






Cervical cancer specific survival in Grande Cuiabá, Mato Grosso State, Brazil

Sobrevida específica do câncer do colo do útero na Grande Cuiabá, Mato Grosso, Brasil

Fernanda Cristina da Silva de Lima^I , Bárbara da Silva Nalin de Souza^{II} ,
Julio Fernando Pinto Oliveira^I , Noemi Dreyer Galvão^{III} ,
Paulo Cesar Fernandes de Souza^{III} 

ABSTRACT: *Objective:* To estimate specific five-year survival in women diagnosed with cervical cancer living in the municipalities of Cuiabá and Várzea Grande, in the state of Mato Grosso, Brazil. *Methods:* This is a retrospective cohort study with information from the Cuiabá Population-based Cancer Registry and the Mortality Information System. To estimate the probability of specific survival in five years, the Kaplan-Meier estimator and the log-rank test were used aiming at verifying if there were statistical differences in the lifetime per groups. To verify the proportionality of the failure rates, the Schoenfeld residual test was used according to the statistical significance level of 0.05. *Results:* Specific five-year survival and median time were 90.0% and 50.3 months, respectively, for cervical cancer. When analyzing by age, the highest specific survival was among women aged 20 to 49 years (91.7%) and median time was 53.3 months. For the histological type, the highest specific survival was among women with adenocarcinoma (92.3%) and the mean survival time was 53.5 months. *Conclusion:* This study showed that specific survival after five years of diagnosis remained about 90% in patients with cervical cancer. Patients aged 20 to 49 years had higher specific survival and there was statistically significant difference only between age groups.

Keywords: Neoplasms of uterine cervix. Survival analysis. Survival rate. Epidemiology. Information systems.



^IUniversidade Federal de Mato Grosso, Foundation for Support and Development – Cuiabá (MT), Brazil.

^{II}Universidade Federal de Mato Grosso, Public Health Institute, Graduate Program – Cuiabá (MT), Brazil.

^{III}Secretaria de Estado de Saúde do Mato Grosso – Cuiabá (MT), Brazil.

Corresponding author: Fernanda Cristina da Silva de Lima. Rua Fernando Correa da Costa, 2367, Bloco CCBS III, Térreo, Sala do VIGICAN, Boa Esperança, CEP: 78060-900, Cuiabá (MT), Brazil. E-mail: fernandacri2005@hotmail.com

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RESUMO: *Objetivo:* Estimar a sobrevida específica em cinco anos de mulheres diagnosticadas com câncer do colo do útero que residem nos municípios de Cuiabá e Várzea Grande, Mato Grosso. *Métodos:* Estudo de coorte retrospectiva com informações provenientes do Registro de Câncer de Base Populacional de Cuiabá e do Sistema de Informação sobre Mortalidade. Para estimar a probabilidade de sobrevivência específica em cinco anos, foram utilizados o estimador de Kaplan-Meier e o teste de *log-rank*. Para verificar a proporcionalidade das taxas de falhas, usou-se o teste de resíduos de Schoenfeld, conforme o nível de significância estatística de 0,05. *Resultados:* A sobrevida específica em cinco anos e o tempo mediano de sobrevida foram de 90% e 50,3 meses, respectivamente, para o câncer do colo do útero. Quando se analisa por idade, a maior sobrevida específica foi entre as mulheres de 20 a 49 anos (91,7%) e o tempo mediano de sobrevida foi de 53,3 meses. Para o tipo histológico, a maior sobrevida específica foi entre as mulheres com adenocarcinoma (92,3%) e o tempo mediano de sobrevida foi de 53,5 meses. *Conclusão:* Este estudo mostrou que a sobrevida específica após cinco anos do diagnóstico se manteve em torno de 90% em pacientes com câncer de colo do útero. As pacientes entre 20 e 49 anos tiveram maiores sobrevidas específicas e houve diferença estatisticamente significativa somente entre as faixas etárias.

Palavras-chave: Neoplasias do colo do útero. Análise de sobrevida. Taxa de sobrevida. Epidemiologia. Sistemas de informação.

INTRODUCTION

Cervical cancer is a major public health issue worldwide. In 2020, 604 thousand new cases and 342 thousand deaths were estimated in the world¹. In Brazil, cervical cancer is the third most common female neoplasm. For the 2020–2022 triennium, over 16 thousand new cases were estimated, with an estimated risk of 16 new cases per 100 thousand women. This neoplasm is the second most common among those affecting women in the state of Mato Grosso, Brazil, with an estimated risk of 12 new cases per 100 thousand women². In 2019, about 105 deaths were reported, resulting in crude and adjusted rates of six deaths for every 100 thousand women³.

Developed countries with organized screening programs, with coverage above 80% and vaccination programs against human papillomavirus (HPV) infection, showed a decline in incidence and mortality^{4,5}. However, in developing countries, cervical cancer incidence and mortality rates were relatively high and survival was low^{1,6-8}.

The CONCORD-3 study, which estimated the five-year net survival trend, showed survival of 50 to 70% in the period from 2000 to 2014. Survival estimates for cervical cancer increased in several European and Asian countries⁸. It is worth mentioning that cervical cancer is preventable, and early detection is the main strategy for controlling the disease.

HPV infection and viral persistence are related to the onset and evolution of cervical cancer⁹. The progression from viral infection to cancer occurs when there are cellular changes, and these can be detected by the preventive examination, namely the Papanicolaou test¹⁰. Other risk factors include early sexual intercourse, multiple sexual partners, high number of pregnancies, smoking, and prolonged use of birth control pills^{10,11}.

Understanding the magnitude of cervical cancer is an important factor for controlling the disease and monitoring early detection programs. This cancer surveillance is carried out by Population-based Cancer Registries (PBCR)^{12,13}.

Cancer survival studies based on information from PBCR can contribute to a more comprehensive analysis of the health system in the world and foster health policies to reduce inequalities⁸. They are used to evaluate the results of the diagnosis and treatment of cervical cancer^{14,15} and are important for assessing the distribution of resources and identifying the main prognostic factors in a given region and population¹⁶. However, in Brazil, there is little information available on the survival of cervical cancer at the population level.

The objective of this study is to estimate specific five-year survival in women diagnosed with cervical cancer living in the municipalities of Cuiabá and Várzea Grande, in the state of Mato Grosso (MT), Brazil.

METHODS

This is a retrospective population-based cohort study with five-year survival analysis in women aged 20 years or older, diagnosed with cervical cancer according to the International Statistical Classification of Diseases and Related Health Problems – 10th revision (ICD-10: C53.0, C53.8, and C53.9), and residents of the municipalities of Cuiabá and Várzea Grande.

The available information on new cases diagnosed with cervical cancer between the years 2008 and 2013 was retrieved from the PBCR Cuiabá, which covers the municipalities of Cuiabá and Várzea Grande, a region called Grande Cuiabá (Great Cuiabá). The study period was defined based on updated information from the university extension project *Vigilância de câncer e seus fatores associados: atualização de registro de base populacional e hospitalar* [Surveillance of cancer and its associated factors: update of population-based and hospital-based registry]. This project was developed in partnership with the Department of Health of Mato Grosso State (*Secretaria de Estado de Saúde de Mato Grosso – SES-MT*), which funded the project, and was effective from April 2016 to March 2021. The registries were retrospectively updated from 2008 to 2016. The study period on survival concerning diagnoses performed between 2008 and 2013 is justified by the fact that nominal information on deaths until 2018 was available, which was obtained from the SES-MT.

In the period from 2008 to 2013, 1,225 women residents of Grande Cuiabá and diagnosed with cervical cancer were registered. Patients diagnosed between January 1st, 2008 and December 31, 2013 were included in the study and were followed up until December 31, 2018, the final follow-up date.

The follow-up of the cases was passive, that is, the incidence information database was cross-checked with the State's mortality information database, which is the routine followed by the PBCR Cuiabá¹⁷. The nominal database of new cases was cross-checked with

the nominal database of the State's Mortality Information System (*Sistema de Informação sobre Mortalidade – SIM*), from January 1st, 2000 to December 31, 2018.

The record linkage technique was used, which aims to identify records related to the same unit (in this case, people) in two different databases. The following variables were matched: patient's name, death (if the patient has died), patient's mother name, and date of birth between the PBCR and SIM databases, using the probabilistic linkage technique by the Reclink III software^{18,19}. Patients who met this criterion were included in the study. Conversely, patients who were not found in the death records were taken as “alive” in their vital status. Hence, there was no active follow-up of patients. According to Bustamante-Teixeira et al., most PBCR use this methodology to determine the vital status of registered patients²⁰.

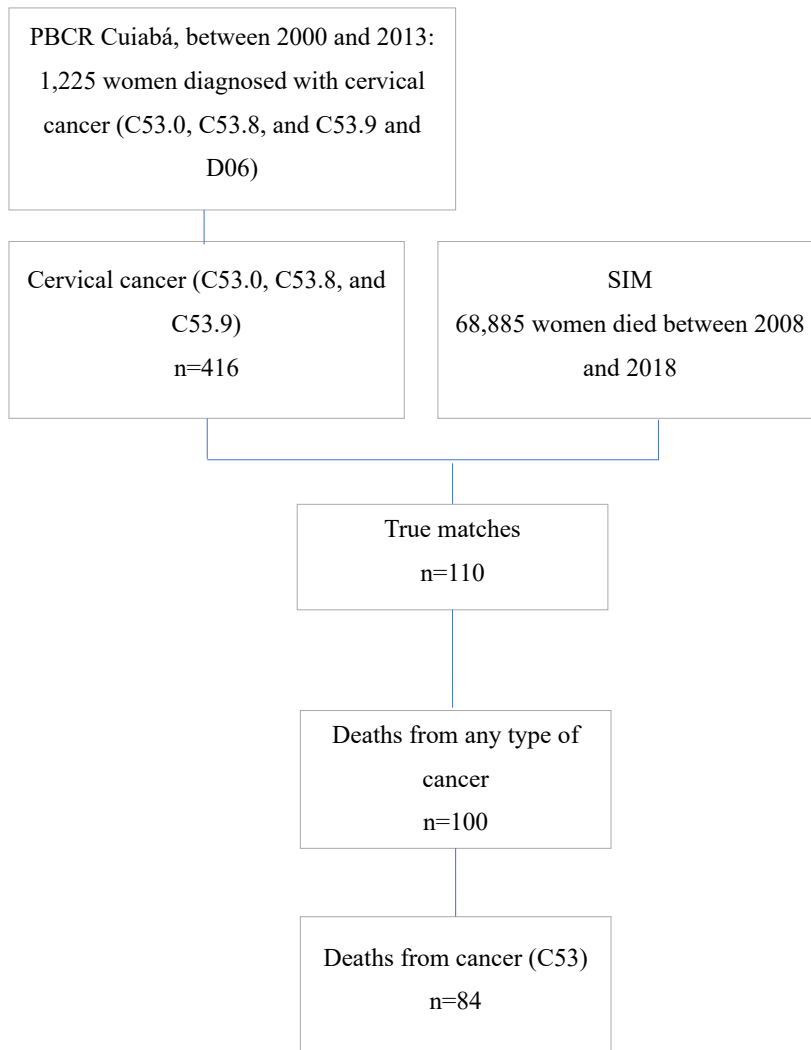
Death from cervical cancer over 60 months was deemed failure. Cases that did not suffer any events during the study period, that is, patients who remained alive at the end of the study, were considered censoring.

Figure 1 shows the flowchart of the matching between the databases of PBCR Cuiabá and the SIM. Records of 1,225 cases of cervical cancer were found. For this study, only cervical cancers were considered, which totaled 416 new cases during the study period. After linkage with the SIM database, 110 true matches were found, of which 100 were due to cancer and 84 due to cervical cancer. An investigation into the medical records altered the cause of death for six women. According to information from the SIM, causes of death as malignant neoplasm of corpus uteri (C54) and Malignant neoplasm of uterus, part unspecified (C55) were corrected for cervical cancer (C53), increasing the total under study.

The independent variables were: age, categorized into three age groups (20 to 49 years, 50 to 69 years, and 70 years or older); and histological type, characterized by cell structure of the tumor (morphology), by microscopic examination, according to Zhou et al.²¹. Coding was performed using the International Classification of Diseases for Oncology — 3rd edition (ICD-O/3)²² – squamous cell or epidermoid carcinoma (morphology: M8010, M8070, M8076, and M8560), adenocarcinoma (morphology: M8140, M8260, M8263, M8310, M8380, and M8480) and other neoplasms (morphology: M8000 and M8020).

Information available on cervical cancer for the period from 2000 to 2016 showed good quality indicators of cervical cancer (which assesses the quality of the registry information by the indicators Histology and Death Certificate Only – DCO). The average was 93.9% (Microscopic Verification — MV) and 5.16% (DCO) (Table 1). This quality was also observed in the SIM database for this period, with the median percentage of 1.52% regarding ill-defined causes in the database. The quality of the information was assessed using the criteria of the International Agency for Research on Cancer (IARC)²³, which have significantly improved over the years, thus enhancing cancer studies²⁴.

All cases diagnosed with other malignancies were excluded from the analysis, as well as cases with a diagnosis of tumors with *in situ* behavior of cervical cancer (ICD-10: D06). In situations in which the same patient had more than one primary tumor, only the first



PBCR: Population-based Cancer Registry; SIM: Mortality Information System.

Figure 1. Flowchart of the matching of the databases of population-based cancer registry, Cuiabá, Brazil, 2008 to 2013.

diagnosis was preserved. Cases with no age and no date of birth were excluded, as well as cases defined as DCO and with no date of death⁸.

To estimate the probability of specific five-year survival, the Kaplan-Meier estimator and the log-rank test were used, aiming at verifying whether there were statistical differences in the lifetime per groups. To verify the proportionality of the failure rates, the Schoenfeld residual test was used according to the statistical significance level of 0.05^{25,26}. Statistical analyses were performed with the R software version 4.2.0²⁷.

Table 1. Quality indicators of Population-based Cancer Registry, Cuiabá, Brazil.

Year	MV (%)	DCO (%)	C76 (%)	C80 (%)
2000	89.08	5.04	3.16	5.32
2001	88.42	7.37	2.70	3.60
2002	96.55	3.45	0.82	2.06
2003	96.67	0.83	1.46	3.10
2004	99.12	0.88	1.62	3.72
2005	90.62	7.29	0.96	3.26
2006	99.03	0.00	0.51	4.05
2007	98.77	1.23	0.71	3.57
2008	90.14	9.86	0.39	3.10
2009	93.90	6.10	0.19	2.64
2010	97.01	2.99	0.29	2.61
2011	93.42	3.95	1.01	1.16
2012	92.42	6.06	1.14	1.52
2013	96.83	1.59	0.24	1.45
2014	92.55	5.32	0.60	2.16
2015	91.07	8.93	0.60	1.92
2016	94.57	5.43	0.48	0.97

Source: Population-based Cancer Registry of Cuiabá.

MV: Microscopic Verification; DCO: Death Certificate Only; C76: other ill-defined locations; C80: unknown primary location.

RESULTS

From 2008 to 2013, 416 new cases of cervical cancer were studied, with the median age of women diagnosed with this cancer being 51 years and 84 deaths from cervical cancer. A total of 329 patients (79.1%) had squamous cell or epidermoid carcinoma; 60 patients (14.4%), adenocarcinoma; and the remaining 27 patients (6.5%), other morphologies (Table 2).

Specific five-year survival and median survival time were 90.0% and 50.3 months, respectively, for cervical cancer (Figure 2). When analyzed by age, the highest specific survival was among women aged 20 to 49 years (91.7%) and median time was 53.3 months. As for histological type, the highest specific survival was among women with adenocarcinoma (92.3%)

Table 2. Calculation of the probability of specific survival using the Kaplan-Meier method and the log-rank test for cervical cancer, Grande Cuiabá, Brazil, 2008 to 2013.

Variables	CC		Deaths from cancer		Five-year survival (%; 95%CI)	Median time (95%CI) (months)	p-value*
	n	%	n	%			
Cervix	416	100	84	100	90 (87.1–92.6)	50.3 (48.5–53.1)	
Age group (years)							
20 to 49	189	45.4	30	35.7	91.7 (88.1–95.5)	53.3 (51.0–55.7)	0.08
50 to 69	170	40.9	42	50	87.2 (82.6–92.0)	48.4 (45.3–51.5)	
70 or older	55	13.2	12	14.3	87.7 (79.7–96.2)	45.7 (39.5–51.9)	
Ignored	2	0.5	–	–	–	–	
Histological type							
SCEC	329	79.1	72	85.7	88.8 (85.6–92.0)	49.4 (47.3–51.6)	0.30
Adenocarcinoma	60	14.4	8	9.5	92.3 (86.1–98.6)	53.5 (49.2–57.8)	
Other neoplasms	27	6.5	4	4.8	90.5 (80.4–99.9)	54.4 (48.1–60.6)	

CC: cervical cancer; 95%CI: 95% confidence interval; SCEC: squamous cell or epidermoid carcinoma; p-value: *log-rank* test (Mantel-Cox); * $p < 0.05$.

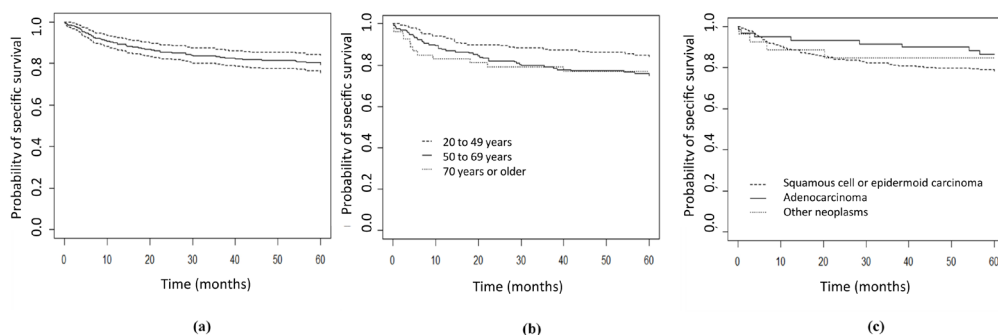


Figure 2. (A) Kaplan-Meier estimated specific survival curve for cervical cancer with 95% confidence interval, by (B) age group and (C) histological type.

and with a median survival time of 53.5 months, and there was no statistically significant difference between histological types (Table 2).

The Schoenfeld residuals plot is shown in Figure 3. It can be observed that there are no significant trends, neither for the two variables nor for the global model. It is noteworthy that the residuals do not have a random pattern around 0, thus suggesting a violation of the principle of proportionality of the risk function.

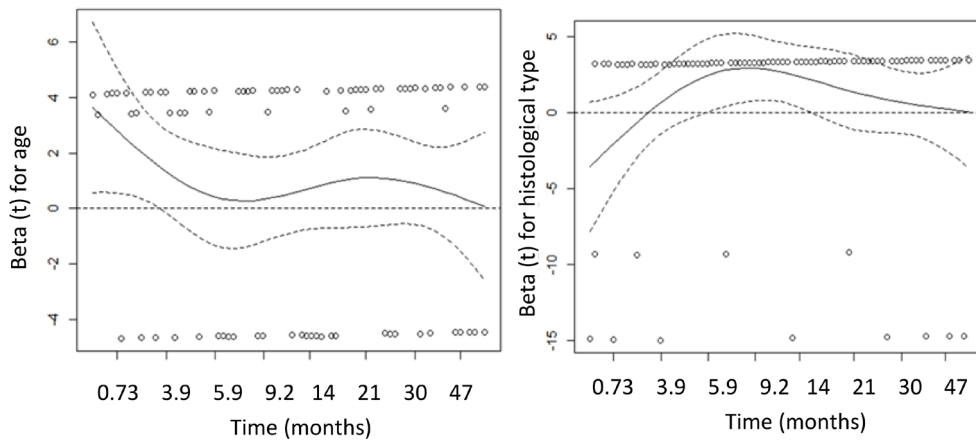


Figure 3. Assumption of proportional risks using standardized Schoenfeld residuals.

DISCUSSION

Survival is a good indicator for the analysis of treatment effectiveness as well as access to services and early diagnosis¹⁴. The PBCR data help to understand the prognostic factors to increase the survival of people with cancer and to know the incidence, distribution, and temporal trend of the disease in the area²⁸.

In Brazil, according to the guidelines for cervical cancer screening published in 2016, access to cervical examination, diagnosis, and preventive treatment of precursor lesions of women aged 25 to 64 years must be guaranteed. The Papanicolaou test is the main strategy for detecting precursor lesions and making an early diagnosis of the disease².

In Grande Cuiabá, the flow of care begins in primary health care (PHC), but municipalities have lower coverage of PHC than recommended (70%), whereas the specialized care of high complexity in these cities is performed in three qualified oncology services, according to the Oncological Care Action Plan (*Plano de Ação da Atenção Oncológica*) in the State of Mato Grosso²⁹.

This study represented a population base, which may help to understand the differences in survival between age groups and the different histological subtypes of cervical cancer. These data contribute to support managers in the development of strategies for coping with disease control.

Regarding the specific survival rate, it remained about 90% in patients with cervical cancer in this study. Patients between 20 and 49 years of age had the highest specific five-year survival rates.

In the United States of America, during the period from 2011 to 2017, the five-year survival rate of early-stage cervical cancer detected by the Papanicolaou test was about 90%³⁰, corroborating this study.

The scientific literature presents different results for the survival of women with cervical cancer between developed and developing countries. A study conducted in Malaysia between 2010 and 2016 found that the five-year cause-specific survival rate was about 90%³¹. Another study, conducted in Japan between 2000 and 2009, reported an 80% specific survival rate for this disease for a three-year follow-up for women over 75 years of age³².

Although no statistically significant difference was found, the survival of the several histological types influences cervical cancer specific survival, as reported in studies^{21,33}. In addition, the various types of HPV play a fundamental role in the etiology of cervical cancer^{34,35}. HPV 16 predominantly presents with squamous cell carcinomas, whereas HPV 18 predominates in adenocarcinomas^{10,36}. Considering that HPV genotypes are identified as an independent prognostic factor of cervical cancer^{37,38}, it is plausible to assume that different HPV genotype profiles in cervical cancer histological subtypes may contribute to variation in survival per histological subtypes.

The CONCORD-2 study showed that there was great variation in the five-year net survival trend for cervical cancer, estimated for Africa, Central America, South America, and Asia. In the period from 2005 to 2009, in 34 of the 61 analyzed countries, the five-year net survival was between 60 and 69%. Lower percentages were estimated for northeastern India, between 32 (Guwahati) and 53% (Sikkim), whereas in Brazil this estimation corresponded to about 61.1% (95% confidence interval – 95%CI 57.4–64.9)³⁹.

The CONCORD-3 study, conducted during the 2000-2014 period, identified that the trend of five-year net survival ranged between 50 and 70%, especially in Central and South America, Asia, and Europe. Survival was higher than 70% in countries such as Japan, Korea, Taiwan, Denmark, Norway, Switzerland, and Cuba. In other countries, such as Argentina, Ecuador, Martinique, Peru, Uruguay, India, Kuwait, Latvia, Lithuania, Bulgaria, Poland, Russia, and Malta, the survival ranged from 50 to 59%.

In the CONCORD-3 study, the estimated five-year net overall survival trend for Brazil indicated a survival of 60.3% (95%CI 56.3–64.3) from 2000 to 2014⁸. The highest survivals were found in high-income countries, which have better structure of access to HPV immunization, early diagnosis, timely appropriate treatment, and palliative care⁸. Nevertheless, the authors observed disparities in survival rates among the different countries, pointing out inequalities in access to health services. However, it should be considered that the method used in CONCORD-3 is different from that developed in this study⁸.

The impact of an organized program is well-documented by the literature and recommendations of the World Health Organization (WHO)⁴⁰. With the coverage of the target population of at least 80% and the guarantee of adequate diagnosis and treatment of altered cases, it is possible to reduce the incidence of this cancer by 60 to 90% on average. Developed countries that implemented organized screening programs reduced the risk of

women developing cervical cancer by 50%⁴¹. In England, there was a reduction of about 70% in cases at an advanced stage⁴².

In the municipality of Cuiabá, according to the Surveillance System for Risk and Protective Factors for Chronic Diseases by Telephone Survey (*Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico – VIGITEL*), in 2019, the distribution of women (from 25 to 64 years of age) who underwent cervical cytology at some point in their lives was 86.9%; and in the last three years, 77.8%⁴³.

Early detection of cervical cancer by cytopathological examination led to a 90% reduction in incidence, having a significant impact on the morbidity and mortality rates of these women⁴⁴.

It is worth noting that old age is an important risk factor in the development of cervical cancer and is associated with more advanced stages of the disease⁴⁴⁻⁴⁶. A systematic literature review showed that the most advanced cases of the disease were associated with age equal to or greater than 50 years in Brazil⁴⁶. In Estonia, a study conducted from 2010 to 2014 showed five-year survival of 89% (95%CI 70–97) in women aged 15 to 29 years and 41% (95%CI 32–50) in those aged over 70 years⁴⁷.

A study conducted in Barbacena (state of Minas Gerais, Brazil), in 2015, reported that cervical cancer was characterized by a bimodal age distribution: a peak at young age and another in postmenopausal, a result compatible with those of this study⁴⁸. Investigations suggest that young women are increasingly being exposed to the causes of cancer such as conditions linked to sexual activity, smoking, socioeconomic status, and use of oral contraceptives^{10,49}.

In Brazil, in 2014, the Ministry of Health incorporated the quadrivalent vaccine against HPV for boys aged 11 to 14 years and girls aged 9 to 14 years into the National Immunization Program⁵⁰. It is expected that, with the advancement of HPV vaccination coverage and with the expansion of coverage through preventive examination, there will be a significant impact on the morbidity and mortality rates of women.

The strength of this study was the use of information from the PBCR, guaranteeing good representativeness of cervical cancer in Grande Cuiabá; however, it has limitations due to the number of variables available in the PBCR. It is noteworthy that data on socio-demographic and clinical variables, such as disease staging or extent, are poorly filled out in the medical records, as well as in the anatomic pathology laboratories, which justifies why these data were not used in this study. Although these variables are not mandatory, this information serves to monitor variations in survival, estimate the demands of health services, assess the effectiveness of early detection programs, and select the best treatment to be performed⁵¹⁻⁵³.

Despite limitations, the present study is fundamental for assessing the quality of provided care, for further clarification of the disease, as well as for implementing actions for cancer control. Furthermore, using information from PBCR, an important source of data for the public health surveillance system, allows to understand the most relevant prognostic factors for cancer survival.

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Erratum



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