

Panorama of Gynecologic Cancer in Brazil

Eduardo Paulino, MD^{1,2}; Andreia Cristina de Melo, PhD^{1,2}; Agnaldo Lopes Silva-Filho, PhD^{2,3}; Luiza de Freitas Maciel, MD^{1,2}; Luiz Claudio Santos Thuler, PhD¹; Paul Goss, PhD^{4,5}; and Angelica Nogueira-Rodrigues, PhD^{2,3}

PURPOSE Little is known, or has been published previously, regarding consolidated data on the epidemiology of gynecologic cancers (GC) in Brazil. This article describes the incidence, morbidity, and mortality of women in Brazil affected with GC between the years of 2000 and 2017.

METHODS Incidence, morbidity, and mortality data from patients with a diagnosis of one out of the five most common GC, cervical (CC), uterine (UC), ovarian (OC), vulvar (VvC), and vaginal (VgC), were obtained from three governmental sources of data.

RESULTS From 2000 to 2015 CC, OC, and VgC incidence rates (IRs) decreased, whereas the IRs for UC and VvC remained relatively stable. Data from 382,932 women with GC were analyzed. Most patients presented with locally advanced or advanced disease at diagnosis: 60.1% of patients with CC, 31.2% of patients with UC, 67.2% of patients with OC, 45.2% of patients with VvC, and 67.0% of patients with VgC. Time from diagnosis to first treatment was ≥ 60 days in 58.0% of patients with CC, 58.5% of patients with UC, 27.0% of patients with OC, 55.3% of patients with VvC, and 52.7% of patients with VgC. Regarding mortality rates (MRs), with the exception of CC, UC, and VvC, which showed a slight decrease, MRs remained stable between 2000 and 2017.

CONCLUSION A comparison with international data indicates that Brazilian patients are diagnosed with more advanced disease and face a longer delay between diagnosis and first treatment. Despite advances in screening and treatment, GC mortality has not decreased satisfactorily in this country.

JCO Global Oncol 6:1617-1630. © 2020 by American Society of Clinical Oncology

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License

INTRODUCTION

Most clinical and epidemiologic data on gynecologic cancers (GC) come from high-income countries (HICs), and there is a dearth of information on low- and middle-income countries (LMICs).¹ Every 3 years, the Brazilian National Cancer Institute (INCA) publishes incidence data. According to the latest publication, cervical cancer (CC), ovarian cancer (OC), and uterine cancer (UC) were the third, seventh, and eighth most common cancers in Brazil, with 16,590, 6,650, and 6,540 new cases, respectively, expected in 2020.² Brazil is a continental country with diverse and highly admixed populations. The North (N)/Northeast (NE) and South (S)/Southeast (SE)/Middle-West (MW) are distinct regions in terms of the development index, in which the N/NE is the poorest (Human Development Index [HDI] = 0.667 and 0.663, respectively) and the S/SE/MW, the richest (HDI = 0.754, 0.766, and 0.757, respectively), with better access to cancer prevention and treatment.³

To date, there has been no population-based analysis of the basic characteristics of GC in Brazil. The

purpose of this study was to describe the whole scenario of women with GC in Brazil, including incidence, morbidity, and mortality, which could mirror other LMICs around the world, to inform future clinical management and local policy decisions.

METHODS

Ethical committee approval was not required because only secondary data available on the Internet were used in this study. The ecological study was conducted based on three governmental sources of data: population-based cancer registries (PBCRs), hospital-based cancer registries (HBCRs), and the National Mortality Information System. Cases were identified according to the International Classification of Diseases (10th revision) codes: C53 (CC), C54/55 (UC), C56 (OC), C51 (vulvar cancer [VvC]), and C52 (vaginal cancer [VgC]).

For incidence analysis, data from 30 Brazilian PBCRs with at least 2 years of consolidated information between 2000 and 2015 were obtained in February 2020. All new cancer cases diagnosed in permanent

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on August 13, 2020 and published at ascopubs.org/journal-go on October 27, 2020: DOI <https://doi.org/10.1200/GO.20.00099>

CONTEXT

Key Objective

What is the panorama of gynecologic cancer (GC) in a developing country? Little is known regarding the epidemiology of GC in low- and low-middle-income countries, places where patients can face many obstacles in receiving preventive care and treatment for many types of cancer. The main purpose of this article was to discuss the current epidemiologic panorama of the five major gynecologic tumors in Brazil.

Knowledge Generated

Compared with international data, Brazilian patients are diagnosed with more advanced disease and face a longer delay between diagnosis and first treatment. Despite advances in screening and treatment, GC mortality has not decreased satisfactorily in this country.

Relevance

These data may also mirror those of other low- and low-middle-income countries, because most barriers are not common to Brazil.

residents in a clearly defined geographic area were considered incident. The raw data are available on the Internet at INCA's site.⁴ Population coverage by the PBCRs is displayed in Appendix Table A1. Crude incidence rates (IRs) of GC per 100,000 women by age group and year of diagnosis were calculated by dividing the number of new cases by the female population. Rates were adjusted according to the female world standard population. The mean IRs allowed the estimation of an annual IR for the country as a whole.

Demographic and clinical data of women with GC who were diagnosed and treated between 2000 and 2016 in 336 Brazilian hospitals (including the 26 states and the Federal District) came from the HBCR Integrator System available on the Internet.⁴ Data were downloaded in December 2019. The following variables were collected: age at diagnosis, self-reported ethnicity/skin color according to the Brazilian Institute of Geography and Statistics,⁵ schooling, marital status, time between diagnosis and first treatment (defined as the time interval between the GC diagnosis in a histopathologic report and the beginning of the first treatment, labeled as < 60 days ν \geq 60 days, using the Brazilian Law of Sixty Days as a reference), Federation of Gynecology and Obstetrics (FIGO) stage, and early death (defined as death occurring before the end of the first line of treatment, that is the first set of therapies that has been applied for antineoplastic drugs uninterrupted or all cancer-directed treatment administered to the patient within 4 months after the initiation of therapy).

Mortality data for GC in Brazil between 2000 and 2017, disaggregated by age and year of diagnosis for the country as a whole, were retrieved on March 2020 from the National Mortality Information System.⁶ Crude annual mortality rates (MRs) of GC per 100,000 women were calculated by dividing the number of deaths by the female population. Rates were adjusted for the female world standard population. The population used as a denominator for IRs and

MRs was estimated by the Interagency Network of Information for Health for the period between 2000 and 2017, taken from the Website of the Department of Informatics of the Ministry of Health of Brazil.⁶

Data were analyzed using SPSS version 21.0. Descriptive statistics were used for demographic, epidemiologic, and clinical characteristics. The analysis was based on valid data; missing data were excluded from the analysis, but they are displayed in the tables. Kolmogorov-Smirnov was used to check the normal distribution of age, and analysis of variance was used to compare mean age between distinct gynecologic cancer subtypes. The χ^2 test was performed to compare the distribution of the categorical variables. To identify changes in incidence and mortality trends, Joinpoint regression analysis was performed. Annual percent changes (APCs) with 95% CIs were calculated. Mean IRs and interquartile ranges were used as measures of central tendency to synthesize IRs for each PBCR and for the Brazilian macroregions. Differences were considered significant when the *P* value was < .05.

RESULTS

Results refer to 2000-2015 incidence data from 30 PBCRs covering 10% to 22% of the Brazilian population, morbidity characteristics of 382,932 patients with GC registered by the Integrator System from 2000 to 2017, and analysis of 203,975 GC deaths recorded between 2000 and 2017. The most relevant characteristics of each are described later in the text and summarized in the tables and figures.

CC

The CC adjusted IR for the whole population fell from 21.15 per 100,000 women in 2000 to 11.44 per 100,000 women in 2015, an APC of -4.6 from 2000 to 2011 and -10.3 from 2011 to 2015 (Fig 1A; Appendix Table A2). IRs were higher in the N region (33.16 per 100,000; Appendix Table A3).

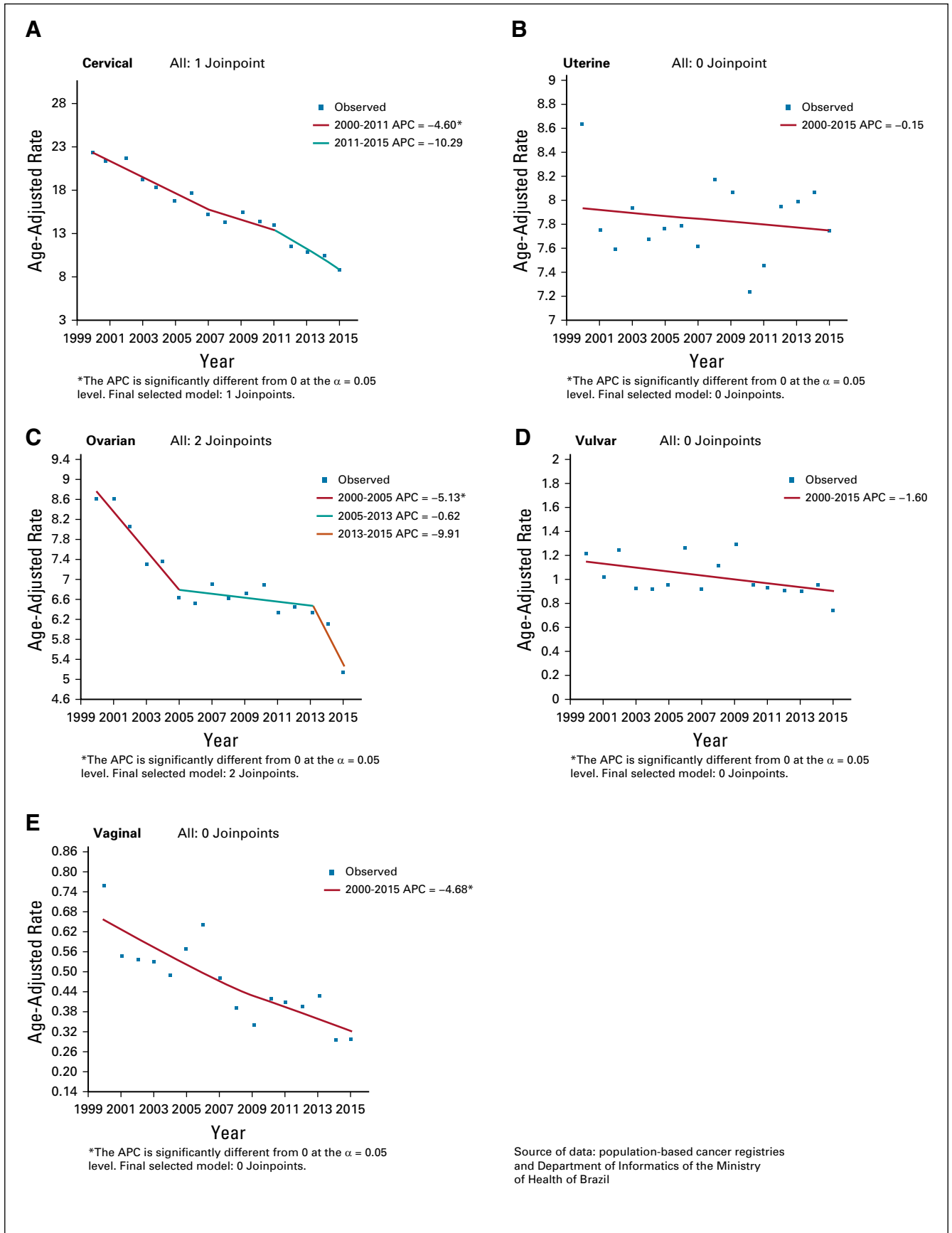


FIG 1. Age-adjusted incidence rates (2000-2015) per 100,000 of gynecologic cancer in Brazil. (A) Cervical cancer. (B) Uterine cancer. (C) Ovarian cancer. (D) Vulvar cancer. (E) Vaginal cancer. APC, annual percent change.

TABLE 1. Epidemiologic Aspects of the Five Major Gynecologic Cancers in Brazil

Variable	Cervical	Uterine	Ovarian	Vulvar	Vaginal	P
Total ^a	261,224 (68.2)	60,830 (15.9)	45,758 (11.9)	10,968 (2.9)	4,152 (1.1)	^b
Age, years, mean (SD)	48.7 (15.2)	61.9 (11.9)	53.3 (16.3)	63.7 (16.3)	58.6 (16.8)	< .001
Ethnicity/skin color						< .001
White	70,485 (37.3)	20,657 (54.6)	14,574 (49.8)	3,683 (51.4)	1,353 (49.5)	
Black	12,808 (6.8)	2,317 (6.1)	1,753 (6.0)	443 (6.2)	165 (6.0)	
Yellow	1,821 (1.0)	287 (0.8)	252 (0.9)	55 (0.8)	27 (1.0)	
Brown (Brazilian mixed race)	103,489 (54.7)	14,526 (38.4)	12,647 (43.2)	2,973 (41.5)	1,182 (43.3)	
Indigenous	613 (0.3)	48 (0.1)	60 (0.2)	6 (0.1)	4 (0.1)	
Missing	72,008	22,995	16,472	3,808	1,421	
Schooling, years						< .001
< 8	122,063 (62.1)	24,053 (55.1)	17,284 (51.1)	5,733 (69.6)	1,831 (62.3)	
≥ 8	74,581 (37.9)	19,591 (44.90)	16,523 (48.90)	2,503 (30.4)	1,109 (37.7)	
Geographic region						< .001
Southeast	103,494 (39.6)	34,244 (56.3)	24,051 (52.6)	6,115 (55.8)	2,004 (48.3)	
South	41,899 (16.0)	11,181 (18.4)	7,711 (16.9)	1,931 (17.6)	689 (16.6)	
Northeast	82,262 (31.5)	12,179 (20.0)	10,656 (23.3)	2,204 (20.1)	1,066 (25.7)	
Middle-West	8,705 (3.3)	1,465 (2.4)	1,282 (2.8)	275 (2.5)	162 (3.9)	
North	24,864 (9.5)	1,761 (2.9)	2,058 (4.5)	443 (4.0)	231 (5.6)	
Period						< .001
2000-2005	71,474 (27.4)	11,846 (19.5)	10,317 (22.5)	2,586 (23.6)	980 (23.6)	
2006-2011	95,439 (36.5)	22,065 (36.3)	16,847 (36.8)	4,047 (36.9)	1,540 (37.1)	
2012-2017	94,311 (36.1)	26,919 (44.3)	18,594 (40.6)	4,335 (39.5)	1,632 (39.3)	

NOTE. Data are presented as No. (%) unless otherwise specified. Source of data: hospital-based cancer registries.

Abbreviation: SD, standard deviation.

^aRow percentage.

^bDoes not apply.

A total of 261,224 new cases were identified from the HBCR Integrator System between 2000 and 2017, corresponding to 68.2% of all GC analyzed. Mean age at diagnosis was 48.7 (± 15.2) years (Table 1). Most patients (60.1%) presented with advanced CC or locally advanced CC (LACC) at diagnosis, and squamous cell carcinoma (SCC) represented 79.2% of the cases (Table 2). Comparing the SE region with other regions, fewer patients were diagnosed with advanced CC or LACC (52.3% in SE v 63.7% to 73.6% in the other regions; Appendix Table A4). The period between diagnosis and first treatment was more than 60 days in 58.0%. Early deaths were as high as 11.0% (Table 2). Regarding mortality, between 2000 and 2015, there was a slight decrease in CC MRs (APC, -0.8), from 5.05 per 100,000 women in 2000 to 4.61 per 100,000 women in 2015; the MR remained stable from 2015 through 2017 (Fig 2A; Appendix Table A2).

UC

Between 2000 and 2015, the UC adjusted IR for the whole population remained relatively stable, with the highest incidence in 2008 (8.14 per 100,000 women) and the lowest

in 2010 (7.23 per 100,000 women; Fig 1B; Appendix Table A2). The S and SE regions showed the highest IRs: 8.71 and 7.36 per 100,000 women, respectively (Appendix Table A3).

A total of 60,830 UC cases were identified from the HBCR Integrator System between 2000 and 2017, corresponding to 15.9% of GC cases analyzed and the second most common GC in this series. Mean age at diagnosis was 62.9 (± 11.9) years (Table 1). Endometrioid (40.5%) and adenocarcinoma NOS (35.5%) tumors were the most common morphologic subtypes. In general, patients were diagnosed more frequently in stages I and II (68.8%). However, in the N, MW, and NE regions, patients were more likely to be diagnosed at stages III and IV than they were in the S and SE regions (32.7% to 34.7% v 30.3% to 31.7%; Appendix Table A4). Time between diagnosis and first treatment exceeded 60 days in 58.5%. Early deaths occurred in 13.3% of patients (Table 2). Regarding mortality, rates decreased between 2002 and 2014, from 3.17 to 2.81 per 100,000 women (APC, -1.2 between 2002 and 2014), and then remained stable until the end of the period (Fig 2B; Appendix Table A2).

TABLE 2. Clinical Aspects of the Five Major Gynecologic Cancers in Brazil

Variable	Cervical	Uterine	Ovarian	Vulvar	Vaginal	P
Total ^a	261,224 (68.2)	60,830 (15.9)	45,758 (11.9)	10,968 (2.9)	4,152 (1.1)	^b
Clinical stage ^c						< .001
Early	74,015 (39.9)	23,980 (68.8)	9,024 (32.8)	3,473 (54.8)	667 (33.0)	
Locally advanced or advanced	111,395 (60.1)	10,897 (31.2)	18,479 (67.2)	2,868 (45.2)	1,356 (67.0)	
Missing	75,814	25,953	18,255	4,627	2,129	
Locally advanced or advanced disease ^c						< .001
2000-2005	31,424 (59.3)	2,048 (28.7)	4,368 (66.5)	778 (47.2)	377 (70.9)	
2006-2011	38,153 (61.3)	3,653 (31.7)	6,667 (67.4)	1,039 (45.9)	444 (65.3)	
2012-2017	41,818 (59.6)	5,196 (32.1)	7,444 (67.4)	1,051 (43.30)	535 (66.0)	
Missing	75,814	25,953	18,255	4,627	2,129	
Most common histology	SCC = 206,853 (79.2) ADENO = 24,728 (9.5) Other = 29,643 (11.3)	Type I = 76.0% EC = 24,652 (40.5) ADENO = 21,610 (35.5) Type II = 7.0% MMT/CCS = 3,345 (5.5) CCC = 906 (1.5) Other = 10,317 (17.0)	ADENO = 12,122 (26.5) SPC = 10,817 (23.6) MC = 4,439 (9.7) EC = 2325 (5.1) Other = 16,056 (35.1)	SCC = 9,121 (83.2) ADENO = 235 (2.1) Other = 1,612 (14.7)	SCC = 2,843 (68.5) ADENO = 556 (13.4) Other = 753 (18.1)	^b
Time to first treatment, days						< .001
< 60	88,217 (42.0)	20,171 (41.5)	25,341 (73.0)	3,732 (44.7)	1,437 (47.3)	
≥ 60	121,969 (58.0)	28,477 (58.5)	9,371 (27.0)	4,622 (55.3)	1,599 (52.7)	
Missing	51,038	12,182	11,046	2,614	1,116	
Early death ^d						< .001
Yes	13,777 (11.0)	2,956 (13.3)	3,991 (20.4)	755 (16.8)	247 (16.0)	
No	110,995 (89.0)	19,267 (86.7)	15,588 (79.6)	3,748 (83.2)	1,298 (84.0)	
Missing	136,452	38,607	26,179	6,465	2,607	

NOTE. Data are presented as No. (%). Source of data: hospital-based cancer registries.

Abbreviations: ADENO, adenocarcinoma; AS, adenosquamous carcinoma; CCC, clear cell carcinoma; EC, endometrial carcinoma; MC, mucinous carcinoma; MMT/CCS, Mullerian mixed tumor or carcinosarcoma; NE, nonepithelial; SCC, squamous cell carcinoma; SPC, serous-papillary carcinoma.

^aRow percentage.^bDoes not apply.^cAdvanced stage: stages II to IV for cervix and vaginal cancer; stages III and IV for ovarian, endometrial, and vulvar cancer.^dEarly death: death at the end of the first line of treatment.

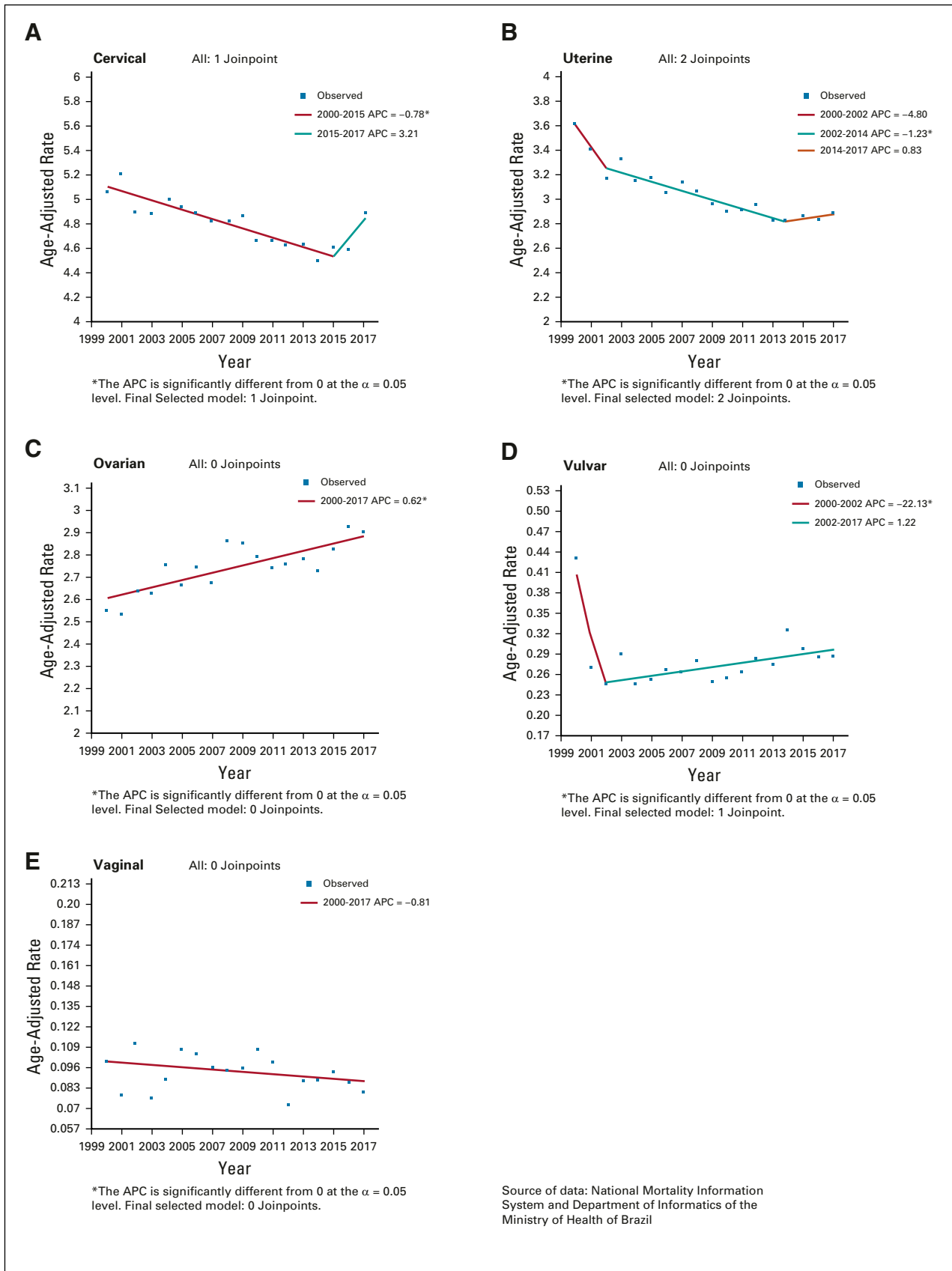


FIG 2. Age-adjusted mortality rates (2000-2017) per 100,000 of gynecologic cancer in Brazil. (A) Cervical cancer. (B) Uterine cancer. (C) Ovarian cancer. (D) Vulvar cancer. (E) Vaginal cancer. APC, annual percentage change.

OC

For OC, between 2000 and 2005, the adjusted IR for the whole population fell from 8.62 to 6.62 (APC, -5.1), remaining without significant changes until 2015 (Fig 1C; Appendix Table A2). The highest IR was observed for the S region (7.86 per 100,000 women; Appendix Table A3)

Over the studied period, 45,758 cases of OC were found in the HBCR Integrator System between 2000 and 2017. Mean age at diagnosis was 53.3 (± 16.3) years (Table 1). Adenocarcinoma NOS and serous histologies were the most common types, representing 26.5% and 23.6%, respectively. Stages III and IV represented 67.2% of the cases. Patients were more likely to be diagnosed with advanced-stage disease in the S, NE, and MW regions (69.3% to 71.0%) than in the other regions (60.6% to 65.2%; Appendix Table A4). Time between diagnosis and first treatment received was greater than 60 days in 27.0%. Early deaths occurred in 20.4% of patients (Table 2).

Regarding mortality, between 2000 and 2017, rates increased by 0.6% a year (APC, $+0.6$) with the lowest rate in 2001 (2.53 per 100,000 women) and the highest rate in 2016 (2.94 per 100,000 women; Fig 2C; Appendix Table A2).

VvC

For VvC, between 2000 and 2015, the adjusted IR for the whole population remained stable, ranging from 1.22 to 0.73 per 100,000 women (Fig 1D; Appendix Table 2). IRs were 1.10 and 1.04 per 100,000 women in the S and SE regions, respectively (Appendix Table A3).

A total of 10,968 cases of VvC were found in the HBCR Integrator System between 2000 and 2017, corresponding to 2.9% of GC. The mean age at diagnosis was 63.7 (± 16.3) years (Table 1). Patients were generally diagnosed at stages II-IV (67.0%), and SCC was the most common histology (83.2%). Time between diagnosis and first treatment exceeded 60 days in 52.7%. Early deaths occurred in 16.0% of patients (Table 2).

Regarding mortality, between 2000 and 2002, the rates decreased from 0.43 in 2000 to 0.24 in 2002 (APC, -22.1) and then increased, reaching 0.29 per 100,000 women in 2017 (APC, $+1.2$; Fig 2D; Appendix Table A2).

VgC

For VgC, between 2000 and 2015, adjusted IR for the world population fell by 4.7% per year (APC, -4.7); over this period, the highest incidence was 0.76 per 100,000 women in 2000 and the lowest incidence was 0.29 per 100,000 women in 2014 and 2015 (Fig 1E; Appendix Table A2). The NE (0.51 per 100,000 women) and MW (0.52 per 100,000 women) regions had the highest IRs (Appendix Table A3).

A total of 4,152 cases of VgC were identified from the HBCR Integrator System between 2000 and 2017. Mean age at

diagnosis was 58.6 (± 16.8) years; Table 1). VgC was diagnosed at locally advanced stages (stages II-IV) in 67.0% of patients, and SCC corresponded to 68.5% of cases. Patients were more likely to be diagnosed at advanced-stage disease in the N region (79.7%; Appendix Table A4). Time between diagnosis and first treatment exceeded 60 days in 52.7% of cases. Early deaths occurred in 16.0% of cases (Table 2).

The VgC MR between 2000 and 2017 remained relatively stable, ranging from 0.10 per 100,000 women in 2000 to 0.08 per 100,000 women in 2017 (Fig 2E; Appendix Table A2).

DISCUSSION

To our knowledge, this is the largest study to be conducted in Brazil evaluating the current demographic and clinical aspects of GC. The severity of the global divide in cancer morbidity and mortality between LMICs and HICs is well known, and it is expected to increase.⁷ Added to that, cancer incidence in LMICs, GC included, may be underestimated, because it is rare for LMICs to have reliable cancer registries and reporting systems. The aim of the current analysis was to collect Brazilian GC data not reported previously and to inform future clinical management and local policy decisions, which may help other LMICs with limited knowledge of their own numbers.

According to the GLOBOCAN database, the prevalence of OC and UC is higher in HICs, particularly northern Europe and North America. In contrast, IRs are much higher for CC in LMICs, where 80% of all cases occur.⁷

Mainly because of its epidemiologic relevance, more information regarding CC in LMICs is now available. The current worldwide estimated age-standardized incidence, according to the WHO, is divided into the following four tiers: 7.3-11.5, 11.5-18.1, 18.1-26, and > 26 cases per 100,000 women¹⁸. According to this analysis, Brazil is at the second lowest tier, but significant heterogeneity exists within the country, and approximately one third of the Brazilian states, all of them located in the northern areas, have an incidence higher than 18.1 cases per 100,000 women, similar to the rates of low-income and lower-middle-income countries (despite the fact that the World Bank currently classifies Brazil as an upper intermediate-income country). In regions with low socioeconomic indexes, such as the N/NE states, CC represented 85.5% and 75.1% of GC, respectively, compared with 65.9% and 57.5%, respectively, in the wealthier S and SE of Brazil. This distribution is in line with the worldwide incidence, with more CC in poorer areas and a higher proportion of UC and OC in richer and more developed regions.⁷ Addressing these internal specificities in LMICs may play a key role in cancer control. For example, the WHO CC Elimination Modeling Consortium predicted that countries that have weaker health systems and a CC incidence of > 20 cases per 100,000 women-years that start human papillomavirus

(HPV) vaccination alone will progress more slowly toward elimination, but that adding screening to HPV vaccination can significantly accelerate CC incidence decline. Tailored strategies are fundamental.

A rising problem in Brazil is EC. The estimated age-standardized IRs vary from one to 30 cases/100,000 women across countries globally, with the highest rates in HICs, where almost two thirds of all cases occur. The incidence of EC is increasing in Brazil, potentially because of more Westernized lifestyles and higher rates of obesity, as well as an increase in life expectancy. Currently, 20.7% of Brazilian women are obese, and 53.9% are overweight.⁸ Therefore, it is imperative to implement EC prevention and early detection policies and improve radiotherapy access.

Most Brazilian patients with GC, with the exception of EC, are diagnosed with locally advanced disease. When analyzing the different time periods, it is remarkable to note that there was no significant impact on tumor stage and GC mortality over time. One possible explanation for the persistent high MR is that prevention and screening strategies have yet to reach the most vulnerable populations. Treatment delays also probably contribute. Compared with other LMICs, considering CC FIGO stage, the Brazilian pattern is similar to North Africa and the Middle East, where approximately 70% of patients present with locally advanced disease at diagnosis.⁷ Because OC is a rapidly proliferating tumor, most patients across the world are at stage III or IV at diagnosis; in Brazil, this figure is 70%.

Focusing on CC, the high illiteracy rate of the current population, coupled with the lower than expected screening coverage in the Brazilian population (79% of patients in the target population were screened in 2013, which is less than the 85% goal), help illustrate the core of the problem.⁹ It has been reported previously that screening acceptance is higher in women with better access to education, and that delivery strategies should be aimed at encouraging older and less educated women to get screened.¹⁰

Regarding access to treatment, Brazilian patients with GC face significant hurdles. Even after the so-called Law of Sixty Days, which guarantees treatment of patients within 60 days of diagnosis, no significant advances have been achieved, with as many as 39% of patients with GC starting treatment after 60 days of diagnosis, and 24% after 90 days (Appendix Fig A1).¹¹ Treatment delay, together with advanced stage at diagnosis (46% in CC compared with 20.6% in American women), may help explain the high percentage of early deaths (13.2%) found in this cohort. In a recent article regarding barriers in primary surgery in OC in Latin America, a number of obstacles, such as access barriers and inadequate resources, are identified.¹² In recent years, Brazil has suffered a shortage of radiation

machines as well as human resources. A Brazilian poll about radiotherapy needs in 2012 showed that 135 machines are necessary to cover the whole population, and to meet these needs, a planned expansion of 80 machines was proposed for 2015.¹³ However, to date, only 22 additional machines are in operation and 16 are in process.^{14,15} Another concern is that there is no formal subspecialization in gynecology oncology in Brazil. Some patients are treated by general gynecologists or general surgeons, who may not be ideally trained in oncologic practices.

The current data emphasize the need for preventive strategies in Brazil. Considering the high CC burden and the fact that it often has the same etiologic factor (HPV) as VvC and VgC, it would be of value if our leaders increased efforts to improve adherence to the national HPV vaccination program. According to the Ministry of Health, there was a 23% decrease in vaccination coverage from 2014 to 2015, a dramatic reduction in 1 year.¹⁶ An article regarding vaccination rates in Latin America confirms this trend.¹⁷ Furthermore, because the vaccine is not therapeutic and patients who will be diagnosed with CC in the next 15 years are already HPV infected, Papanicolaou test screening method adherence must also be reinforced.

This analysis has several limitations inherent to retrospective studies, such as the inadequacy of the collected information, confounding factors, and missing information. Because this is partly a hospital-based study, the cohort does not represent the entire Brazilian population; hospital-based studies are more susceptible to selection bias than are studies that are based on population registries, which were used here only for incidence data. Moreover, over the period of this study, changes in GC classification and staging have taken place. In the current study, the IRs of CC and EC were estimated without the elimination of hysterectomized women from the population at risk, because of a lack of these specific data. Conversely, strengths should also be mentioned, such as the high number of patients included, the use of trained professionals for data collection, the coverage of all regions in Brazil, and the use of incidence data from VvC and VgC, which, to our knowledge, had never been reported before in this country.

GC causes significant burden in Brazil, and these data could mirror those of other LMICs. Most patients present with advanced-stage disease at diagnosis and face long waiting times to start treatment, and therefore, a high percentage of early deaths occur. In addition, GC mortality has not been decreasing satisfactorily in this country. It is necessary to restructure GC control in Brazil, including technology incorporation and doctor training. Special emphasis should be placed on HPV vaccination and Papanicolaou test adherence, because CC continues to be at the core of the GC problem in Brazil.

AFFILIATIONS¹Brazilian National Cancer Institute, Rio de Janeiro, Brazil²Brazilian Gynecologic Oncology Group, Grupo EVA, Brazil³Federal University of Minas Gerais, Minas Gerais, Brazil⁴Global Cancer Institute, Boston, MA⁵Massachusetts General Hospital, Boston, MA**CORRESPONDING AUTHOR**

Angelica Nogueira-Rodrigues, PhD, School of Medicine, Federal University of Minas Gerais, Street Alfredo Balena 110, Belo Horizonte – Minas Gerais, Brazil; e-mail: angelica.onco@uol.com.br.

PRIOR PRESENTATION

Presented at the Annual Meeting of the Gynecological Oncology Society, March 12-15, 2017, National Harbor, MD.

AUTHOR CONTRIBUTIONS

Conception and design: Eduardo Paulino, Paul Goss, Angelica Nogueira-Rodrigues

Administrative support: Andreia Cristina de Melo

Provision of study material or patients: Andreia Cristina de Melo, Paul Goss, Angelica Nogueira-Rodrigues

Collection and assembly of data: Eduardo Paulino, Andreia Cristina de Melo, Agnaldo Lopes Silva-Filho, Luiza de Freitas Maciel, Luiz Claudio Santos Thuler

Data analysis and interpretation: Eduardo Paulino, Andreia Cristina de Melo, Agnaldo Lopes Silva-Filho, Luiza de Freitas Maciel, Luiz Claudio Santos Thuler, Angelica Nogueira-Rodrigues

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/site/misc/authors.html.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Eduardo Paulino

Honoraria: AstraZeneca, MSD, Roche

Consulting or Advisory Role: AstraZeneca, MSD, Roche

Speakers' Bureau: MSD, AstraZeneca, Roche

Travel, Accommodations, Expenses: AstraZeneca, Roche, MSD

Andreia Cristina de Melo

Honoraria: MSD Oncology, Novartis, BMS Brazil

Speakers' Bureau: BMS Brazil, MSD Oncology

Research Funding: Roche (Inst), MSD Oncology (Inst), BMS Brazil (Inst), Novartis (Inst), Clovis Oncology (Inst), AstraZeneca (Inst)

Travel, Accommodations, Expenses: MSD Oncology

Angelica Nogueira-Rodrigues

Honoraria: Roche, MSD, AstraZeneca

Consulting or Advisory Role: Roche, AstraZeneca, MSD, Eisai

No other potential conflicts of interest were reported.

REFERENCES

1. American Cancer Society: Cancer Facts & Figures 2018. Atlanta, GA: American Cancer Society, 2018
2. Instituto Nacional de Câncer: Estatísticas de câncer [in Portuguese]. <https://www.inca.gov.br/numeros-de-cancer>
3. Atlas do Desenvolvimento Humano no Brasil [in Portuguese]. <http://atlasbrasil.org.br/2013/>
4. Instituto Nacional de Câncer. <https://www.inca.gov.br/>
5. Instituto Brasileiro de Geografia e Estatística. <https://www.ibge.gov.br/>
6. DATASUS. <https://datasus.saude.gov.br/>
7. International Agency for Research on Cancer: Cancer today. <http://gco.iarc.fr/today/home>
8. Ministério da Saúde. <http://portalquivos2.saude.gov.br/>
9. de Oliveira MM, Andrade SSC de A, de Oliveira PPV, et al: Cobertura de exame Papanicolaou em mulheres de 25 a 64 anos, segundo a Pesquisa Nacional de Saúde e o Sistema de Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico, 2013 [in Portuguese]. Rev Bras Epidemiol [epub ahead of print on August 27, 2018] http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1415-790X2018000100413&Ing=pt&tlng=pt
10. Croso C, Vóvio C, Masagão V: Latin America: Literacy, adult education and the international literacy benchmarks. AED 71, 2008 <https://www.dv-international.de/en/adult-education-and-development/editions/aed-712008/national-and-regional-reflections-on-operationalising-the-benchmarks/latin-america-literacy-adult-education-and-the-international-literacy-benchmarks/>
11. Paulino E, de Melo AC, Nogueira-Rodrigues A, et al: Gynecologic cancer in Brazil and the law of sixty days. J Gynecol Oncol 29:e44, 2018
12. Paulino E, Nogueira Rodrigues A, Strasser-Weippl K, et al: Barriers to primary debulking surgery for advanced ovarian cancer in Latin America. Int J Gynecol Cancer 27:1645-1649, 2017
13. Ministério da Saúde: Portaria No. 931, de 10 de Maio de 2012 [in Portuguese]. https://bvsms.saude.gov.br/bvs/saudelegis/gm/2012/prt0931_10_05_2012.html
14. Ministério da Saúde: Plano de expansão da radioterapia no SUS [in Portuguese]. <https://www.saude.gov.br/ciencia-e-tecnologia-e-complexo-industrial/complexo-industrial/plano-de-expansao-da-radioterapia-no-sus>
15. de Araújo LP, de Sá NM, Atty ATdM: Necessidades atuais de radioterapia no SUS e estimativas para o ano de 2030 [in Portuguese]. Rev Bras Cancerol 62:35-42, 2016
16. Ministério da Saúde: PNI-Programa Nacional de Imunizações [in Portuguese]. <https://www.saude.gov.br/images/pdf/2017/julho/28/Boletim-informativo.pdf>
17. Nogueira-Rodrigues A, Bukowski A, Paulino E, et al: An alert to Latin America: Current human papillomavirus vaccination trends highlight key barriers to successful implementation. Cancer 123:2193-2199, 2017
18. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018

APPENDIX

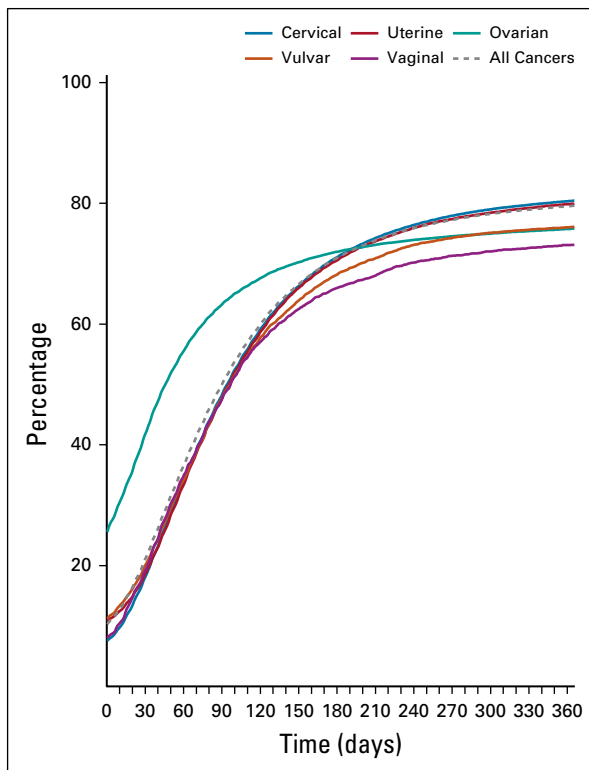


FIG A1. Cumulative percentage of women treated per day after diagnosis, by cancer type.

TABLE A1. Brazilian Population Covered by PBCRs, Brazil, 2000-2015

Year	PBCR ^a Coverage Population	Brazilian Population	Level of Representation (%)
2000	34,390,912	173,448,354	20
2001	37,470,968	175,885,184	21
2002	37,983,777	178,276,114	21
2003	38,868,975	180,619,076	22
2004	38,653,167	182,911,508	21
2005	39,144,892	185,150,822	21
2006	32,984,962	187,335,121	18
2007	32,875,966	189,462,729	17
2008	35,003,352	191,532,420	18
2009	34,577,794	193,543,989	18
2010	33,645,039	195,497,791	17
2011	33,496,820	197,397,018	17
2012	29,127,081	199,242,462	15
2013	25,214,241	201,032,714	13
2014	23,563,176	202,768,337	12
2015	20,818,797	204,450,380	10

NOTE. Source of data: population-based cancer registries and Department of Informatics of the Ministry of Health of Brazil.

Abbreviation: PBCR, population-based cancer registry.

^aPBCRs with data available from 2000 to 2015: State of Alagoas (2010-2011), Angra dos Reis (2007-2014), Aracajú (2000-2014), Regional of Barretos (2000-2015), Belém-Ananindeua (2000-2015), Belo Horizonte (2000-2015), Campinas (I: 2000-2005, II: 2010-2015), Campo Grande (2000-2003, 2008-2012), Cuiabá-Várzea Grande (2000-2011), Curitiba (2000-2015), Distrito Federal (2000-2009), Florianópolis (2008-2014), Fortaleza (2000-2009), Goiânia (2012-2013), Jahu (2000-2015), João Pessoa (2000-2015), Manaus (2000-2011), Mato Grosso Interior (2001-2005), Natal (2000-2008), Palmas (2000-2013), Poços de Caldas (2007-2013), Porto Alegre (2000-2012), Recife (2000-2014), Vitória Metropolitan Region (2000-2012), State of Roraima (2003-2010), Salvador (2000-2005), Santos (2008-2009), São Paulo (2000-2015), Teresina (2000-2006).

TABLE A2. Incidence and Mortality Trends in Age-Adjusted Rates, Brazil, 2000-2017

Incidence/Mortality	Segment	Lower End Point	Upper End Point	APC	Lower CI	Upper CI	Test (t)	Prob > t
Incidence								
Cervical	1	2000	2011	-4.6 ^a	-5.5	-3.7	-11.3	0.0
	2	2011	2015	-10.3 ^a	-15.7	-4.5	-3.8	0.0
Uterine	1	2000	2015	-0.2	-0.6	0.3	-0.6	0.5
Ovarian	1	2000	2005	-5.1 ^a	-7.3	-2.9	-5.2	0.0
	2	2005	2013	-0.6	-2.1	0.9	-0.9	0.4
	3	2013	2015	-9.9	-21.5	3.3	-1.8	0.1
Vulvar	1	2000	2015	-1.6	-3.4	0.2	-1.9	0.1
Vaginal	1	2000	2015	-4.7 ^a	-6.4	-3.0	-5.7	0.0
Mortality								
Cervical	1	2000	2015	-0.8 ^a	-1.0	-0.6	-9.3	0.0
	2	2015	2017	3.2	-0.6	7.2	1.8	0.1
Uterine	1	2000	2002	-4.8	-10.5	1.3	-1.8	0.1
	2	2002	2014	-1.2 ^a	-1.6	-0.8	-7.0	0.0
	3	2014	2017	0.8	-1.8	3.6	0.7	0.5
Ovarian	1	2000	2017	0.6 ^a	0.4	0.9	5.3	0.0
Vulvar	1	2000	2002	-22.1 ^a	-37.7	-2.6	-2.4	0.0
	2	2002	2017	1.2 ^a	0.3	2.1	3.0	0.0
Vaginal	1	2000	2017	-0.8	-2.0	0.3	-1.5	0.2

NOTE. Source of data: population-based cancer registries, National Mortality Information System, and Department of Informatics of the Ministry of Health of Brazil.

Abbreviations: APC, annual percent change; Prob, probability.

^aThe APC is significantly different from 0 at $\alpha = 0.05$.

TABLE A3. Age-Adjusted Incidence Rates per 100,000 by PBCR, Brazil, 2000-2015

PBCR	Cervical			Uterine			Ovarian			Vulvar			Vaginal		
	Mean	P25	P75	Mean	P25	P75	Mean	P25	P75	Mean	P25	P75	Mean	P25	P75
Southwest region	10.80	8.49	12.28	7.36	5.92	8.69	5.86	4.76	6.75	1.04	0.59	1.38	0.38	0.13	0.47
Angra dos Reis (2007-2014)	12.59	9.41	17.95	4.58	2.92	5.55	3.40	2.21	4.29	1.30	1.00	1.43	0.33	0.00	0.24
Belo Horizonte (2000-2015)	13.44	11.10	12.55	7.74	7.21	8.54	7.09	6.56	7.68	0.99	0.83	1.03	0.44	0.28	0.48
Campinas (I: 2000-2005; II: 2010-2015)	7.61	6.64	7.87	7.71	5.14	10.65	6.60	4.61	8.05	0.73	0.31	1.01	0.41	0.22	0.56
Distrito Federal (2000-2009)	18.30	12.44	20.30	7.43	6.73	8.40	6.56	5.40	7.71	0.99	0.68	0.98	0.64	0.35	0.54
Vitória Metropolitan Region (2000-2012)	11.74	9.54	13.69	3.56	2.17	5.32	3.80	3.13	4.43	0.42	0.38	0.50	0.21	0.10	0.30
Jahu (2000-2015)	8.49	6.87	10.86	10.54	7.00	13.31	7.03	5.64	7.77	0.87	0.00	1.52	0.65	0.00	1.12
Poços de Caldas (2007-2013)	7.45	5.96	8.07	8.62	7.02	9.82	5.59	4.32	7.08	1.86	0.45	3.17	0.30	0.00	0.51
Regional of Barretos (2000-2015)	9.25	7.60	10.93	5.96	5.34	6.47	3.81	3.07	4.88	0.80	0.44	1.31	0.17	0.00	0.18
Santos (2008-2009)	6.17	5.97	6.37	8.24	7.76	8.71	6.93	6.05	7.81	1.08	0.69	1.46	0.11	0.06	0.17
São Paulo (2000-2015)	12.97	9.35	14.24	9.26	7.89	10.10	7.74	6.64	7.83	1.34	1.10	1.43	0.52	0.31	0.61
South region	13.92	11.54	16.19	8.71	7.78	9.70	7.86	6.21	8.33	1.10	0.70	1.49	0.44	0.27	0.56
Curitiba (2000-2015)	12.75	10.73	14.70	8.26	7.51	9.33	7.24	6.44	7.88	0.87	0.69	1.01	0.21	0.12	0.33
Florianópolis (2008-2014)	15.56	13.66	18.00	9.39	8.29	10.16	7.65	6.74	8.25	1.39	0.69	2.17	0.49	0.31	0.69
Porto Alegre (2000-2012)	13.45	10.24	15.87	8.47	7.54	9.62	8.68	5.45	8.87	1.04	0.71	1.30	0.61	0.39	0.67
Middle-West region	19.00	15.90	21.01	5.58	4.76	5.71	5.29	4.70	5.77	0.74	0.56	0.91	0.52	0.30	0.68
Campo Grande (2000-2003, 2008-2012)	19.41	15.39	20.54	5.91	5.47	6.52	7.53	6.69	8.67	1.11	0.97	1.33	0.69	0.26	1.00
Cuiabá-Várzea Grande (2000-2011)	27.89	20.97	33.15	5.99	4.01	5.79	5.70	4.61	6.60	0.82	0.53	0.91	0.50	0.21	0.66
Goiânia (2012-2013)	13.07	12.28	13.86	6.85	6.51	7.20	5.48	5.44	5.52	0.62	0.46	0.77	0.49	0.45	0.52
Mato Grosso Interior (2001-2005)	15.61	14.96	16.50	3.55	3.06	3.34	2.43	2.04	2.30	0.41	0.27	0.64	0.41	0.29	0.55
Northeast region	19.98	15.98	22.58	6.81	5.74	7.76	6.80	5.95	7.73	0.80	0.56	0.96	0.51	0.25	0.65
Aracajú (2000-2014)	18.87	13.38	21.28	8.81	7.58	9.70	7.58	6.18	9.11	1.03	0.77	1.26	0.60	0.00	0.73
Fortaleza (2000-2009)	20.87	18.3	21.85	6.50	5.80	7.15	8.32	7.43	8.92	0.56	0.40	0.71	0.45	0.30	0.50
João Pessoa (2000-2015)	20.41	16.81	24.74	7.93	5.93	10.39	6.38	5.11	8.33	0.95	0.59	1.03	0.75	0.36	1.04
Natal (2000-2008)	16.66	11.76	21.27	8.94	7.25	9.74	7.26	6.21	8.35	0.95	0.46	1.38	0.34	0.19	0.4
Recife (2000-2014)	20.67	13.53	26.6	8.31	6.83	9.87	6.95	6.37	7.47	0.89	0.72	1.02	0.41	0.20	0.56
Salvador (2000-2005)	14.83	14.19	15.66	6.27	5.28	7.03	6.61	6.32	6.69	0.81	0.60	1.06	0.58	0.38	0.79
State of Alagoas (2010-2011)	19.79	19.02	20.56	4.13	4.12	4.13	4.77	4.71	4.83	0.53	0.52	0.55	0.69	0.60	0.78
Teresina (2000-2006)	27.72	20.88	28.67	3.56	3.11	4.08	6.50	5.24	8.11	0.68	0.43	0.65	0.22	0.00	0.39
North region	33.16	26.15	38.98	5.68	4.27	6.29	5.14	3.43	6.43	0.57	0.30	0.67	0.36	0.17	0.49
Belém-Ananindeua (2000-2015)	31.25	25.55	37.75	4.94	4.33	5.30	5.55	4.76	6.11	0.91	0.61	1.11	0.75	0.57	0.91
Manaus (2000-2011)	44.15	39.78	46.87	5.17	4.20	6.04	5.31	4.26	5.86	0.78	0.59	0.92	0.24	0.11	0.26
Palmas (2001-2012)	32.61	25.00	34.3	6.98	3.86	7.18	7.21	3.01	10.53	0.19	0.00	0.00	0.00	0.00	0.00
State of Roraima (2003-2010)	24.63	14.25	36.98	5.64	4.68	6.63	2.49	1.68	3.22	0.41	0.00	0.66	0.46	0.00	0.80

NOTE. Source of data: population-based cancer registries and Department of Informatics of the Ministry of Health of Brazil. Abbreviations: P25, 25th percentile; P75, 75th percentile; PBCR, population-based cancer registry.

TABLE A4. Distribution of Selected Characteristics According to Brazilian Macroregion Where Hospital is Located, Brazil, 2000-2015

Variable	Southeast	South	Northeast	Middle-West	North
Total ^a	169,908 (44.4)	63,411 (16.6)	108,367 (28.3)	11,889 (3.1)	29,357 (7.7)
Age, years, mean (SD)					
Cervical	48.7 (15.4)	46.3 (15.1)	49.9 (15.3)	48.2 (14.8)	48.8 (14.4)
Uterine	62.6 (11.6)	62.1 (12.2)	61.0 (12.3)	58.2 (12.9)	58.0 (12.0)
Ovarian	53.8 (16.0)	54.5 (15.9)	52.5 (16.8)	50.3 (17.1)	48.0 (17.3)
Vulvar	64.0 (16.1)	64.0 (16.1)	64.0 (16.9)	61.1 (16.7)	59.3 (16.7)
Vaginal	59.2 (17.2)	58.3 (16.5)	59.2 (16.4)	54.7 (18.4)	54.8 (14.5)
Time to first treatment \geq 60 days					
Cervical	52,757 (61.2)	20,167 (56.8)	33,318 (54.0)	3,295 (45.0)	12,432 (64.2)
Uterine	16,860 (59.6)	4,979 (56.2)	5,250 (58.5)	557 (45.7)	831 (65.1)
Ovarian	4,961 (26.5)	1,479 (24.4)	2,153 (28.6)	272 (25.6)	506 (38.5)
Vulvar	2,847 (58.7)	646 (44.3)	809 (55.2)	112 (45.3)	208 (62.8)
Vaginal	837 (55.6)	253 (51.7)	354 (47.6)	46 (37.1)	109 (63.0)
Locally advanced or advanced clinical stage ^b					
Cervical	43,789 (52.3)	16,596 (70.1)	36,517 (63.7)	2,662 (73.6)	11,831 (69.3)
Uterine	6,945 (30.3)	1,881 (31.7)	1,699 (34.7)	162 (33.1)	210 (32.7)
Ovarian	10,703 (65.2)	3,160 (70.9)	3,729 (71.0)	368 (69.3)	519 (60.6)
Vulvar	17,41 (41.7)	440 (52.3)	540 (50.8)	50 (61.0)	97 (53.0)
Vaginal	761 (65.2)	202 (68.0)	303 (68.4)	31 (75.6)	59 (79.7)
Early death ^c					
Cervical	5,777 (18.4)	1,655 (6.8)	3,923 (8.7)	367 (7.0)	2,055 (10.8)
Uterine	1,624 (18.3)	501 (9.1)	623 (10.9)	69 (8.2)	139 (10.6)
Ovarian	1,647 (24.8)	792 (16.9)	1,159 (19.7)	128 (14.9)	265 (17.5)
Vulvar	432 (24.1)	146 (13.6)	120 (10.7)	15 (8.2)	42 (12.4)
Vaginal	118 (22.8)	46 (14.2)	60 (13.4)	3 (3.5)	20 (11.7)

NOTE. Data are presented as No. (%) unless indicated otherwise. Source of data: hospital-based cancer registries.

Abbreviation: SD, standard deviation.

^aRow percentage.

^bAdvanced stage: stages II to IV for cervix and vaginal cancer; stages III and IV for ovarian, endometrial, and vulvar cancer.

^cEarly death: death at the end of the first line of treatment.