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Population-based study: breast cancer mortality trend in women in the state of Paraná from 2000 to 2017

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ABSTRACT

Objective: Breast cancer is one of the main challenges in Brazilian public health due to the high associated mortality. Mortality has different patterns according to age group, usually increasing with age. The demographic stability in Paraná, with the growth of the elderly population, has a direct impact on the epidemiology of this disease. This study aimed to assess, on a population-based basis, the rates and trends of mortality from breast cancer among the age groups of women in the state of Paraná from 2000 to 2017. **Methods:** A statistical descriptive retrospective series study was carried out to analyze, on a population-based basis, the trend in breast cancer mortality rates among the age groups of women in the state of Paraná, from 2000 to 2017. The trend analysis of annual mortality rates was carried out through the software and simple linear regression models. **Results:** The population-based analysis showed that women aged 45–54 and 55–64 years had the highest number of deaths during the study period. However, when calculating the mortality rates by age group, it was observed that the mortality pattern increases proportionally to the longevity of the female population in the state. Trend analyses indicated an upward trend in mortality among women aged 25–34 years throughout the study period. The same trend was observed in women aged 35–44 years, but in a shorter period, from 2005 to 2017. **Conclusion:** Mortality rates, per 100,000 women, were directly proportional to age, increasing with age, indicative of greater mortality from the disease in elderly women. There was a trend of increasing mortality, with statistical significance, in the age groups from 25 to 34 and 35 to 44. The others were considered stable trends.

KEYWORDS: age distributions; age-specific death rates; mortality rates; breast tumor.

INTRODUCTION

Breast cancer is the largest cause of cancer death in Brazil and worldwide and is the most frequent type, except for non-melanoma skin tumors. One in four diagnosed cases of cancer in women is breast cancer, and the global incidence progressive increasing in both developed and developing countries[1-3]. In Brazil, there were estimated 59,700 new cases of the disease in 2018, representing 29.5% of the total incidence of cancer, with an associated mortality rate of 14%[4]. In the Brazilian regions, the South has the second highest incidence of breast cancer, with a rate of 65 cases per 100,000 women, behind only Southeast Region[3,5,6].

It is a heterogeneous disease, with multiple factorial etiologies and a complex relationship of hormonal, genetic, and environmental factors, and is closely related to the aging process. Postmenopausal women have considerably higher incidence and mortality rates than women of reproductive age; the peak occurs from 65 to 80 years[7-10]. Exposure to carcinogenic agents for long periods, mutations by failure in cellular DNA repair, and prolonged latency period could explain the higher frequency of neoplasia[9]. However, breast tumors tend to have a faster developmental profile and are biologically more aggressive in younger patients[9,11].

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The current demographic scenario in Brazil has had a rapid growth of the elderly population. The estimate is that in 2030 we will have an age pyramid similar to that of developed countries, and by 2060 the number of Brazilians over 65 years old could quadruple. Paraná follows the same accelerated pattern of population aging. The elderly population in the state, in 2021, represents 16% of the population of Paraná (1.8 million inhabitants), which represents an increase of 4.8 percentage points in relation to the 2010 IBGE Census[12].

The aging process Brazilian population goes through and the natural history of breast cancer have a direct impact on the epidemiological health profile of the female population, which justifies the importance of a population-based study in epidemiological evaluations of breast cancer mortality, as well as on the assessments of the target population for public policies to screen the disease.

Our study aimed to analyze, on a population basis, the rates and trends mortality from breast cancer among the age groups of women in the state of Paraná, from 2000 to 2017.

METHODS

A retrospective time series study was carry out to analyze, on a population basis, the trend of breast cancer mortality rates in the age groups of women in the state of Paraná, from 2000 to 2017.

Data on all deaths were extracted from records in the Mortality Information System of Paraná/DATASUS (SIM/DATASUS), from the tabulation from 1999, which had breast cancer as their base cause (CID10 code: C50). Information on the female population of Paraná was collected from the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* — IBGE) based on the 2000 and 2010 demographic censuses and intercensus population projections for non-census years. Work performed with public domain data in accordance to item III, sole paragraph, article 1st, of Brazilian resolution nº 510 of the National Health Council, Ministry of Health, of April 7, 2016: Will not be registered or evaluated by the CEP/CONEP system, research that uses information in the public domain.

With this information, mortality rates per 100,000 women were calculated for each age group during all years of the study. For this calculation, Excel version 2007 was used.

Analyses were performed in six age groups (i.e., from 25 to 34 years; from 35 to 44 years; from 45 to 54 years; from 55 to 64 years; and 75+ years), using the age stratification criteria of the World Health Organization (WHO), every 10 years. Women aged 15–24 years were excluded from the analysis due to insufficient data during the study period.

For the trend analyses, annual mortality rates were calculated, considering as dependent variable "y" and the years of the period studied as the independent variable "x"; mortality rates were standardized by the direct method.

Initially, trend analysis was carried using the Joinpoint program version 4.8.0.1, provided by the National Cancer Institute of the United States, with free access (http://surveillance.cancer.gov/joinpoint/). This program estimates the annual percentage variation (APV), translation of annual percent chance (APC) in English, from a segmented linear regression (Joinpoint regression) and identifies inflection points by intensive statistical methods.

This program provides a 95% confidence interval (95%CI) around APC to determine whether the APC for each segment differs significantly from zero.

The U.S. National Cancer Institute establishes a systematic methodology to characterize trends in studies on cancer incidence and mortality. This methodology is applied globally in research on the disease and is contained in a public document called Cancer Trends Progress Report[13] that, based on the values of the APC, characterizes the trends of the series object of the study, taking into account the following criteria:

- If the absolute value of APC is less than or equal to 0.5% per year ($-0.5 \leq APC \leq 0.5$) and the APC is not statistically significant, the series trend is considered stable.
- When the APC value is greater than 0.5% per year in absolute value ($APC<-0.5$ or $APC>0.5$) and the APC is not statistically significant, the series trend is considered to vary and not significant.
- If APC is statistically significant and significantly positive, it is characterized as an increase trend.
- Variations with statistically significant and significantly negative APC are characterized as a decreasing trend.

In general, APC is significantly different from zero if $APC<-0.5$ or $APC>0.5$. It is also established that APC is statistically significant if $p<0.05$ using Student's t-test.

Although somewhat arbitrary, these categorizations provide a consistent and standardized method for characterizing trends in disparate measures. Statistical significance and the absolute value of change for incidence and mortality trends were used to ensure consistency with all major publications on national cancer trends.

Each inflection point reflects changes in the increase or decline in death rates. The Bayesian information criterion was used to find the inflection points, and for the choice of models, trend variations with a level of statistical significance of 5% were considered.

To complement the trend analyses, simple linear regression models were performed. In the equations ($y=a+bx$) of the model lines, "x" received the minimum value of zero in 2000 and the maximum of 17 in 2017. The value (b), which multiplies "x" in each equation, is the slope coefficient of the line, that is, the greater the module of "b," the more inclined up, from left to right, is the line. Negative value of "b" indicates downward slope, which is equivalent to the decline in the rate trend over that period. Positive value of "b" indicates an upward slope, which is equivalent to the increase in the rate trend over that period. The probability (p) of "b" being statistically equal to zero is equivalent to the fact that there was no change in rates over time.

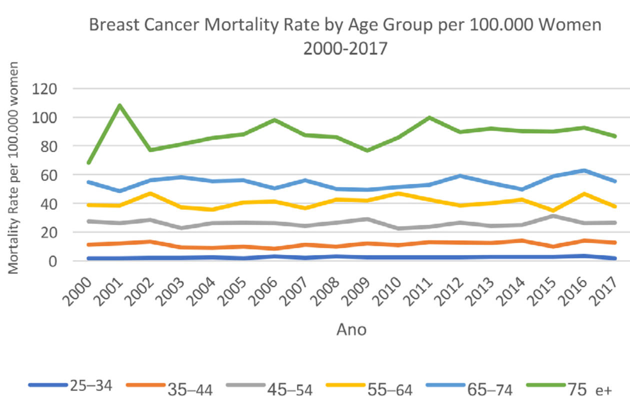
The linear trend equations and model adjustment statistics (R^2 value and the p-value of the model adequacy test) were obtained using the SPSS program, version 19.0. The level of significance adopted was 5%.

RESULTS

The results of the analysis of the historical series of breast cancer mortality in the state of Paraná, between 2000 and 2017, indicated inequalities between the patterns observed for older and younger women.

Initially, with data analysis, it was possible to observe the gross number of deaths per age group over the period studied. The women aged 45–54 and 55–64 years had the highest number of registered deaths. Then, mortality rates were calculated for every 100,000 women, by age group, to observe the behavior of deaths in the population.

Figure 1 shows the behavior of mortality rates per group of 100,000 women in each age group. It is noted that in all years,



Source: Research database (2020).

Figure 1. Behavior of breast cancer mortality rates.

the younger the younger, the lower the mortality rates, while the mortality of those over 75 years is higher compared to the other rates. This age stratum also showed an atypical variation from 2000 to 2002.

The trend in mortality rates for each series formed by age groups in the period was analyzed using Joinpoint. The results are shown in Table 1, which contains the values of the APC, as well as the CI for each age group.

These models only presented inflection for the second age group (from 35 to 44 years), which did not occur in the other.

The analyses of the last four age groups (45–54, 55–64, 65–74, and 75+ years) did not present statistical significance in the APC value, so the trend of the series in these age groups is considered stable.

Regarding the results observed in the age groups in which the APC value presented statistical significance, it was possible to identify an increase in mortality rates of women over 25 and less than 34 years between 2000 and 2017 (APC=1.86; 95%CI 0.1–3.7).

For women aged over 35 and under 44 years, from 2005 to 2017, there was a trend of the series in these age groups (APC=2.71; 95%CI 0.6–4.8).

To expand the information obtained with the Joinpoint system on the trend of the series of the four age groups, whose APC value resulted without statistical significance, the information generated by the linear regression models was used. The results of the equations of the models found values of R^2 and the respective p-values of the F-test are presented by age group in Table 2.

In the analyses of the constructed models, results similar to those obtained by the *Joinpoint* system were obtained. The coefficient of the variable "x" in each constructed model indicates the variation of the mortality rate in the series that corresponds to the respective age group.

The equation of the first line ($y=0.282+0.006x$) represents that, since the year 2000 ($x=0$), for each year from 2001 to 2017, the mortality rate for breast cancer in Paraná, in the age group representing women over the age of 25 and less than 34 years,

Table 1. Average percentage change values according to Joinpoint setting. Paraná, 2000–2017.

Variable	Age group	*Joinpoint*	APC	95%CI – APC		p-value
				LL	UL	
Crude mortality rate from breast cancer	25–34	0	1.86*	0.1	3.7	0.0
	35–44	1 (2004)	-6.44 (2000–2004)	-18.3	7.1	0.3
			2.71* (2004–2017)	0.6	4.8	0.0
	45–54	0	0.1	-0.7	1.0	0.8
	55–64	0	0.3	-0.7	1.3	0.5
	65–74	0	0.4	-0.3	1.1	0.2
	75 +	0	0.4	-0.5	1.3	0.4

APC: average percentage change; CI: confidence interval; LL: lower limit; UL: upper limit. *p<0.05.

increased by 0.006 units on average, from the value 0.282. Similar interpretations can be made with the values obtained in each of the lines constructed for each age group.

The R^2 value of the model for the first age group is low, indicating a regular adjustment. The significance of the coefficient of the variable "x" (p=0.04), which represents the year of the study period, and "y" the positive value, suggests an increase in mortality rates in the age group in this period. A result similar to that obtained with the *Joinpoint* system, which shows a tendency to increase in this age group for the study period. When the model was adjusted for the series of the second age group, the R^2 value was low and the coefficient of the variable "x" was not significant.

Two models were created, the first for the period from 2000 to 2003, which did not improve the adjustment made at the beginning, and the second, from 2004 to 2017, achieving substantial improvement in the adjustment and significance of the variable. Again, the model indicated an increase in mortality rates in the second age group, but only from 2004 to 2017, a result similar to that obtained with the *Joinpoint* system, which adjusted an inflection point, indicating an increase trend at the end of the period considered.

Regarding the models of the series of the third and fourth age groups, the R^2 value of each adjusted model was low and the coefficient of the variable "x" was not significant. This result indicates that there was no change in mortality rates in these age groups over time.

In the series of the fifth age group, a situation similar to that occurred in the second was presented: the R^2 value of the adjusted model was low and the coefficient of the variable "x" was nonsignificant. Two models were soon made, one for the period from 2000 to 2008 and another from 2009 to 2017. With this division of the original period, a substantial improvement was achieved in the adjustment and significance of the variable for the second period. Even so, it was not enough to say that there was a rising trend in the 65–74 years age group.

Table 2. Result of trend analysis and adjusted model of breast cancer mortality rate, according to age group, in the state of Paraná, from 2000 to 2017.

Variable	Age group	Model	R^2	p-value
Age group	25–34	y=0.282+0.006x (*)	0.229	0.044
	35–44 (period 2000–2007)	y=2.859+0.002x	0.191	0.893
	35–44 (period 2000–2003)	y=1.451-0.052x	0.106	0.674
	35–44 (period 2004–2017)	y=0.962+0.039x (*)	0.539	0.003
	45–54	y=2.859+0.002x	0.001	0.893
	55–64	y=3.189+0.006x	0.012	0.670
	65–74 (period 2000–2017)	y=2.638+0.090x	0.065	0.307
	65–74 (period 2009–2017)	y=2.075+0.051x	0.370	0.081
	75+	y=1.685+0.008x	0.063	0.316

*Significant at 5%.
Source: Research database (2020).

DISCUSSION

As in the whole world, Brazil will see an increase in the number of people affected with some type of cancer in the coming years, as a consequence of the greater population aging and exposure to a considerable number of new carcinogenic agents.

According to data from the SIM, in the Southern states of Brazil, the pathology is very close to cardiovascular diseases as the main cause of death[14].

Early diagnosis and timely treatment in the most at-risk populations can reduce these numbers, making cancer a chronic disease, prolonging the patient's life by many years.

This study made it possible to know the temporal patterns of mortality from breast cancer in women in the state of Paraná, from 2000 to 2017. In the first analysis, the results showed that women aged 45–54 and 55–64 years registered the highest number of deaths in the period studied. However, when the crude mortality rates were calculated by age group, it was observed that the mortality pattern increased directly proportional to the increase in age.

The higher number of deaths in lower age groups, in the first analysis, is explained by the larger population in these strata. This result, however, does not show that mortality affects younger women more. When calculating the mortality rate and standardization per 100,000 women, it can be seem that the behavior of mortality in Paraná remains proportional to the natural history of the disease, which has as its pattern higher mortality in older age groups[15].

There is evidence of higher mortality rates in older women also in other regions of the country. Evaluating data regarding older women from other states, such as the others in the South and Southeast, between 1980 and 2005, higher rates were found as the age group increased[16].

After an initial study, the trend of mortality rates by age group over time was interpreted, applying the Joinpoint method and simple linear regression. This system, widely applied in time series analyses, has as main function to calculate changes in the trend according to the APC. However, a disadvantage of the use of this calculation formula is the uncertainty in estimating the number of inflection points, which may not correspond to the actual variation[17].

Linear regression models have an advantage of high statistical power, although the nonlinearity of the data can be cited as a disadvantage, it is compensated by the centralization of the historical series[18].

The use of these two models allowed the analysis of the APC in rates to be complemented by the observation of discrete oscillations, verified only through the regression method[19].

It was observed that breast cancer mortality tends to increase in women from two age groups: 25–34 and 35–44 years old, with an APC that varies between age groups, increasing with age.

A similar result was found by Martin et al. who, evaluating the mortality trend in Brazil comparing two age groups: women aged 50 years or less and over 50 years, found growing trend in mortality of younger women[20,21].

Paraná exhibits high levels of industrialization and, according to the latest research published by the IBGE, has the fourth highest Human Development Index (0.749) of Brazilian states. This coincides with a greater life perspective and consequently greater aging of the population. According to the 2000 IBGE census, Paraná counted 428,326 women aged over 60 years, while the 2010 census indicated an increase to 635,627[14].

Considering the demographic transition through which the state goes, which is an important factor in understanding the epidemiological profile of breast cancer, the results obtained in the present study showed, on a population basis, higher mortality in older women, but there was a trend of growth, with statistical significance, of mortality only in younger women in the age groups of 25–34 and 35–44 years.

Although our work is a descriptive analysis and not of an inferential nature, using statistics to support it, we can assume that the global increase in the longevity of women in Paraná was the factor responsible for raising the mortality rates of folder patients compared to those of younger patients.

In contrast, an increasing trend in women of younger age groups may be associated with coverage of the breast cancer screening plan in the state and the tumor development profile, which is faster and more aggressive in these patients[9,11].

Mammography is the only screening test with proven efficacy to reduce breast cancer mortality; however Paraná, in 2012, registered a percentage of mammographic coverage (ratio between the number of tests performed and expected tests) of only 35.9%, well below 70% recommended by the WHO[3,22-24].

We should also consider that there is a disproportion in the offer of mammography in different age groups, considering that our screening model is opportunistic and not organized. In the latter, women of more advanced age groups would be the most benefited, in compliance with the greater compulsory call of heath services[23,24].

The Ministry of Health currently recommends biannual screening, from the age of 50 years, and excludes women between 40 and 49 years from screening programs, which can result in insufficient reach of the target population and uncontrolled growth of mortality from the disease in women of younger age groups[3,25,26].

In Brazil, it is essential to expand the coverage of screening services in the state and adapt the target population of the services, in addition to offering an organized screening model (characterized by the active search for patients) to the detriment of the predominant screening method, which is opportunistic, performed at the time of a medical cosultation[25].

CONCLUSION

The results obtained in the present analysis allow us to conclude that breast cancer mortality rates in women in the state of Paraná are directly proportional to age groups, evidencing higher mortality in older women.

Analyzing the behavior of mortality trends by age group, there was growth, with statistical significance, only in women of younger age groups, from 25 to 34 and from 35 to 44 years, with an average increase that differs between them. Among these, the one that includes women aged between 35 and 44 years presented the highest average annual increase; however, for this group, the trend was not uniform throughout the period.

These data showed the need for public health models with organized screening programs associated with the active search of the target population.

AUTHORS' CONTRIBUTION

GZF, VSC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. LRB, VMB: Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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