

Breast and gynecologic cancers as a Brazilian health priority

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SUMMARY

OBJECTIVE: Cancer imposes a profound burden on low- and middle-income countries where 65% of the global cancer deaths occurred in 2020. The objective of the present review was to describe female cancer epidemiology in Brazil, barriers to prevention, screening, and treatment, and to propose strategies to a better control.

METHODS: For the process of literature search and scientific acquisition, we have utilized the terms “female cancer” AND “breast cancer,” AND “cervical cancer” AND “endometrial cancer” AND “ovarian cancer” AND “Brazil” in PubMed. References of the articles included in this review were manually searched in order to identify relevant studies on the topic. The official Brazilian epidemiology data were extensively analyzed at the governmental site www.inca.gov.br.

RESULTS: Considering cases of breast and gynecologic cancers together, 105,770 new cases are expected to be diagnosed yearly, positioning female cancer as the highest cancer incidence in Brazil. Female breast cancer is the most common and the leading cause of death from cancer in the female population in all regions of Brazil, except in the North, where cervical cancer ranks first. Cervical cancer, a preventable disease, corresponds to the third-most common neoplasia in women, with higher incidences in the North and Northeast regions of Brazil. An upward trend has been observed in endometrial cancer incidence, a tendency that follows the increase of its two most common risk factors: population aging and obesity. Ovarian cancer currently occupies the eighth position among female cancers in Brazil, but it is the most lethal gynecologic cancer. The main strategies to reduce female cancer mortality rates are the reduction of inequalities in healthcare services and the early diagnosis of cases. The lack of a specific national cancer program results in a reactive and unplanned approach to healthcare provision, ultimately leading to suboptimal resource utilization and higher expenditure.

CONCLUSION: Analyzed together, breast and gynecologic cancers correspond to the leading cause of cancer in Brazil. A heterogeneous group, female cancer includes diseases with a high primary and secondary prevention potential. The organization of a female cancer program in Brazil prioritizing primary and secondary prevention strategies, such as adequate mammography screening and human papillomavirus vaccination coverage, could significantly improve female cancer control in the country.

KEYWORDS: Neoplasms. Women. Epidemiology. Prevention and control.

INTRODUCTION

Cancer imposes a profound burden on low- and middle-income countries (LMICs), where 65% of the global cancer deaths occurred in 2020¹. The Brazilian National Cancer Institute (INCA) expects more than 704,000 new cancer cases annually for the triennium from 2023 to 2025. Excluding non-melanoma skin cancer, 483,000 new cases are expected, with 50.5% of them (244,000 cases) in women. In the female population, breast cancer (BC) is the most common neoplasia with 73,610 new cases per year, followed by colorectal cancer with 23,660 cases, and cervical cancer (CC) with 17,010 cases². Considering cases of breast and gynecologic cancers together, 105,770 new cases are expected to be diagnosed yearly, positioning female cancer as the highest cancer incidence in Brazil.

BC is the most common incident, excluding non-melanoma skin cancers, and the most prevalent tumor in all Brazilian regions². It is also the leading cause of death from cancer in the female population in all regions of Brazil, except in the North, where CC ranks first. The BC mortality rate adjusted for age was 11.84 deaths per 100,000 women in 2020, with the highest rates in the Southeast and South regions, with 12.64 and 12.79 deaths per 100,000 women, respectively. In the Brazilian cancer mortality rate historical series, it is possible to observe an upward trend over the past few decades, with a certain deceleration and stabilization in the South and Southeast regions, and an increase in the other regions, between 2000 and 2015³. Limited data on the clinical characteristics, treatment, and outcomes of patients diagnosed with BC are

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available in Brazil. The AMAZONA retrospective cohort study enrolled 4,912 patients within 28 Brazilian institutes from June 2008 to January 2009⁴. Over 2,200 women were included in the analysis. A high proportion of patients diagnosed with BC younger than 50 years old was reported (41%), and approximately 70% of the patients had hormonal-receptor-positive disease. The characteristics of those young women with BC were later evaluated in the prospective AMAZONA III study. Out of 2,888 women diagnosed with BC, 486 (17%) were younger than 40 years old and presented more frequently with stage III, T3/T4, grade 3 tumors, HER-2-positive, luminal B-like disease, and triple-negative subtypes⁵.

The lifetime risk of BC for a woman is about 12%, a percentage with the potential to increase significantly when a pathogenic variant in a gene predisposing to BC is found. For instance, the cumulative risk of BC by the age of 80 years is 72% for *BRCA1* mutation carriers (mut) and 69% for *BRCA2*mut. It is of utmost importance to perform a genetic evaluation in case of suspicion of hereditary BC.

The CC incidence rate is approximately 15 per 100,000 women, which corresponds to the third-most common neoplasia in women, with higher incidences in the North and Northeast regions of Brazil^{2,6}. The CC-adjusted incidence rate for the whole population fell from 21.15 per 100,000 women in 2000 to 11.44 per 100,000 women in 2015, an annual percentage change of -4.6 from 2000 to 2011 and -10.3 from 2011 to 2015⁷. Incidence rates were higher in the Northern region (20.48 per 100,000), followed by the Northeast region (17.59 per 100,000)⁶. The mean age of CC diagnoses is 48.7 years. It was also observed that 62% of the patients have less than 8 years of schooling and 60% are diagnosed in stages II–IV, locally advanced disease. Squamous cell carcinoma is the most common histology (79%), followed by adenocarcinoma (9.5%)⁷. Recent data have shown that, as for mortality, between 2000 and 2020, 108,590 deaths from CC occurred nationwide. The mean age-adjusted mortality rates according to race/skin color were 3.7/100,000 for white, 4.2/100,000 for black, 2.8/100,000 for yellow, and 6.7/100,000 for indigenous women. Taking the mortality rates in white women as a reference, there was a 27% increase in death risk in black women (RR=1.27) and 82% in indigenous women (RR=1.82)⁸.

Uterine cancer has recently surpassed ovarian cancer and become the second-most common gynecologic cancer in Brazilian women with an estimated risk of 7.08 new cases per 100,000 women^{6,7}. This tendency follows the increase of the two most common risk factors for uterine cancer: population aging and obesity. According to the Ministry of Health, 33% of Brazilian women were overweight and 32% were obese in 2022,

in contrast to 29 and 16.5%, respectively, in 2010⁹. Regarding population aging, life expectancy in Brazilian women increased and reached 80.5 years in 2021¹⁰. The highest incidence rates of uterine cancer were seen in the higher-income regions of the country, such as in the southern and southeastern states. The mean age at diagnosis was 61.9 years with 55% of the patients reporting less than 8 years of schooling. The majority of uterine cancer patients are diagnosed with early-stage disease (68% with stages I–II)⁷.

Ovarian cancer occupies the eighth position among female cancers in Brazil and is more common in the Southeastern and Southern regions. Between 2000 and 2005, the adjusted incidence rate for the population declined from 8.62 to 6.62 (an annual percentage change of -5.1), remaining without significant changes until 2015. The mean age of diagnosis for ovarian cancer is 53.3, with 51% having less than 8 years of schooling and 67% diagnosed in stages III–IV⁷. Approximately 25% of ovarian cancer patients have a genetic predisposition to cancer, half of them with a pathogenic variant in *BRCA1* or *BRCA2*. Genetic testing is essential for hereditary ovarian cancer control and to tailor maintenance therapy with PARP inhibitors.

BARRIERS TO DISEASE CONTROL AND STRATEGIES TO OVERCOME IT

Despite the existence of a publicly funded healthcare system offering universal coverage, there are still wide socioeconomic and ethno-racial inequities in access to healthcare in Brazil¹¹. Brazil reports a global health expenditure of 9% of its gross domestic product. However, only half of this budget is provided by the government to cover 75% of the population under the public healthcare system, and the other half is paid by the remaining 25% of Brazilians through their private health insurances^{12,13}.

Starting with screening, mammographic screening has been described as an effective method to detect early BC. Women who regularly participate in a screening program can have their risk of dying of BC reduced by up to 60%¹⁴. INCA issued an official recommendation for BC screening in 2004, updated in 2015, which recommends mammography biennially for women aged 50–69 years. However, in Brazil, mammographic screening has been an opportunistic procedure. Despite educational campaigns, mammography coverage is currently around 35% of the target population, well below the 70% recommended worldwide¹⁵.

Changing gears to CC, this is a highly preventable neoplasia with periodically performed Pap smears and vaccinations. In 2020, the World Health Organization (WHO) launched a

global Cervical Cancer Elimination Initiative and stated that 90% of girls should be vaccinated by the age of 15 years, 70% of women should be screened with high-performance tests by the ages of 35 and 45 years, and 90% of precancerous lesions should be treated. The coverage of fully vaccinated girls in Brazil was only 57.1% in 2021, although an increase was seen compared to 2020 (46.7%)¹⁶. Multiple barriers to vaccination can be listed: limited understanding of human papillomavirus (HPV) and HPV-related diseases, being unaware of or forgetting about the need for additional doses, safety concerns about the vaccine, discomfort related to talking about sexual behavior, lack of time for discussions about the vaccine among clinicians, lack of a clear recommendation from a healthcare provider, and parental belief that their children is too young for the vaccine and/or not sexually active¹⁷. The advent of HPV prophylactic vaccination offers a potential large step toward CC prevention. Based on the high incidence of HPV-related cancers, the strong carcinogenic potential of certain HPV strains, and numerous trials proving high efficacy of vaccines, prophylactic immunization is considered one of the most important tools to alter the incidence of HPV-associated cancers in countries throughout Latin America and other LMICs worldwide. Large-scale HPV immunization can reduce lives lost due to preventable cancers and relieve health systems strained by costly treatment of late-stage cancers. However, despite its proven efficacy and safety, vaccine uptake has been lower than expected, and among the several reasons for this are high cost of the HPV vaccine and requirement for multiple doses, limited knowledge of HPV vaccine efficacy and safety, cultural barriers, insufficient provider recommendations, and inadequate implementation strategies. Brazil is in danger of repeating the low adherence to Pap smear screening for HPV vaccination. Brazil has a long history of high vaccination coverage with robust national immunization programs, especially compared to other developing regions. So, the country needs to properly utilize its existing vaccination platform. Regarding Pap smear, Brazilian consolidated coverage is around 20%, and it is not homogeneous among all regions, with the highest rate in the South and the lowest in the Northeast. The main reasons reported by Brazilian women not to perform it are as follows: feeling that it is not necessary (45%), having no formal recommendation to perform (14%), and being ashamed (13%)¹⁸.

Unfortunately, there is no reliable screening test to detect ovarian cancer in its earlier stages, leading to a diagnosis at advanced stages (FIGO III and IV) in around 75% of the cases. Every woman with a diagnosis of ovarian cancer should be offered germline *BRCA1/2* testing since this information helps delineate treatment and, when a mutation is detected, should

also trigger germline testing in healthy relatives. For women who carry mutations in a propensity gene, it is recommended to perform prophylactic salpingo-oophorectomy¹⁹. Unfortunately, access to genetic testing is still dismal in the public health system as well as the availability of genetic counseling.

Timely access to proper treatment continues to be an issue in Brazil. The time interval between diagnosis and treatment of BC and the impact of health insurance coverage were analyzed in a cohort from the AMAZONA III study, with 1,709 stage I–III patients²⁰. The diagnosis-to-treatment interval was higher in women treated in the public versus in the private system (56 vs. 34 days, $p < 0.0001$), independent of clinical stage, type of treatment (systemic vs. surgery upfront), subtype, and country region²⁰. According to the Panorama of Gynecologic Cancer in Brazil, the time to start treatment after having a confirmatory biopsy is over 30 days in more than 70% of gynecologic cancer patients. Access to proper treatment is also an issue. For instance, endometrial cancer is usually diagnosed in its early stages (FIGO stages I–III), where treatment consists mainly of surgery and radiotherapy. Surgery has evolved in the past 10–15 years and is done preferentially via minimally invasive surgery (MIS). Unfortunately, access to MIS (laparoscopic or robotic) is not a reality in the public health system. Brazil also faces a lack of radiotherapy facilities (including brachytherapy), and the distribution is not homogeneous across the country²¹. CC, which is usually diagnosed in locally advanced stages (FIGO stages II–IV) where radiotherapy is necessary, also struggles with this challenge. Another common issue in gynecologic cancers is the lack of trained specialists since there is no formal gynecologic oncology subspecialization or society in Brazil.

Access to cutting-edge systemic treatments is fundamental for improving survival outcomes. In Sistema Único de Saúde, there is still no access to therapies like cyclin inhibitors, pertuzumab, immunotherapy, and PARP inhibitors, among others, that provide clinically meaningful benefits. Of note, some of these treatments are already officially incorporated into the public system, but, for several reasons, patients still do not have access to them.

There is a great need to expand hereditary cancer testing and counseling in Brazil, and changing current policies is essential to accomplishing this goal. Vigilance in the ongoing implementation, understanding Brazil's unique social and structural barriers, and mounting a strong and timely response to this public health problem are crucial to attaining a significant impact. Increased knowledge and awareness of genetics education among nongenetic healthcare professionals, as well as the general population, public health officials, and patient organizations, would not only increase access to genetic services

for patients, but also advance translational efforts to improve cancer care and outcomes.

Focusing on minorities, worldwide, the transgender patient population remains underrepresented in cancer research and cancer care standards. Additionally, the acceptance of transgender rights does not translate automatically to competence in administering equitable patient care. In one study of surveyed healthcare providers, only 35% felt comfortable and 29% felt equipped to provide routine gynecologic care to transgender females and transgender males, respectively²². In the same study, 59% of providers were unaware of BC screening recommendations for transgender females²². Furthermore, transgender patients frequently report significant distrust of the healthcare system related to experiences of discrimination and marginalization²³.

Recently, INCA launched national recommendations on healthy nutrition and exercise to educate the population about the risks of a sedentary lifestyle and poor eating habits and their relationship to cancer. Concerted efforts now need to be made to ensure that these primary prevention measures reach the public.

The main international strategies to reduce female cancer-mortality rates are the reduction of inequalities in healthcare services and the early diagnosis of cases. In many countries, the lack of specific National Cancer Control Programmes results in a reactive and unplanned approach to healthcare provision, ultimately leading to suboptimal resource utilization

and higher expenditure¹². The organization of a comprehensive female cancer program in Brazil prioritizing primary and secondary prevention strategies could improve breast and gynecologic cancer control.

AUTHORS' CONTRIBUTIONS

ANR: Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **DDR:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **DAS:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **EP:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **LCGL:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **MS:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **MRM:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **PMH:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing.

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