for the Northern and Northeastern regions [32]. Additional evaluation of smaller regions may show regional differences that represent inequity even within the healthier populations. Another limitation is that we could not evaluate the effect of the HPV vaccination campaign in Brazil since it began in recent years (2014 for females and 2017 for males) [2,44].

5. Conclusions

We showed relevant differences in cervical cancer mortality that may be used to guide efforts to improve the implementation of effective prevention programs so as to reduce the inequity gap between regions.

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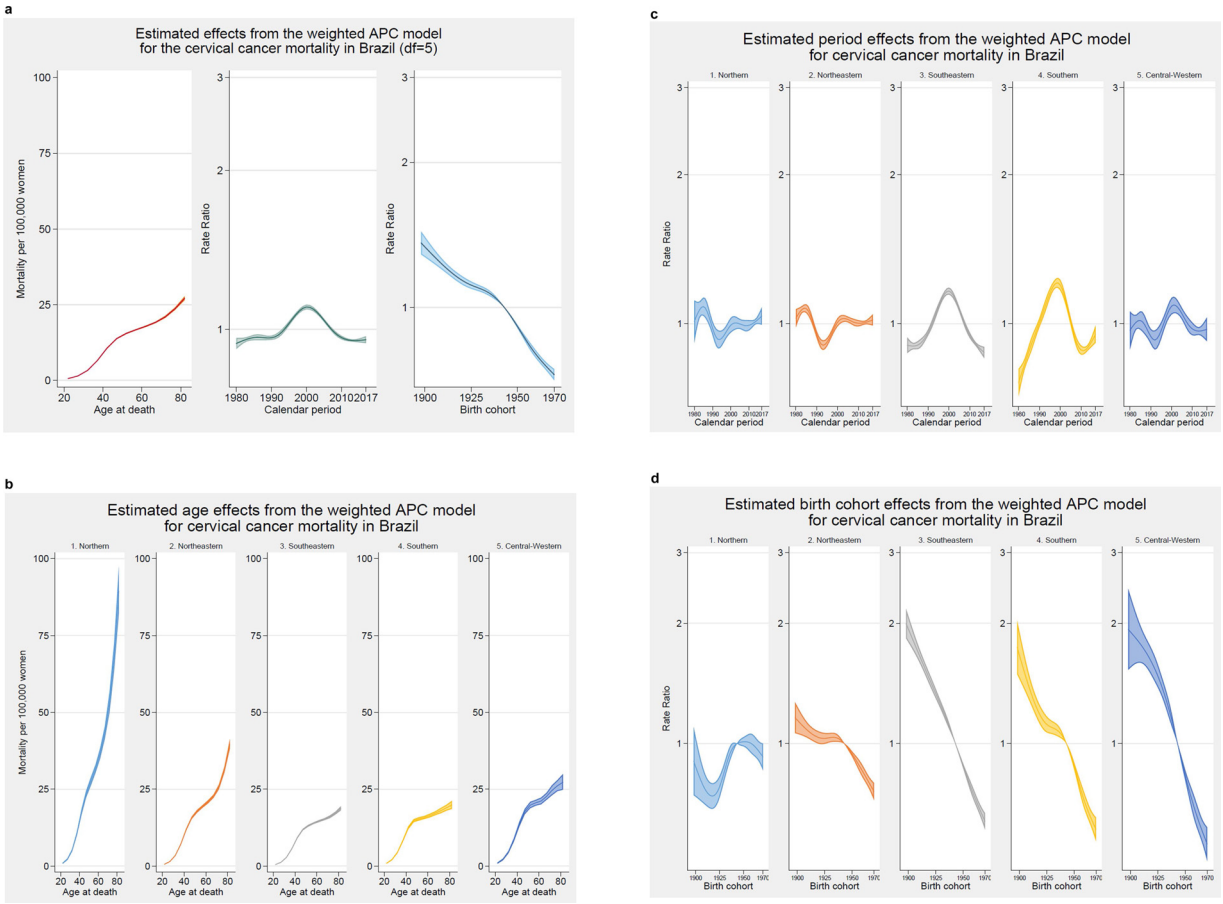

Fig. 3. a) Estimated effects from the APC model for cervical cancer mortality rates per 100,000 women for Brazil, 1980–2017 (reference period 2001; reference birth cohort 1943). The red line represents the age-specific mortality rates. The green line represents the period effects as rate ratios (log scale). The blue line represents the birth cohort effect in rate ratios (log scale). The regions surrounding the lines are 95 % confidence intervals. b) Estimated period and cohort-adjusted age effects from the APC model for cervical cancer mortality rates per 100,000 women by region, 1980–2017 (reference period 2001; reference birth cohort 1943). The regions surrounding the lines are 95 % confidence intervals. c) Estimated age and cohort-adjusted period effects from the APC model for cervical cancer mortality rates per 100,000 women by region, 1980–2017 (reference period 2001; reference birth cohort 1943). The regions surrounding the lines are 95 % confidence intervals. d) Estimated age and period-adjusted birth cohort effects from the APC model for cervical cancer mortality rates per 100,000 women by region, 1980–2017 (reference period 2001; reference birth cohort 1943). The regions surrounding the lines are 95 % confidence intervals (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Declaration of Competing Interest

The authors declare not to present any conflict of interest to declare.

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.jcpo.2020.100230.

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