ORIGINAL ARTICLE

Age-period-cohort effect on cervical cancer mortality in the Center-West of Brazil, 1980-2019

Efeito da idade-período-coorte na mortalidade por câncer do colo do útero no Centro-Oeste do Brasil, 1980-2019

Efecto edad-período-cohorte en la mortalidad por cáncer de cuello uterino en el Centro-Oeste de Brasil, 1980-2019

Karina Cardoso Meira[1]
Taynãna César Simões[2]
Rafael Tavares Jomar[3]
Eder Samuel Oliveira Dantas[1]
Cosme Marcelo Furtado Passos da Silva[4]
Carinne Magnago[5]

[1] Universidade Federal do Rio Grande do Norte (UFRN), Natal, Rio Grande do Norte, Brasil.

[2] Fundação Oswaldo Cruz (FIOCRUZ - MG), Belo Horizonte, Minas Gerias, Brasil.

[3] Instituto Nacional de Câncer (INCA), Rio de Janeiro, Rio de Janeiro, Brasil.

[4] Fundação Oswaldo Cruz (FIOCRUZ - RJ), Rio de Janeiro, Rio de Janeiro, Brasil.

[5] Universidade de São Paulo (USP), São Paulo, São Paulo, Brasil.

Corresponding author:
Karina Cardoso Meira
E-mail: karina.meira@ufrn.br

How to cite this article: Meira KC, Simões TC, Jomar, Dantas, Silva CMFP, Magnago C. Age-period-cohort effect on cervical cancer mortality in the Center-West of Brazil, 1980-2019. Rev. Eletr. Enferm. 2024;26:75551. https://doi.org/10.5216/ree.v26.75551 English, Portuguese.

Received: 13 March 2023
Accepted: 06 November 2023
Published online: 04 June 2024

ABSTRACT

Objectives: to analyze the effect of age-period-cohort on cervical cancer mortality rates in the Center-West of Brazil. **Methods:** ecological time series study from 1980 to 2019, utilizing data from the Mortality Information System and population estimates from the Brazilian Institute of Geography and Statistics. Age-period-cohort effect models with Poisson distribution were employed. **Results:** 19,260 deaths were observed, corresponding to an average standardized mortality rate of 17.23/100,000 women. The age effect indicated a progressive increase in rates as age advanced. The period effect showed a reduction in the risk of death in the Federal District (2015-2019), Mato Grosso do Sul (2010-2014), and Mato Grosso (2010-2019), as well as an increase in Goiás (2015-2019). The cohort effect showed an increase in the risk of death for those born before 1950-1954 and a reduction in the generations from 1955-1959 onwards. **Conclusion:** there is evidence of an age-period-cohort effect on mortality from cervical cancer in the Brazilian Center-West, which calls for the strengthening of actions for its prevention and control aimed at women of cohorts and ages at greater risk of dying from this cause.

Descriptors: Mortality; Uterine Cervical Neoplasms; Age Factors; Periodicity; Cohort Effect.

RESUMO

Objetivos: *analisar o efeito da idade-período-coorte nas taxas de mortalidade por câncer do colo do útero no Centro-Oeste do Brasil.* ***Métodos:*** *estudo ecológico de séries temporais, de 1980 a 2019, cujas fontes de dados foram o Sistema de Informação sobre Mortalidade e as estimativas populacionais do Instituto Brasileiro de Geografia e Estatística. Modelos de efeito idade-período-corte com distribuição de Poisson foram usados.* ***Resultados:*** *observaram-se 19.260 óbitos, correspondente à taxa de mortalidade padronizada média de 17,23/100 mil mulheres. O efeito da idade indicou aumento progressivo das taxas com o avançar da idade. O efeito do período evidenciou redução do risco de morte no Distrito Federal (2015-2019), Mato Grosso do Sul (2010-2014) e Mato Grosso (2010-2019), além de aumento em Goiás (2015-2019). O efeito da coorte revelou aumento do risco de morte para as nascidas antes de 1950-1954 e redução nas gerações a partir de 1955-1959.* ***Conclusão:*** *há evidências de efeito da idade-período-coorte na mortalidade por câncer do colo do útero no Centro-Oeste brasileiro, o que demanda fortalecimento de ações para sua prevenção e controle voltadas para mulheres de coortes e idades sob maior risco de morrer por essa causa.*

Descritores: Mortalidade; Neoplasias do Colo do Útero; Fatores Etários;

Periodicidade; Efeito de Coortes.

RESUMEN

Objetivos: *análisis del efecto de la edad-período-cohorte en las tasas de mortalidad por cáncer de cuello uterino en el centro-oeste de Brasil.* ***Métodos:*** *estudio de series temporales ecológicas, de 1980 a 2019, cuyas fuentes de datos fueron el Sistema de Información de Mortalidad y las estimaciones de población del Instituto Brasileño de Geografía y Estadística. Se utilizaron modelos de efecto edad-período-corte con distribución de Poisson.* ***Resultados:*** *se registraron 19.260 fallecimientos, lo que corresponde a una tasa media de mortalidad estandarizada de 17,23/100.000 mujeres. El efecto edad indicó un aumento progresivo de las tasas con el avance de la edad. El efecto período mostró una reducción del riesgo de muerte en el Distrito Federal (2015-2019), Mato Grosso do Sul (2010-2014) y Mato Grosso (2010-2019), así como un aumento en Goiás (2015-2019). El efecto cohorte mostró un aumento del riesgo de muerte para los nacidos antes de 1950-1954 y una reducción en las generaciones a partir de 1955-1959.* ***Conclusión:*** *hay evidencias de un efecto edad-período-cohorte en la mortalidad por cáncer de cuello uterino en el Centro-Oeste brasileño, lo que exige el refuerzo de las acciones para su prevención y control dirigidas a las mujeres de cohortes y edades con mayor riesgo de morir por esta causa.*

Descriptores: *Mortalidad; Neoplasias del Cuello Uterino; Factores de Edad; Periodicidad; Efecto de Cohortes.*

INTRODUCTIOLN

Cervical cancer (CC) is considered a preventable disease, as it can be screened in the pre-malignant stages by cytopathological examination (Pap smear), and there is an effective vaccine to control infection by the Human Papilloma Virus (HPV), the main cause of this type of cancer[1,2]. Despite the existence of preventive measures, CC maintains a high morbidity burden worldwide[3,4]. In 2020, 604,000 new cases and 342,000 deaths were estimated, representing the fourth most incident and lethal type of cancer among women[1].

In Brazil, CC also has high incidence and mortality rates, with marked differences in the magnitude of these indicators depending on the region's level of socioeconomic development[4-7]. For each year of the 2023-2025 triennium, 17,010 new cases were estimated, corresponding to the third most incident neoplasm among Brazilian women (15.38 new cases/100,000), excluding non-melanoma skin cancer[4]. In the North and Northeast of the country, it is the second most frequent neoplasm among its residents (20.48 new cases/100,000 and 17.59 new cases/100,000, respectively); in the Center-West, the third (16.66 new cases/100,000); in the South, the fourth (14.55 new cases/100,000); and in the Southeast, the fifth (12.93 new cases/100,000)[4]. A similar trend is observed in mortality rates, the highest magnitudes of which belong to the states in the North, Northeast, and Center-West regions[5-10].

The Center-West region occupies approximately 20.0% of the country's territory, has a low demographic density, and is made up of three states and the Federal District, which is home to the capital of Brazil, totaling four states. It has high incidence and mortality rates for CC compared to Brazil as a whole and to regions with greater socioeconomic development, such as the South and Southeast[8-10]. For the states of the Center-West for each year of the 2023-2025 triennium, incidence rates were estimated to oscillate between 11.05/100,000 and 17.73/100,000, respectively in the Federal District (DF) and Mato Grosso do Sul (MS)[4]. As for mortality rates, the Center-West recorded 4.92 deaths/100,000 in the 2020-2021 biennium, with variations ranging from 4.79/100,000 to 5.43/100,000, respectively observed in the Federal District (DF) and Mato Grosso (MT)[11].

The evaluation and planning of CC prevention and control policies must consider that HPV vaccine coverage, early diagnosis through Pap smears, and timely treatment of early lesions[12-14] are not uniformly distributed across age groups, time periods, and birth cohorts. Therefore, in order to better understand the behavior of this neoplasm over time, the use of age-period-cohort models is advantageous, as it helps to understand the effect of these three factors on the evolution of mortality from this cause, minimizing the limitations of classic trend models[12-14].

Trend studies of mortality rates from CC in the Center-West of Brazil investigated their temporal evolution by age and period, finding a downward trend both in the capitals and in the inland municipalities[5,8,11]. However, they did not evaluate the cohort effect, an important component in assessing the temporal trend of health problems. Given that women from different generations (birth cohorts) are distinctly influenced by changes in sexual and reproductive behavior, by policies to prevent and control CC, and by cancer care policies[6,7,12-14], it is clear that they have been exposed in different ways to these and other factors associated with this type of neoplasm. Therefore, the use of age-period-cohort models to analyze trends in mortality from CC is an important tool for the surveillance of this type of cancer.

Considering the lack of studies that have used age--period-cohort models to evaluate the temporal trend

of mortality from CC in the Center-West, and recognizing the potential contribution of this type of analysis to both the National Cancer Prevention and Control Policy[15] and the Strategic Action Plan for Tackling Chronic Diseases and Non-Communicable Diseases in Brazil 2021-2030[16], this study set out to analyze the effect of age-period-cohort on mortality rates from cervical cancer in the Center-West of Brazil.

METHODS

This is an ecological time series study, from 1980 to 2019, which was carried out in the Center-West and its respective states, namely: Federal District (DF), Goiás (GO), Mato Grosso (MT), and Mato Grosso do Sul (MS). The population consisted of women aged 20 or over whose cause of death was CC. The Mortality Information System (SIM) and population estimates from the Brazilian Institute of Geography and Statistics (IBGE) were used as data sources.

Using the TabWin program (version 3.6, 2022, DATASUS, Brazil), mortality records were extracted from the SIM website (https://datasus.saude.gov.br/informacoes-de-saude-tabnet/) on March 20th, 2022. In the 1980-2019 period, the ninth and tenth revisions of the International Statistical Classification of Diseases and Related Health Problems (ICD) were in force, so the ICD-9 179 and ICD-10 C53 codifications (C53. 0: malignant neoplasm of endocervix; C53.1: malignant neoplasm of exocervix; C53.8: malignant neoplasm of overlapping sites of cervix uteri; and C53.9: malignant neoplasm of cervix uteri, unspecified) were used to define deaths from CC[17,18].

Population data was obtained from the IBGE website (https://www.ibge.gov.br/) based on the 1980, 1991, 2000 and 2010 demographic censuses. For the intercensal years from 2013 to 2019, we used data from the projection of the population of the states by sex and age groups: 2000-2060[19].

The death records were then corrected for the quality of the information and underreporting due to the high rate of undefined causes and problems with the coverage of death records presented in the SIM[5-8]. The correction process was carried out in six stages, through proportional redistribution by year, age group, and state:

- Stage 1 - Redistribution of ignored age: the ignored age was redistributed proportionally among the age groups specified in the study, considering year, age group, and state.
- Stage 2 - Redistribution of ill-defined causes: 50% of deaths classified as ill-defined causes were redistributed proportionally among defined natural causes.
- Stage 3 - Redistribution of incomplete cancer diagnoses: deaths recorded as incomplete cancer diagnoses (total and female genital tract) were redistributed proportionally, considering the total number of cancers by year, age group, and state.
- Stage 4 - Redistribution of uterine cancer, part unspecified: deaths classified as part unspecified were proportionally redistributed to CC, based on their proportion in relation to all uterine cancers (CC and endometrial cancer).
- Stage 5 - Correction of deaths for poor certification of records: the results obtained in the previous stages were added to the number of deaths from CC originally recorded in the SIM, resulting in the correction of deaths in relation to poor certification of death records[5-8].
- Stage 6 - Correction for underreporting of deaths: the results obtained in step 5 were multiplied by the correction factors proposed for the years under investigation[20].

After that, crude death rates from CC were calculated, according to age group and state, per 100,000 women. The age groups were stratified every five years (20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, and ≥80). The truncated rates for open interval ages (≥80 years) were estimated by year. Once the rates per age group and period had been obtained, the crude rates were standardized using the direct method, with the world population proposed by Segi and modified by Doll and Hiil as the standard population[21].

The age-period-cohort effect was adjusted by Poisson regression, using estimable functions proposed by Holford[13,14], implemented in the models adjusted by the Epi package in the R software[22]. This package makes it possible to estimate and compare the fit of six sub-models to the data, namely: Age, Age-drift (linear effect of age), Age-cohort, Age-period-cohort, Age-period and Age-drift (linear effect of period plus linear effect of cohort). Age-period-cohort models were estimated for the Center-West and for each of its states. The statistical analysis thus included 13 age groups, eight periods (in five years, from 1980-1984 to 2015-2019) and 20 birth cohorts (in five years, from 1900-1904 to 1995-1999).

Poisson models estimated by estimable functions limit the analysis to linear combinations of the curvature effects of the time terms (age, period and cohort). The linear trend of the effects is divided into two components: the linear effect of age and the drift effect (lin-

ear effect of the period added to the linear effect of the cohort)[13,14]. Poisson regression, which is part of generalized linear models, is used to evaluate the effect of variables of interest on a response variable, the nature of which is a count, by estimating the natural logarithm of the mean of this response variable as a function of a linear predictor that considers the possible exposure variables[13,14].

Therefore, the age-period-cohort effects were estimated based on regression models with a Poisson distribution for the number of deaths observed in each age group *i* and period *j*, with the effects being additively related to the logarithm of the expected mortality rate , according to Holford's proposal[13,14],

$$ln(E[r_{ij}]) = ln\left(\frac{\theta_{ij}}{N_{ij}}\right) = \mu + \alpha_i + \beta_j + \gamma_k + \varepsilon_{ij}$$

where indicates the expected rate, the number of observed deaths, and the population at risk of death at age group and period . The parameter represents the average effect, represents the effect of age group , the effect of period , the effect of cohort , and the random error of age and period.

In each scenario, the six estimated age-period-cohort sub-models were compared in a nested way via residual deviance statistics and p-value. Models with the best fit were considered to be those with the lowest residual deviance and p-value <0.05[13,14].

Based on the best-fit model, estimated age-specific mortality rates and relative risks (RR) were extracted for each period and cohort, according to the respective reference categories. The 1995-1999 period was chosen as the reference because it preceded the consolidation of the National Cervical Cancer Control Program in 2001[23]. The reference birth cohort chosen was 1950-1954, since median cohorts have a greater number of observations, enabling more parsimonious models to be adjusted. In addition, women born after 1960 suffered a greater impact from urbanization, sexual revolution and habits, thus modifying the risk of exposure to the main factors related to CC[13,14]. Interval estimates were obtained with a 95% confidence interval (95%CI) and considered statistically significant if p-value <0.05[13,14].

Because the data was freely accessible and did not identify the subjects, this study was not submitted to a research ethics committee.

RESULTS

Between 1980 and 2019, the Center-West recorded 11,956 deaths from CC, corresponding to an average standardized mortality rate without correction of deaths of 10.57/100,000. After correcting deaths for poor certification of records, 17,288 deaths were recorded (average standardized mortality rate of 15.47/100,000) and, after correcting for underreporting of records, 19,260 deaths were recorded (average standardized mortality rate of 17.23/100,000).

In all the states, the stage of correcting the poor certification of deaths that most contributed to the increase in the number of records was the proportional redistribution of those classified as uterine cancer by part unspecified. The number of deaths classified in this way was higher than the number of records declared as cancer of the uterine body. The highest percentage increases in mortality rates, both for poor quality certification and underreporting, occurred in the 1980s and 1990s (Table 1).

From the 2000s onwards, there was a reduction in standardized mortality rates in all age groups, with the highest rates observed in women aged ≥80 years and the lowest in those aged 20-24 years. In the last five-year period, they increased again in the 20-24 to 45-49 age groups (Figure 1A). The evaluation, according to cohort and age group, showed a decrease from the 1900 (age group ≥80 years) to the 1975 generation (age group 40-44 years). In the 1980-1984 to 1995-1999 cohorts (20-24 to 30-34 age groups), there was a reduction with a subsequent increase (Figure 1B).

Similarly, there was a positive gradient in the average mortality rates from CC with advancing age in all the states, with the highest magnitude in the MS and the lowest in the DF (Figure 2A), and a reduction in the rates of the oldest generations in relation to the youngest (Figure 2B).

The age-period-cohort models fitted the data better as they had lower residual deviance and a p-value <0.001 (Table 2), and were therefore chosen to estimate the RR and 95%CI.

After estimating the effects, the complete age-period-cohort model showed that mortality rates adjusted for the cohort and period effects increased progressively with advancing age throughout the Center-West and in the respective states (Table 3). About the period effect adjusted for the effect of age and cohort, considering the reference period and the entire Center-West region, there was an increase in the risk of death in 2000-2004 (RR=1.09; 95%CI: 1.06-1.12) and a reduction in this risk in 2010-2014 (RR=0.93; 95%CI: 0.90-0.95). In the states specifically, there was a reduction in the risk of death from CC in the Federal District in 2015-2019 (RR=0.91; 95%CI: 0.85-0.98), in MS in 2010-2014 (RR=0.89; 95%CI: 0.84-0.95) and in MT in the last

Table 1 - Standardized cervical cancer mortality rates (per 100,000 women), by five-year period, Center-West, Brazil, 1980-2019

Mortality rate	5-year period								TMP
	1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2019	
Federal District									
No correction	20.82	18.16	15.72	12.74	10.44	9.32	8.77	7.99	12.43
Corrected for poor certification	26.00	24.81	25.24	20.11	16.30	13.09	10.61	8.97	14.31
Corrected for underreporting	26.00	24.81	25.24	20.11	16.30	13.09	10.61	8.97	14.31
Goiás									
No correction	13.94	12.87	10.50	11.96	10.73	9.06	8.62	9.06	10.45
Corrected for poor certification	23.02	20.47	18.26	17.65	15.74	13.00	11.93	13.00	15.26
Corrected for underreporting	23.98	21.32	19.85	19.18	16.93	13.98	12.83	13.98	16.36
Mato Grosso do Sul									
No correction	13.20	13.55	13.05	12.10	12.87	13.18	10.62	10.96	12.16
Corrected for poor certification	24.67	25.20	24.65	21.71	21.04	18.63	13.41	14.39	18.40
Corrected for underreporting	24.92	25.45	24.65	21.71	21.92	19.41	13.97	14.99	18.89
Mato Grosso									
No correction	6.83	9.40	8.32	13.30	10.43	12.73	9.45	9.12	9.86
Corrected for poor certification	12.60	17.28	14.96	21.40	18.11	17.73	13.36	12.13	14.97
Corrected for underreporting	13.12	18.00	15.43	22.06	19.06	18.66	14.07	12.77	16.03
Center-West									
No correction	13.73	13.29	11.46	12.33	11.02	10.53	9.20	9.32	10.57
Corrected for poor certification	22.16	21.57	20.08	19.48	17.27	14.91	12.23	11.87	15.47
Corrected for underreporting	27.50	26.76	21.77	21.13	18.84	16.26	13.35	12.95	17.23

Note: Average standardized mortality rate.

two five-year periods. On the other hand, after a reduction in risk in 2005-2014, there was an increase in risk in GO in 2015-2019 (RR=1.05; 95%CI: 1.01-1.10) (Table 3).

Regarding the cohort effect adjusted for age and period in the Center-West, there was a constant reduction in the risk of death from older cohorts to younger ones, with RR ranging from 2.26 (95%CI: 2.08-2.46) in the 1900-1904 cohort to 0.61 (95%CI: 0.55-0.67) in the 1995-1999 cohort. Similar results were observed in all the states except MT, where the increase in risk for the older cohorts was not significant. In this state, the RR reduction only occurred in the 1955-1969 generations ($RR_{1955-1959}$=0.91, 95%CI: 0.85-0.91; $RR_{1960-1964}$=0.88, 95%CI: 0.81-0.96; $RR_{1965-1969}$=0.90, 95%CI: 0.83-0.98), with a non-significant increase from the 1975-1979 generation onwards (Table 3).

DISCUSSION

The age-period-cohort model was the best fit to the data for the entire Center-West region. The age effect indicates a progressive increase in standardized mortality rates from CC as age advances. The effect of the period adjusted for age and cohort shows a reduction in the risk of death in the DF in 2015-2019, in MS in 2010-2014,

Figure 1 - Standardized mortality rates from cervical cancer, by cohort and age group, Center-West, Brazil, 1980-2019

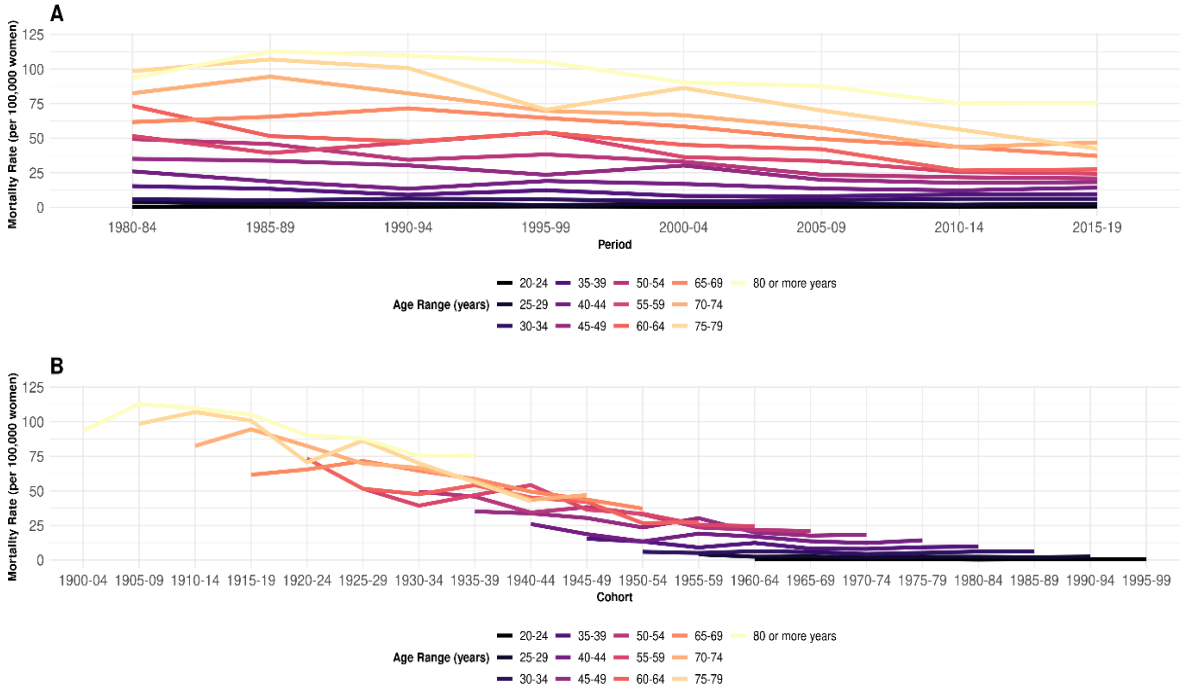
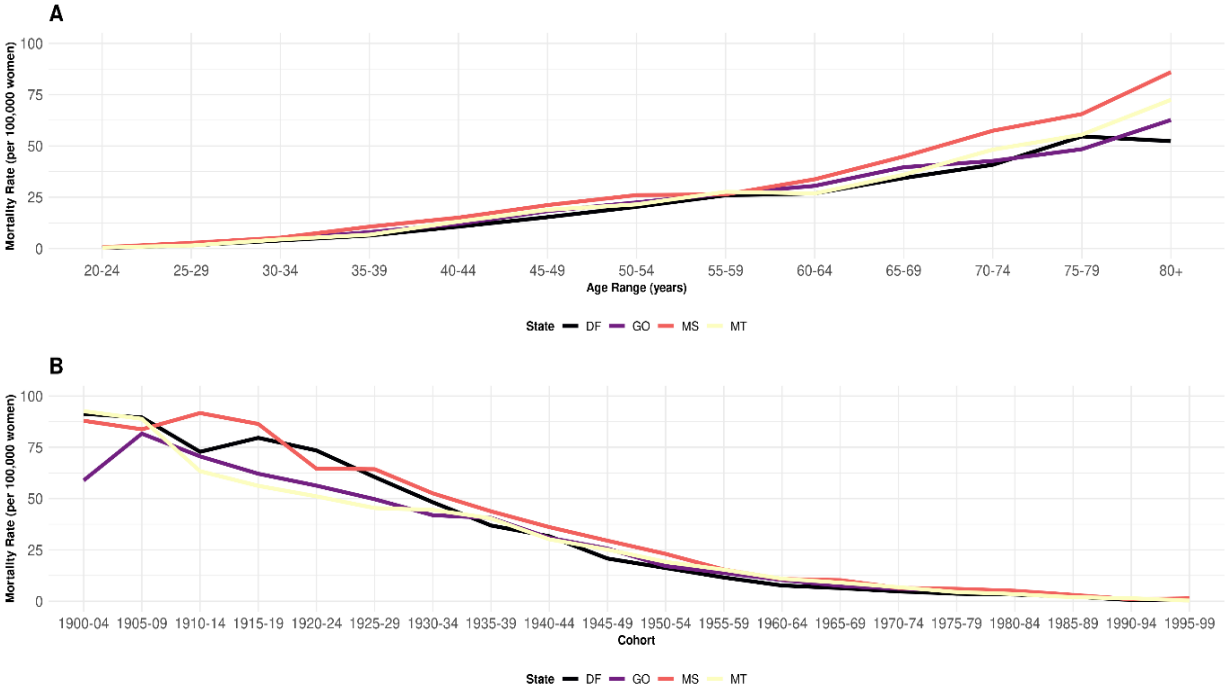


Figure 2 - Standardized mortality rates from cervical cancer, by age group and cohort, Center-West, Brazil, 1980-2019



Note: Federal District (DF); Goiás (GO); Mato Grosso do Sul (MS); Mato Grosso (MT).

Table 2 - Sequential construction of age-period-cohort models for cervical cancer mortality, Center-West, Brazil, 1980-2019

Models	Degrees of freedom	*Residual deviance*	p value
Center-West			
Age	99	1,753.13	
Age-drift[a]	98	704.73	<0.001
Age-cohort	95	588.78	<0.001
Age-period-cohort	92	537.37	<0.001
Age-period	95	663.22	<0.001
Age-drift[b]	98	704.73	<0.001
Federal District			
Age	99	579.73	
Age-drift[a]	98	194.01	<0.001
Age-cohort	95	153.05	<0.001
Age-period-cohort	92	134.44	<0.001
Age-period	95	183.13	<0.001
Age-drift[b]	98	194.01	<0.001
Goiás			
Age	99	667.62	
Age-drift[a]	98	328.25	<0.001
Age-cohort	95	274.84	<0.001
Age-period-cohort	92	263.10	<0.001
Age-period	95	313.22	<0.001
Age-drift[b]	98	328.25	<0.001
Mato Grosso do Sul			
Age	99	384.70	
Age-drift[a]	98	220.18	<0.001
Age-cohort	95	205.38	<0.001
Age-period-cohort	92	183.15	<0.001
Age-period	95	200.39	<0.001
Age-drift[b]	98	220.18	<0.001
Mato Grosso			
Age	99	293.33	
Age-drift[a]	98	267.26	<0.001
Age-cohort	95	261.81	<0.001
Age-period-cohort	92	182.38	<0.001
Age-period	95	190.90	<0.001
Age-drift[b]	98	267.26	<0.001

Note: [a] Age-drift: linear trend of age-specific rates, which is equal to the sum of the age and period slopes ($\alpha_L+\beta_L$), where α_L and β_L are the linear trends of age and period, respectively; [b] Age-drift: represents the longitudinal trend of age, which is equal to the sum of the period and cohort slopes ($\beta_L+\gamma_L$), where β_L and γ_L are the linear trends of period and cohort, respectively.

Table 3 - Age-period-cohort effect on standardized cervical cancer mortality rates, Center-West, Brazil, 1980-2019

Continue...

	Relative Risk (CI95%)				
Age	**Center-West**	**Federal District**	**Goiás**	**Mato Grosso do Sul**	**Mato Grosso**
20-24	2.11 (1.94-2.29)	1.80 (1.42-2.86)	1.67 (1.44-1.93)	2.32 (1.91-2.82)	0.75 (0.59-0.96)
25-29	3.83 (3.59-4.09)	3.27 (2.73-3.91)	3.01 (2.70-3.37)	4.06 (3.49-4.72)	1.57 (1.30-1.88)
30-34	6.95 (6.63-7.29)	5.93 (5.21-6.75)	5.45 (5.03-5.90)	7.11 (6.37-7.94)	3.26 (2.86-3.72)
35-39	12.62 (12.20-13.06)	10.77 (9.79-11.84)	9.84 (9.29-10.43)	12.44 (11.48-13.49)	6.78 (6.18-7.45)
40-44	22.24 (21.56-22.94)	18.88 (17.25-20.66)	17.27 (16.39-18.20)	21.08 (19.56-22.71)	13.56 (12.42-14.80)
45-49	32.76 (31.81-33.73)	26.93 (24.86-29.17)	25.38 (24.15-26.67)	29.39 (27.37-31.56)	21.38 (19.75-23.16)
50-54	36.24 (35.28-37.22)	28.33 (29.52-30.92)	28.08 (26.81-29.40)	30.19 (28.26-32.25)	23.91 (21.90-26.09)
55-59	35.91 (34.78-37.08)	28.38 (26.20-30.74)	27.80 (26.33-29.36)	28.51 (26.33-30.88)	26.11 (24.06-28.33)
60-64	38.59 (37.54-39.67)	28.71 (26.49-31.11)	29.65 (28.30-31.06)	31.22 (29.17-33.42)	30.14 (27.65-32.85)
65-69	43.47 (42.04-44.95)	28.87 (26.42-31.56)	32.70 (30.90-34.60)	37.37 (34.47-40.51)	36.27 (32.9-39.96)
70-74	47.79 (46.25-49.39)	28.86 (26.55-31.38)	35.18 (33.33-37.14)	43.92 (40.57-47.56)	44.88 (40.77-49.39)
75-79	51.43 (49.68-53.23)	28.77 (26.07-31.74)	37.28 (35.14-39.55)	50.51 (46.60-54.76)	56.30 (50.34-62.97)
≥80	55.14 (52.41-58.00)	28.65 (24.91-32.96)	39.40 (36.12-42.97)	57.89 (51.58-64.96)	70.80 (60.84-82.39)
	Relative Risk (CI95%)				
Period	**Center-West**	**Federal District**	**Goiás**	**Mato Grosso do Sul**	**Mato Grosso**
1980-1984	0.95 (0.93-0.98)	0.86 (0.80-0.92)	0.99 (0.94-1.03)	0.94 (0.89-1.00)	0.78 (0.73-0.84)
1985-1989	0.98 (0.97-0.99)	0.98 (0.96-1.00)	0.99 (0.98-1.00)	1.01 (0.97-1.07)	0.92 (0.91-0.94)
1990-1994	1.01 (0.98-1.03)	1.10 (1.03-1.17)	1.01 (0.96-1.04)	0.89 (0.84-0.94)	1.09 (1.04-1.14)
1995-1999			Reference		
2000-2004	1.09 (1.06-1.12)	1.06 (0.98-1.14)	1.03 (0.98-1.08)	1.15 (1.08-1.23)	1.26 (1.19-1.33)
2005-2009	1.02 (0.98-1.02)	1.04 (0.95-1.06)	0.96 (0.93-0.99)	1.01 (0.97-1.07)	1.26 (1.19-1.33)
2010-2014	0.93 (0.90-0.95)	0.96 (0.90-1.03)	0.93 (0.90-0.97)	0.89 (0.84-0.94)	0.90 (0.84-0.96)
2015-2019	0.99 (0.96-1.01)	0.91 (0.84-0.98)	1.04 (1.01-1.09)	0.98 (0.91-1.04)	0.79 (0.74-0.84)
	Relative Risk (CI95%)				
Cohort	**Center-West**	**Federal District**	**Goiás**	**Mato Grosso do Sul**	**Mato Grosso**
1900-1904	2.26 (2.08-2.46)	4.29 (3.38-5.45)	2.19 (1.90-2.51)	2.13 (1.74-2.60)	1.04 (0.80-1.37)
1905-1909	2.08 (1.94-5.22)	3.66 (3.01-4.46)	2.02 (1.80-2.27)	1.96 (1.67-2.31)	1.0 5 (0.83-1.31)
1910-1914	1.91 (1.81-20.02)	3.13 (2.68-3.66)	1.87 (1.70-2.04)	1.81 (1.59-2.06)	1.04 (0.86-1.26)
1915-1919	1.75 (1.68-1.82)	2.67 (2.37-3.01)	1.72 (1.61-1.85)	1.66 (1.51-1.84)	1.04 (0.89-1.22)
1920-1924	1.61 (1.56-1.66)	2.28 (2.09-2.49)	1.59 (1.51-1.68)	1.53 (1.42-1.66)	1.04 (0.92-1.80)
1925-1929	1.48 (1.44-1.52)	1.95 (1.80-2.10)	1.74 (1.41-1.54)	1.42 (1.31-1.52)	1.04 (0.94-1.15)
1930-1934	1.36 (1.32-1.40)	1.66 (1.52-1.80)	1.36 (1.29-1.43)	1.31 (1.21-1.41)	1.03 (0.94-1.15)
1935-1939	1.24 (1.21-1.27)	1.39 (1.28-1.51)	1.20 (1.19-1.31)	1.22 (1.15-1.31)	1.03 (0.94-1.14)
1940-1944	1.12 (1.09-1.14)	1.13 (1.06-1.21)	1.13 (1.08-1.17)	1.14 (1.09-1.22)	1.02 (0.94-1.11)
1945-1949	0.98 (0.92-1.01)	0.90 (0.83-0.98)	0.99 (0.94-1.04)	1.04 (0.97-1.11)	0.99 (0.93-1.07)
1950-1954			Reference		
1955-1959	0.72 (0.70-0.74)	0.57 (0.53-0.61)	0.71 (0.68-0.75)	0.74 (0.69-0.80)	0.91 (0.85-0.98)
1960-1964	0.66 (0.64-0.68)	0.48 (0.44-0.52)	0.65 (0.62-0.69)	0.67 (0.63-0.73)	0.88 (0.81-0.96)
1965-1969	0.64 (0.62-0.66)	0.48 (0.44-0.52)	0.63 (0.60-0.67)	0.65 (0.60-0.69)	0.90 (0.83-0.98)
1970-1974	0.63 (0.62-0.66)	0.48 (0.42-0.53)	0.63 (0.60-0.66)	0.63 (0.59-0.68)	0.96 (0.88-1.04)
1975-1979	0.63 (0.60-0.65)	0.47 (0.42-0.54)	0.63 (0.58-0.68)	0.63 (0.56-0.69)	1.02 (0.91-1.14)

Table 3 - Age-period-cohort effect on standardized cervical cancer mortality rates, Center-West, Brazil, 1980-2019

Conclusion.

	Relative Risk (CI95%)				
Cohort	Center-West	Federal District	Goiás	Mato Grosso do Sul	Mato Grosso
1980-1984	0.62 (0.59-0.67)	0.47 (0.40-0.55)	0.63 (0.57-0.69)	0.62 (0.54-0.72)	1.08 (0.92-1.27)
1985-1989	0.62 (0.58-0.67)	0.47 (0.38-0.58)	0.63 (0.50-0.71)	0.62 (0.52-0.74)	1.15(0.94-1.42)
1990-1994	0.62 (0.56-0.68)	0.46 (0.36-0.60)	0.63 (0.54-0.73)	0.61 (0.49-0.76)	1.23 (0.94-1.60)
1995-1999	0.61 (0.55-0.67)	0.46 (0.34-0.63)	0.63 (0.53-0.76)	0.60 (0.46-0.78)	1.30 (0.95-1.79)

Note: Confidence interval of 95% (CI95%).

and in MT in 2010-2019, as well as an increase in GO in the period 2015-2019. The cohort effect adjusted for age and period shows an increase in the risk of death for those born before 1950-1954 and a reduction in the generations from 1955-1959 onwards.

The study also shows a high proportion of deaths classified as unspecified and low coverage of death records in the 1980s and 1990s, similar to what is observed in other regions of Brazil[5-8]. This finding suggests low specificity in the diagnosis of CC, which may be related to the low coverage of the screening program in the country (<80% in 57.7% of states)[24] and limitations in the quality of the collection and evaluation of Pap smears and poor completion of death certificates[8], especially in regions of high socioeconomic vulnerability[8,25,26]. In addition, the accurate diagnosis of precursor lesions and CC does not always guarantee the start or continuity of treatment, since there are weaknesses in access to specialized oncology services, which are concentrated in the capitals and metropolitan regions of southern and southeastern Brazil[27-29], favoring diagnoses at an advanced stage or in a situation where it is not possible to discriminate the exact topography of the tumor, whether on the cervix or the body of the uterus[27-30].

Inequalities in cytopathological test coverage and access to the cancer care network may contribute to the differences in incidence and mortality observed between Brazilian regions[4-8]. Despite the reduction in the magnitude of mortality rates from CC, the states in the Center-West still maintain rates higher than those accepted by the World Health Organization (5.0 deaths/100,000), with approximately 16.0 deaths/100,000 in the period 2000-2015[10], similar to those in countries without a universal and free screening program[1].

The states in the Center-West region showed differences in the magnitude of the rates and the time trend of mortality from CC. The highest rates were in MS and the lowest in the DF. There was a reduction in the risk of death in the last two five-year periods in MT and an increase in the last five-year period in GO. This difference may be due to the interaction of the following conditions: presence, time of implementation and quality of screening programs, access to timely treatment, prevalence of risk and protective factors for CC in the population, and access to therapeutic innovations for advanced disease[1,4,5-8,30-32]. It should be noted that these conditions have different impacts, depending on the age group, generation of birth, and socio-economic conditions and access to health care in the place of residence[6,7,30-32].

The age effect found is related to the physiological changes resulting from aging and exposure to risk and protective factors for CC throughout life[5-8,11-14,33-39]. In the Center-West and its respective states, mortality rates from CC increased progressively with age, as observed in states in other regions of Brazil[6,7] and in more developed countries[33-39]. It is believed that this is due to the lower coverage of Pap smears in women aged 50 and over[1,23,24,33]. In 2013, there was a progressive reduction in the coverage of this test in Brazil in women aged 35-44, ranging from 83.2% (95%CI: 81.6-84.6) to 71.0% in women aged 55-64 (95%CI: 68.7-73.3)[24]. This reduction is partly due to the lower frequency of gynecological consultations after the reproductive period, because women's health care policies still focus more on the pregnancy-puerperal period[23,24,26-28]. In this context, previous studies have identified that the chances of being diagnosed with advanced-stage CC increase as women get older[27-29].

The period effect represents structural changes that affect all age groups simultaneously, such as health policies and therapeutic innovations to prevent a certain disease[12-14]. In this sense, a period effect is expected after the implementation of prevention and control programs for CC with high coverage and quality, which promote a reduction in the risk of death from this neoplasm years after its implementation due to the increased diagnosis of precursor lesions and early-stage disease[1,31,37], as observed in developed countries[33-39]. The reduction in the risk of death in most of the states in the Center-West in the last five-year period of the historical series is similar to that observed in states in the South and Southeast

regions of Brazil[7]. It is believed that the reduction in mortality rates and the risk of death in the 2000s are related to the expansion of primary care and the cancer care network in the same decade[7,8]. However, these advances in health policies were not able to reduce the likelihood of dying from CC in GO, which had a similar profile to the states in the Northeast (Maranhão and Piauí) and North regions of Brazil[7,8].

In the Center-West and its respective states, the risk of death increased among those born before 1950-1954 and decreased among those born after the 1950s. These findings corroborate those observed in the states in the South and Southeast of Brazil and in developed countries[6,7,33-39]. This increased risk in older generations is due to their lower exposure to the main preventive measure for CC, the cytological examination[1,23,24], thus favoring diagnosis at an advanced stage[27-29]. It is worth mentioning that the higher prevalence of comorbidities in older women hinders the use of therapeutic interventions based on the use of platinum (Cisplatin), radiotherapy and brachytherapy in more advanced cases, for which surgery is not the standard treatment[33-39]. In addition, depending on their general condition and presence of comorbidities, some women may not be eligible for surgery due to the high surgical risk or for chemotherapy treatment, such as in the presence of altered renal function[33,35,37].

On the other hand, the reduction in the risk of death in the younger cohorts in the Center-West and respective states may be related to the interaction between the effects of age and period[31-37]. This is because, although they have been more exposed to risk factors such as early initiation of sexual activities, use of oral contraceptives, smoking, and a greater number of sexual partners[33-39], the generations born in recent decades have greater access to health services following the advent of the Unified Health System (SUS), the expansion of primary care, and the cancer care network. Therefore, they are more likely to know about CC and its preventive measures, enabling greater coverage of cytological examination[23,24] and a lower chance of diagnosis at an advanced stage, which increases their survival compared to older cohorts[27-29].

Despite the progress observed in mortality from CC in the states of the Center-West, high mortality rates have persisted over the last five years, signaling the presence of barriers in the National Cervical Cancer Control Program in the region. The World Health Organization urges countries to reduce new cases by 40% by 2050 by adopting measures that include screening 70% of all women before the age of 35 and re-examining them before the age of 45 using high-precision DNA-based HPV tests, and treating 90% of those diagnosed with invasive cancer[1]. Brazil has made a commitment to eliminate CC, but in order to do so, it needs to make efforts to correct the limitations of the screening program and the fragmentation of the health services network.

The study has some limitations, such as the high percentage of garbage codes and the low coverage of death records. These were minimized by correcting for poor certification of death records, which allowed for more reliable estimates[5-8]. Another limitation is the linear relationship between the three time effects (age, period, and cohort). This means that we can determine any of the factors based on information from the other two, i.e. Age=Period-Cohort; Cohort=Period-Age; Period=Age+Cohort. This perfect linear relationship between the temporal factors prevents the estimation of the complete model (age-period-cohort) and is known as the non-identifiability problem[12-14]. Many methodologies have been proposed to correct this limitation, but there is no consensus in the literature on the best methodological strategy to use. Therefore, this study adopted the methodology most frequently recommended by authors who have established comparisons between classic statistical methods, i.e. estimable functions[12-14].

The knowledge produced in this investigation implies a recommendation for greater focus on health actions aimed at women aged 50-64 in order to increase the coverage of cytological examinations in this age group.

The importance of ensuring the principle of equity in the SUS is emphasized, strengthening CC prevention and control actions in women of cohorts and ages at greater risk of dying from this cause. Finally, there is a need for future studies on the spatial-temporal evaluation of mortality from CC and the evaluation of quality indicators of the National Program for Cervical Cancer Control and their correlation with sociodemographic and health indicators in the municipalities of the Center-West.

CONCLUSION

In this time series from 1980 to 2019, in which 19,260 deaths were analyzed in the Center-West region of Brazil, corresponding to an average standardized mortality rate of 17.23/100,000 women, the age-period-cohort effect on mortality is evident, in which there is a progressive increase in mortality rates as age advances; a reduction in the risk of death in the Federal District (2015-2019), Mato Grosso do Sul (2010-2014), and Mato Grosso (2010-2019), and an increase in Goiás (2015-2019). In addition, there was an increase in the

risk of death for those born before 1950-1954 and a reduction in generations from 1955-1959 onwards.

The reduction in the risk of death in the last five years and in the youngest cohorts has not been able to reduce mortality rates, with rates remaining high in all age groups.

Funding

This study received financial support from the National Council for Scientific and Technological Development (CNPq-425819/2018-3) and the Coordination for the Improvement of Higher Education Personnel (CAPES, Funding Code 001).

Conflicts of interest

None.

Author contributions - CRediT

KCM: conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; and writing - review & editing.
TCS: conceptualization; data curation; formal analysis; investigation; methodology; resources; software; supervision; validation; visualization; writing – original draft; and writing - review & editing.
RTJ: investigation; software; supervision; validation; visualization; writing – original draft; and writing - review & editing.
ESOD: investigation; software; supervision; validation; visualization; writing – original draft; and writing - review & editing.
CMFPS: data curation; formal analysis; methodology; writing – original draft; and writing - review & editing.
CM: conceptualization; investigation; resources; software; supervision; validation; visualization; writing – original draft; and writing - review & editing.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 Feb;71(3):209-49. https://doi.org/10.3322/caac.21660

2. Bergman H, Buckley BS, Villanueva G, Petkovic J, Garritty C, Lutje V, et al. Comparison of different human papillomavirus (HPV) vaccine types and dose schedules for prevention of HPV-related disease in females and males. Cochrane Database Syst Rev. 2019 Nov;(11):CD013479. https://doi.org/10.1002/14651858.cd013479

3. Lemp JM, De Neve JW, Bussmann H, Chen S, Manne-Goehler J, Theilmann M, et al. Lifetime prevalence of cervical cancer screening in 55 low- and middle-income countries. JAMA. 2020;324(15):1532-42. https://doi.org/10.1001/jama.2020.16244

4. Instituto Nacional de Câncer. Estimativa 2023. Incidência do câncer no Brasil [Internet]. Rio de Janeiro: INCA; 2020 [cited 2022 July 03]. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2023.pdf

5. Silva GA, Jardim BC, Ferreira VM, Junger WL, Girianelli VR. Cancer mortality in the Capitals and in the interior of Brazil: a four-decade analysis. Rev Saude Publica. 2020 Dec;54:1-19. https://doi.org/10.11606/s1518-8787.2020054002255

6. Meira KC, Silva GWS, Santos J, Guimarães RM, Souza DLB, Ribeiro GPC, et al. Analysis of the effects of the age-period-birth cohort on cervical cancer mortality in the Brazilian Northeast. Plos One. 2020 Feb;15(2):e0226258. https://doi.org/10.1371/journal.pone.0226258

7. Meira KC, Magnago C, Mendonça AB, Duarte SFS, Freitas PHO, Santos J, et al. Inequalities in temporal effects on cervical cancer mortality in states in different geographic regions of Brazil: an ecological study. Int J Environ Res Public Health. 2022 May;19(9):5591. https://doi.org/10.3390/ijerph19095591

8. Girianelli VR, Gamarra CJ, Silva GA. Disparities in cervical and breast cancer mortality in Brazil. Rev Saúde Pública. 2014 June;48(3):459-67. https://doi.org/10.1590/S0034-8910.2014048005214

9. Reis NVS, Andrade BB, Guerra MR, Teixeira MTB, Malta DC, Passos VMA. The global burden of disease study estimates of brazil's cervical cancer burden. Annals of Global Health. 2020 June;86(1):1-12. https://doi.org/10.5334/aogh.2756

10. Rodrigues NCP, O'Dwyer G, Andrade MKN, Monteiro DLM, Reis IN, Frossard VC, et al. Mortality by colon, lung, esophagus, prostate, cervix and breast cancers in Brazilian capitals, 2000-2015: a multilevel analysis. Ciênc. saúde coletiva. 2022 Mar;27(3):1157-70. https://doi.org/10.1590/1413-81232022273.47092020

11. Instituto Nacional de Câncer. Atlas On-line de Mortalidade [Internet]. Rio de Janeiro: INCA; 2023. [cited 2023 Oct 23]. Available from: https://www.inca.gov.br/app/mortalidade

12. Yang Y, Land KC. Age-period-cohort analysis: new models, methods, and empirical applications. Boca Raton (NW): Chapman & Hall/CRC; 2013.

13. Holford TR. Approaches to fitting age-period-cohort models with unequal intervals. Stat Med. 2006;25(6):977-93. https://doi.org/10.1002/sim.2253

14. Robertson C, Gandini S, Boyle P. Age-period-cohort models: a comparative study of available methodologies. J Clin Epidemiol. 1999 June;52(6):569-83. https://doi.org/10.1016/s0895-4356(99)00033-5

15. Brasil. Ministério da Saúde. Portaria nº 874, de 16 de maio de 2013. Institui a Política Nacional para a Prevenção e Controle do Câncer na Rede de Atenção à Saúde das Pessoas com Doenças Crônicas no âmbito do Sistema Único de Saúde (SUS). Diário Oficial da União; 2013. [cited 2023 Oct 23]. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/gm/2013/prt0874_16_05_2013.html

16. Ministério da Saúde. Plano de Ações Estratégicas para o Enfrentamento das Doenças Crônicas e Agravos não Transmissíveis no Brasil 2021-2030. Brasília: Ministério da Saúde; 2021 [cited 2023 Oct 23]. Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/svsa/doencas-cronicas-nao-transmissiveis-dcnt/09-plano-de-dant-2022_2030.pdf

17. Organização Mundial da Saúde. Manual da classificação estatística internacional de doenças, lesões e causas de óbito: 9a rev. São Paulo: Centro da OMS para a Classificação de Doenças em Português/MS/USP/ OPAS; 1985. v 1.

18. Organização Mundial da Saúde. Classificação Estatística Internacional de Doenças e Problemas Relacionados à Saúde: CID-10 Décima revisão. Trad. do Centro Colaborador da OMS para a Classificação de Doenças em Português. 3 ed. São Paulo: EDUSP; 1996.

19. Instituto Brasileiro de Geografia e Estatística. Sistema IBGE de recuperação automática [Internet]. Rio de Janeiro: IBGE; 2022. Available from: https://sidra.ibge.gov.br/home/pimpfrg/centroeste

20. Queiroz BL, Freire FHMA, Gonzaga MR, Lima EEC. Estimativas do grau de cobertura e da mortalidade adulta (45q15) para as unidades da federação no Brasil entre 1980 e 2010. Rev Bras Epidemiol. 2017 May;20(Suppl 1):21-33. https://doi.org/10.1590/1980-5497201700050003

21. Doll R, Payne PM, Waterhouse JAH. Cancer incidence in five countries. International Union Against Cancer. Berlin: Springer-Verla; 1966.

22. Carstensen B. Age-period-cohort models for the Lexis diagram. Statist Med. 2007;26(15):3018-45. https://doi.org/10.1002/sim.2764

23. Ministério da Saúde, Instituto Nacional de Câncer José Gomes da Silva (INCA). Viva Mulher 20 anos: história e memória do controle do câncer do colo do útero e de mama no Brasil. Catálogo de documentos [Internet]. Rio de Janeiro: INCA; 2018. [cited 2023 Nov 02]. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files/media/document/programa_viva_mullher_2018_completo.pdf

24. Instituto Nacional de Câncer. Controle do Câncer do Colo do Útero [Internet]. Rio de Janeiro: INCA; 2022. [cited 2023 Oct 18]. Available from: http://www.inca.gov.br/utero

25. Costa RFA, Longatto-Filho A, Pinheiro C, Zeferino LC, Fregnani JH. Historical Analysis of the Brazilian Cervical Cancer Screening Program from 2006 to 2013: A Time for Reflection. PLoS One. 2015;10(9):e0138945. https://doi.org/10.1371/journal.pone.0138945

26. Ribeiro CM, Silva GA. Avaliação da produção de procedimentos da linha de cuidado do câncer do colo do útero no Sistema Único de Saúde do Brasil em 2015. Epidemiol Serv Saude. 2018; 27(1):e20172124. https://doi.org/10.5123/s1679-49742018000100004

27. Thuler LCS, Aguiar SS, Bergmann A. Determinantes do diagnóstico em estádio avançado do câncer do colo do útero no Brasil. Rev Bras Ginecol Obstet. 2014 June;36(6):237-43. https://doi.org/10.1590/s0100-720320140005010

28. Oliveira NPD. Desigualdades no diagnóstico e mortalidade por câncer de mama e colo do útero no Brasil [Tese na internet]. [Natal]: Universidade Federal do Rio Grande do Norte; 2020 [cited 2022 Feb 01]. Available from: https://repositorio.ufrn.br/jspui/handle/123456789/30744

29. Renna Júnior NL, Silva GA. Tendências temporais e fatores associados ao diagnóstico em estágio avançado de câncer do colo uterino: análise dos dados dos registros hospitalares de câncer no Brasil, 2000-2012. Epidemiol Serv Saude. 2018;27(2):e2017285. https://doi.org/10.5123/S1679-49742018000200003

30. Meira KC, Silva GA, Silva CMFP, Valente JG. Efeito idade-período-coorte na mortalidade por câncer do colo uterino. Rev Saúde Pública. 2013 June;47(2):1-8. https://doi.org/10.1590/S0034-8910.2013047004253

31. Nascimento MI, Massahud FC, Barbosa NG, Lopes CD, Rodrigues VC. Premature mortality due to cervical cancer: study of interrupted time series. Rev Saude Publica. 2020;54:1-10. https://doi.org/10.11606/s1518-8787.2020054002528

32. Vaccarella S, Lortet-Tieulent J, Plummer M, Franceschi S, Bray F. Worldwide trends in cervical cancer incidence: impact of screening against changes in disease risk factors. Eur J Cancer. 2013 Oct;49(15):3262-73. https://doi.org/10.1016/j.ejca.2013.04.024

33. Wang J, Lee H, Xue Z, Wang L, Bai Z. Temporal trends of common female malignances on breast, cervical, and ovarian cancer mortality in Japan, Republic of Korea and Singapore: application of the age-period-cohort model. Biomed Res Int. 2018 Mar 21;2018:5307459. https://doi.org/10.1155/2018/5307459

34. Arbyn M, Raifu AO, Weiderpass E, Bray F, Anttila A. Trends of cervical cancer mortality in the member states of the European Union. Eur J Cancer. 2009 Oct;45(15):2640-8. https://doi.org/10.1016/j.ejca.2009.07.018

35. Bray F, Carstensen B, Moller H, Zappa M, Zakelj MP, Lawrence G, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol

Biomarkers Prev. 2005 Sep;14(9):2191-99. https://doi.org/10.1158/1055-9965.epi-05-0231

36. Small W Junior, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, et al. Cervical cancer: a global health crisis. Cancer. 2017 May;123(13):2404-12. https://doi.org/10.1002/cncr.30667

37. Ojamaa K, Innos K, Baburin A, Everaus H, Veerus P. Trends in cervical cancer incidence and survival in Estonia from 1995 to 2014. BMC Cancer. 2018 Nov;18:1075. https://doi.org/10.1186/s12885-018-5006-1

38. Moon EK, Oh CM, Won YJ, Lee JK, Jung KW, Cho H, et al. Trends and age-period-cohort effects on the incidence and mortality rate of cervical cancer in Korea. Cancer Res Treat. 2017;49(2):526-33. https://doi.org/10.4143/crt.2016.316

39. Utada M, Chernyavskiy P, Lee WJ, Franceschi S., Sauvaget C, Gonzalez AB, et al. Increasing risk of uterine cervical cancer among young Japanese women: comparison of incidence trends in Japan, South Korea and Japanese-Americans between 1985 and 2012. Int J Cancer. 2019;144(9):2144-52. https://doi.org/10.1002/ijc.32014