



Time series and risk factors associated with mortality in women with cervical cancer from 2000 to 2021

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ABSTRACT

Introduction: Cervical cancer is a significant public health problem worldwide. The development of cervical neoplasms is associated with persistent infection by oncogenic subtypes of the HPV virus, which are responsible for around 70% of cervical cancers. A study carried out in Brazil between 2002 and 2021 recorded 133,429 deaths from cervical cancer.

Methodology: An observational, retrospective, cross-sectional, quantitative study was carried out using data collected by the Cancer Registry Service of the Haroldo Juaçaba Hospital/Ceará Cancer Institute (HHJ/ICC) over 22 years.

Results: The sample consisted of 9096 women. The mean age was 51.4 ± 15.5 , ranging from 15 to 100, with a median age of 60 years. Median overall survival was 59.77. The most frequent histological type was squamous cell carcinoma, with 8023 (88.2 %) cases. Around 25 % of patients ($n = 2270$) entered the service with stage 4A. The most common treatment was radiotherapy combined with chemotherapy ($n = 3270$, 35.9 %), followed by surgical removal ($n = 1909$, 21.0 %). In multivariate analysis, age ($p = 0.019$), race ($p = 0.016$), low level of education ($p < 0.001$), tumor location, staging ($p < 0.001$), and treatment ($p = 0.011$) were risk factors independently associated with a higher chance of death in the sample studied.

Conclusion: The sociodemographic characteristics of mortality from cervical cancer in patients followed up at the Haroldo Juaçaba Hospital (HHJ/ICC) highlight the higher frequency of deaths in women aged over 60, indigenous and black, with low levels of education, as well as clinical variables related to tumor location, staging and type of treatment.

1. Introduction

Cervical cancer is a significant public health problem worldwide. According to the World Health Organization (WHO), in 2020, more than 500,000 women were diagnosed, and almost 342,000 died. Approximately 80 % of cases occur in underdeveloped and developing countries due to the lack of an adequate and effective screening program (Sarmiento, 2022).

Currently, cervical cancer is considered to be eradicable through vaccination against the most prevalent types of oncogenic HPV and the screening and treatment of precursor lesions. Lesions are detected by cervical cytopathology tests, which should be carried out every three years on all women who have started having sex and/or are aged 25 or

over (Nacional, 2023).

In Brazil, it is estimated to be the third most common malignant neoplasm among women. For each year of the 2023–2025 triennium, 17,010 new cases were calculated for the country, corresponding to an estimated risk of 15.38 cases per 100,000 women. The Northeast region ranks second in incidence, with a relevance of 17.59 cases per 100,000 women (Nacional, 2023).

The most common histological type is Squamous Cell Carcinoma (SCC), which accounts for approximately 75 % to 80 % of all cervical cancers, while adenocarcinoma accounts for approximately 20 % (Abu-Rustum, 2020 Jun).

The development of cervical neoplasms is associated with persistent infection by oncogenic subtypes of the HPV (Human Papillomavirus)

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virus, especially HPV-16 and HPV-18, which are responsible for around 70 % of cervical cancers. Although it is a necessary factor, HPV infection alone is not sufficient for the development of uterine cervical cancer, as it is a widespread infection among women all over the world (Bruni, et al., 2021).

In addition to aspects related to HPV infection, factors linked to immunity, genetics, and sexual behavior can also influence the appearance of precursor lesions or cancer. Intrinsic factors are characterized by age, gender, ethnicity, race, and genetic inheritance or heredity. Extrinsic factors include smoking and alcoholism, inadequate eating habits, a sedentary lifestyle, obesity, and occupational exposure, among others. The interaction between the two factors determines the individual cancer risk (Diz and Medeiros, 2009).

The International Federation of Gynecology and Obstetrics (FIGO) system and the Classification of Malignant Tumors (TNM) system are the most widely used staging systems for cervical cancer. In addition to the staging systems, complementary imaging tests such as computed tomography (CT) and magnetic resonance imaging (MRI) of the pelvis can be requested (Knoth et al., 2020).

Around 35 % of cases are still diagnosed at an advanced stage, occurring in countries where the majority of women still don't have access to cervical cancer prevention programs. In addition, women's low adherence to screening and diagnosis of chronic non-communicable diseases has been one of the most important factors to consider for cervical cancer screening and diagnosis in low- and middle-income countries (Shrestha et al., 2018).

Treatment options vary depending on the stage at which the cancer is detected. It usually consists of a curative intent intervention through surgery and/or chemoradiation (Abu-Rustum, 2020 Jun).

Therapeutic interventions in the treatment of cervical cancer can result in changes in gynecological anatomy and physiology, leading to complications such as early menopause, vaginal stenosis, shortening of the vaginal canal, atrophy of the vaginal mucosa, fibrosis, adhesions, urinary incontinence, fecal incontinence, dyspareunia, decreased vaginal lubrication, pelvic pain, pelvic, vulvar and lower limb lymphedema (Sarmiento, 2022).

Considering the representation of estimated incidence rates for malignant cervical neoplasia for the Northeast region and given that the ICC is a reference in cancer care in the North-Northeast, this study investigated whether, over a period of 22 years, there were patterns of occurrence related to sociodemographic characteristics and the evolution of mortality in patients with cervical cancer registered at the Cancer Institute of Ceará.

2. Materials e methods

2.1. Type, place, and period of the study

An observational, retrospective, cross-sectional, quantitative study was conducted using data collected by the Cancer Registry Service of the Haroldo Juaçaba Hospital/Ceará Cancer Institute (HHJ/ICC) over 22 years (01.01.2000 to 31.12.2021). This study was submitted to and approved by the Research Ethics Committee of the Faculdade Rodolfo Teófilo / ICC with a certificate of ethical appraisal of 71589823.2.0000.5528.

2.2. Population, inclusion, and exclusion criteria

The population consisted of records of women diagnosed with cervical cancer over 22 years (01.01.2000 to 31.12.2021) tabulated by the Cancer Registry Service of the Haroldo Juaçaba Hospital/Instituto do Câncer do Ceará (HHJ/ICC).

Records of patients with more than one primary tumor were excluded, as were records that did not contain the clinical information necessary to assess sociodemographic and clinical-therapeutic factors.

Table 1

Sociodemographic and Clinical-pathological profile of women with cervical cancer.

	n (%)
Total	9096
Age (51,4 ± 15,5, 15–100)	
Up to 60	4538 (49.9 %)
>60	4558 (50.1 %)
Race/ethnicity	
White	2018 (22.2 %)
Brown	6827 (75.1 %)
Others	251 (2.8 %)
Level of education	
Illiterate	1151 (19.2 %)
Incomplete primary education	1951 (32.6 %)
Complete elementary school	1979 (33.0 %)
High School	651 (10.9 %)
Higher education	258 (4.3 %)
Origin	
Fortaleza	3008 (44.2 %)
Metropolitan area	1137 (16.7 %)
Inland	2664 (39.1 %)
Month of diagnosis	
January	766 (8.4 %)
February	680 (7.5 %)
March	685 (7.5 %)
April	698 (7.7 %)
May	792 (8.7 %)
June	778 (8.6 %)
July	803 (8.8 %)
August	838 (9.2 %)
September	705 (7.8 %)
October	786 (8.6 %)
November	782 (8.6 %)
December	783 (8.6 %)
Local tumor	
Endocervix	3694 (40.6 %)
Cervix	5402 (59.4 %)
Histological type	
Squamous cell carcinoma	8023 (88.2 %)
Adenocarcinoma	953 (10.5 %)
Outros	120 (1.3 %)
Staging	
1A	1773 (19.5 %)
1B	867 (9.5 %)
2A	358 (3.9 %)
2B	1624 (17.9 %)
3A	186 (2.0 %)
3B	1890 (20.8 %)
4A	2270 (25.0 %)
4B	128 (1.4 %)
Treatment	
No treatment	1347 (14.8 %)
Surgery	1909 (21.0 %)
Radiotherapy	1746 (19.2 %)
Radiotherapy + Chemotherapy	3270 (35.9 %)
Surgery + Radiotherapy	362 (4.0 %)
Surgery + Radiotherapy + Chemotherapy	267 (2.9 %)
Chemotherapy + Radiotherapy + Surgery	195 (2.1 %)

2.3. Data collection

The Hospital Cancer Registry service routinely collects all admissions of cancer patients to the institution. The following variables were collected: patient's full name, age, ICD code of the primary tumor, race, origin, schooling, form of access to the hospital (SUS or private), location of the tumor, TNM staging, treatment, date of last visit and date of death. After the CEP approved the project, a spreadsheet was generated which collected all the information on patients diagnosed with ICD C53. Data collection was based on the information contained in these patients' records.

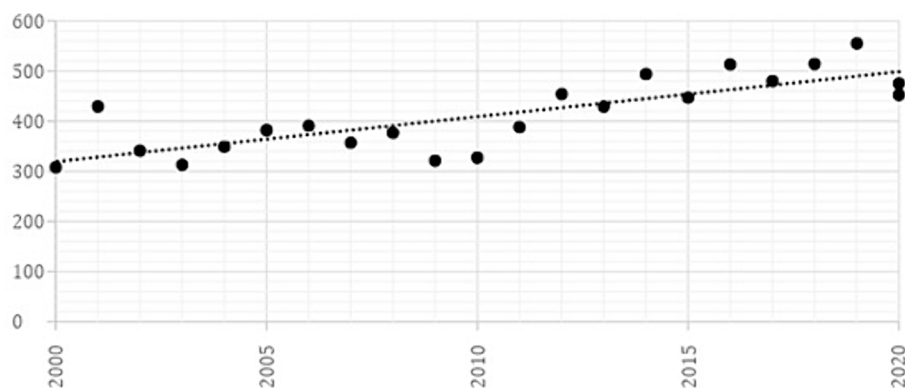


Fig. 1. Incidence rate of women with cervical cancer in 2000 to 2021.

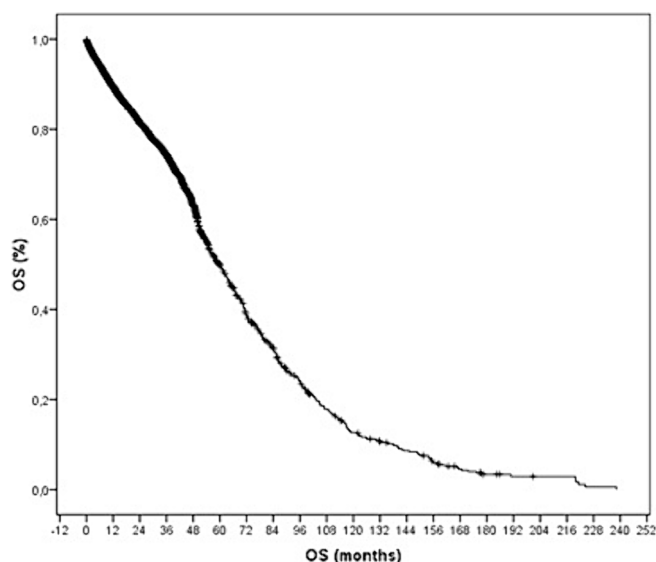


Fig. 2. Overall survival rate of women with cervical cancer in 2000 to 2021.

2.4. Statistical analysis

The data was exported from the hospital cancer registry system to SPSS v20.0 for Windows, where the analysis was carried out using a 95 % confidence level. Absolute and percentage frequencies were calculated for each variable associated with overall survival using Kaplan-Meier curves, the Mantel-Cox log-rank test, and the Cox regression model.

3. Results

The sample consisted of 9096 women followed up at the Haroldo Juaçaba Hospital during the 22 years of the historical series. The mean age was 51.4 ± 15.5 , ranging from 15 to 100, with a median age of 60. A total of 4558 women were over 60, and 4538 were under 60. The most frequent race was brown, with 6827 women, followed by white ($n = 2018$) and other ($n = 251$) (Table 1).

Illiterate women comprised 19.2 % of the sample, and women with incomplete or complete primary education comprised 65.5 % of the sample. The smallest part of the sample was patients with secondary education (10.9 %) or higher education (4.3 %).

About territorial origin, most of the patients were from the capital (44.2 %), followed by the interior of the state (39.1 %) and the metropolitan area (16.7 %). There was no significant variation in the month of diagnosis of these patients, with a slight peak in August and the lowest

number in March (Table 1).

The average number of annual cases was 413.45 ± 73.29 , with an estimated significant increase ($p < 0.001$, $r^2 = 0.631$; $y = 8.966x - 17612$) (Fig. 1).

The most frequent location of the tumor was in the cervix, with 5402 and 3694 tumors originating in the endocervix. The most frequent histological type was squamous cell carcinoma (SCC), with 8023 cases. Most patients came to the service with stage 4A (25.0 %). The most frequently used treatment was radiotherapy associated with chemotherapy (35.9 %), followed by surgical removal (21.0 %) (Table 1).

The median overall survival was 59.77 (95 % CI=56.44–63.10) months, with a mean follow-up time of 23.80 ± 19.83 (95 % CI=23.39–24.20, range = 1–238 months) (Fig. 2).

Patients aged over 60 ($p < 0.001$), of brown race ($p = 0.001$), illiterate, or with incomplete primary education ($p < 0.001$) showed a significant reduction in overall survival. However, the origin of the patients did not significantly influence this outcome ($p = 0.132$) (Table 2).

Lesions on the neck ($p < 0.001$) and of the squamous cell carcinoma type ($p = 0.010$) had better overall survival, and staging was directly associated with a worse prognosis ($p < 0.001$). Patients undergoing surgery alone had the best overall survival, and patients undergoing chemoradiotherapy followed by surgery had the worst overall survival ($p < 0.001$) (Table 2).

In multivariate analysis, age ($p = 0.019$), race ($p = 0.016$), low level of education ($p < 0.001$), tumor location, staging ($p < 0.001$), and treatment ($p = 0.011$) were risk factors independently associated with a greater chance of death in the sample studied. The tumor's location in the endocervix was the risk factor most strongly related to this outcome (hazard risk = 1.904, 95 %CI=1.592–2.278) (Table 3).

4. Discussion

Cervical cancer occurs more frequently in disadvantaged populations with heterogeneous characteristics of greater vulnerability linked to poverty, race/color, and unfavorable living conditions, negatively impacting the search for and access to health services.

In this sample, the prevalence of cervical cancer by the average age group was 51.4 ± 15.5 , ranging from 15 to 100, with a median age of 60. This is in line with the study by Kau (2019) (Kau et al., 2019 Mar), who reported a mean age of 57.2 ± 14.3 years in a 16-year retrospective analysis of cervical cancer incidence in Taiwan.

As for the older age group, in addition to having a lower prevalence of timely treatment, our study shows that women over 60 have a lower survival rate than patients under 60. This is partly due to the frailty context and comorbidities, which are more frequent in this population. These factors can serve as a barrier to participation related to access and care for people with cervical cancer within the scope of public care services (Reiser et al., 2021 Feb).

Table 2

Influence of sociodemographic and clinical-pathological profile on overall survival of women with cervical cancer in a 22-year time series.

	n	SG (%)	SG (months)	p-Value
Total	9067	6955 (76.7 %)	59.77 (56.44–63.10)	–
Age				<0,001
Up to 60	4517	3734 (82.7 %)	62.10 (55.36–68.84)	
>60	4550	3221 (70.8 %)	55.17 (51.26–59.08)	
Race				0,011
White	2012	1469 (73.0 %)	60.67 (54.75–66.59)	
Brown	6807	5292 (77.7 %)	58.53 (54.44–62.62)	
Others	248	194 (78.2 %)	63.23 (41.43–85.03)	
Level of education				<0,001
Illiterate	1147	662 (57.7 %)	34.77 (30.27–39.27)	
Incomplete primary education	1943	1230 (63.3 %)	40.83 (37.11–44.55)	
Elementary school complete	1969	1639 (83.2 %)	64.80 (58.01–71.59)	
High school	649	535 (82.4 %)	71.07 (36.26–105.88)	
Higher	256	225 (87.9 %)	85.83 (30.07–141.59)	
Origin				0,132
Fortaleza	3001	2514 (83.8 %)	74.10 (65.21–82.99)	
Metropolitan area	1135	961 (84.7 %)	70.60 (62.74–78.46)	
Inland	2658	2301 (86.6 %)	78.17 (66.30–90.04)	
Tumor site				<0,001
Endocervix	3692	2643 (71.6 %)	50.63 (47.30–53.96)	
Cervix	5375	4312 (80.2 %)	64.43 (58.60–70.26)	
Histological type				0,010
Squamous cell carcinoma	7995	6144 (76.8 %)	60.20 (56.31–64.09)	
Adenocarcinoma	952	731 (76.8 %)	56.00 (48.26–63.74)	
Others	120	80 (66.7 %)	58.10 (35.45–80.75)	
Staging				<0,001
1A	1761	1691 (96.0 %)	95.67 (88.23–103.11)	
1B	865	719 (83.1 %)	64.67 (56.36–72.98)	
2A	358	261 (72.9 %)	51.40 (43.04–59.76)	
2B	1619	1222 (75.5 %)	50.73 (46.44–55.02)	
3A	186	125 (67.2 %)	47.23 (35.81–58.65)	
3B	1888	1147 (60.8 %)	42.93 (38.77–47.09)	
4A	2263	1748 (77.2 %)	69.93 (61.71–78.15)	
4B	127	42 (33.1 %)	16.57 (10.61–22.53)	
Treatment				<0,001
No treatment	1341	898 (67.0 %)	60.53 (49.56–71.50)	
Surgery	1897	1814 (95.6 %)	85.83 (69.87–101.79)	
Radiotherapy	1742	1098 (63.0 %)	49.20 (44.60–53.80)	
Radiotherapy + Chemotherapy	3266	2488 (76.2 %)	52.37 (48.68–56.06)	
Surgery + radiotherapy	362	305 (84.3 %)	66.67 (58.35–74.99)	

Table 2 (continued)

	n	SG (%)	SG (months)	p-Value
Surgery + radiotherapy + chemotherapy	264	229 (86.7 %)	55.07 (49.16–60.98)	
Chemotherapy + Radiotherapy + Surgery	195	123 (63.1 %)	39.47 (29.48–49.46)	

*p < 0.05, Log-Rank Mantel-Cox test. Data expressed as absolute and percentage frequency or median and 95 % confidence interval.

Table 3

Multivariate analysis of risk factors for cervical cancer mortality in a 22-year time series.

	p-Value	HR (IC95%)
Risk of death		
Age	0,019	1,209 (1,031–1,416)
Race	0,016	1,205 (1,035–1,403)
Level of education	<0,001	0,843 (0,779–0,912)
Origin	0,856	1,008 (0,929–1,093)
Tumor site	<0,001	1,904 (1,592–2,278)
Histological type	0,206	1,096 (0,951–1,263)
Staging	<0,001	1,126 (1,097–1,156)
Treatment	0,011	1,067 (1,015–1,123)

*p < 0.05, Cox regression. HR=hazard risk; 95 %CI=95 % confidence interval.

Information on race/color was obtained by self-declaration during the screening process for access to hospital services and was classified according to IBGE definitions as white, brown, black, yellow, and indigenous. The inclusion of the race/color question in national information systems makes it possible to trace the epidemiological profile of the population, revealing indicators that show racial inequalities in the country and supporting the implementation of health actions that address the actual demands of the black population (Geraldo et al).

In this study, the racial distribution of the sample showed a higher prevalence of lesions in women who declared themselves to be brown (n = 6827, 75.1 %), followed by white (n = 2018, 22.2 %) and other (n = 251, 2.8 %) races. Women who considered themselves yellow or indigenous had lower survival rates when compared to brown, white, and black women. The study by Luiz (2023) (Luiz, et al., 2002), carried out in Brazil between 2002 and 2021, recorded 133,429 deaths from cervical cancer. Of these, 68,325 (51.2 %) occurred in the black population. For the year 2021, the same study found that mortality among indigenous people was 123.5 % higher than among white people. This corroborates our sample. These data suggest difficulties or inequalities in access to health services and the poor distribution of social resources fostered by racial disparities.

Most women had incomplete primary education or were illiterate about schooling. It was found that women with complete or incomplete higher education had a survival rate of 90 months, while illiterate women had a survival rate of 50 months. According to Baezconde-Garbatati (2019) (Baezconde-Garbanati et al., 2019), cervical cancer is related to a low level of education, which may be the result of reduced access to information about the disease in general, including early diagnosis and treatment. As a result, it is a neoplasm that still represents a public health problem, given that it can be eradicated.

Associated with low levels of education, lay people tend to inadequately report signs and symptoms of their illnesses, which leads to poorer health outcomes, delays in seeking medical services, a higher incidence of hospitalization, and consequently higher mortality rates (Baezconde-Garbanati et al., 2019). In underdeveloped countries such as Brazil, patients with low education have low adherence to conventional cervical cancer screening methods (Galindo et al., 2023 May 25). The low level of knowledge plays role in late cervical cancer diagnosis. A systematic review with meta-analysis showed that health education strategies for women significantly increase cervical cancer screening

rates (Musa et al., 2017 Sep 5; Brun-Micaleff et al., 2014 Mar) Furthermore, navigation nursing has been showing how to improve these women's journey during treatment. This approach improve adherence to antineoplastic treatment, as a low educational level impair in cancer treatment adherence (Bateman et al., 2019 Jan).

Therefore, patients with low education present manifestations later and in longer stages, significantly increasing the mortality rate (Guedes et al., 2005). The number of deaths from this cancer is associated with late diagnosis in advanced stages. Patients diagnosed at earlier stages undergo less aggressive treatments and have fewer complications related to cancer therapies and, consequently, a lower risk of death. At the same time, our results show that the more advanced the tumor, the greater the risk of complications from cancer treatment and the lower the disease-free survival rate. These findings are similar to those of Deressa's study (2021) (Deressa et al., 2021), which showed that the majority of patients had stage III or IV disease at the time of their first visit to the oncologist and points out that the five-year survival rate for patients diagnosed with early-stage cervical cancer detected by Pap smear is close to 90 %.

In the early stages of cancer, conservative surgical treatments can be considered, thus avoiding the complications and morbidities caused by more radical surgeries. Current scientific evidence recommends radiotherapy, chemotherapy, and brachytherapy for larger lesions. This clinical characteristic interferes with the quality of life of women with cervical cancer. Given this problem, it is essential to prioritize policies for screening, early diagnosis, and guaranteeing timely treatment to increase survival and improve outcomes (Sobral et al., 2022).

The median overall survival recorded was 60 months, with around 50 % of the population dying before 60 months and 50 % surviving beyond that. This differs from the results of Deressa (2021) (Deressa et al., 2021), who found that the estimated probability of overall survival at 60 months was 28.4 %, with a median overall survival time of 23 months.

It was observed that the location of the home of origin was not a factor significantly impacting life expectancy, even with the need to move between municipalities. This differs from the Brazilian study by Coutinho (2020) (Coutinho et al., 2020), which found that 54.9 % of the population did not live in the same municipality as the treatment unit and that individuals who needed to move to another location had a 16 % greater chance of delay than those who were treated in the same municipality of residence.

5. Conclusion

The sociodemographic characteristics of mortality from cervical cancer in patients followed up at the Haroldo Juaçaba Hospital (HHJ/ICC) highlight the higher frequency of deaths in women aged over 60, indigenous and black, with low levels of education, as well as clinical variables related to tumor location, staging and type of treatment.

CRedit authorship contribution statement

Talita de Oliveira Lima: Writing – original draft. **José Erialdo da Silva Junior:** Investigation. **Giulianna Aparecida Vieira Barreto:** Writing – review & editing. **Max Wellington Sátiro Justino:** Writing – review & editing. **Maria Lia Coutinho Carvalho:** Writing – review & editing. **Marcelo Gurgel Carlos da Silva:** Formal analysis, Data curation. **Daniele Alves Ferreira:** Visualization. **Lúcio Flávio Gonzaga Silva:** Supervision. **Paulo Goberlânio de Barros Silva:** Supervision, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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