

# Mortality trends of breast cancer in BRICS countries from 1990 to 2019: an age–period–cohort analysis of the Global Burden of Disease study 2019

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**Brazil, Russia, India, China and South Africa (BRICS) account for nearly half of the world's population. We aimed to analyse mortality trends of breast cancer across the BRICS countries from 1990 to 2019. Breast cancer mortality estimates were obtained from the Global Burden of Disease Study 2019. An age–period–cohort model was adopted to estimate age, period and cohort effects on breast cancer mortality between 1990 and 2019. Results showed that breast cancer caused 0.23 million deaths across the BRICS countries in 2019, accounting for 32.7% of the total death caused by breast cancer worldwide. China had the largest number of deaths, followed by India. All five BRICS countries showed positive percentage changes in deaths from 1990 to 2019. The age-standardized mortality rates (ASMRs) in India, South Africa and China presented increased trends. South Africa presented the fastest increased rate with age. Downward period trends were observed in China, South Africa, Brazil and Russia, while an upward trend was seen in India, with the period rate ratio increasing from 0.95 to 1.17. In conclusion, the disease burden of breast cancer is still heavy across the BRICS countries. It is important to pay more attention to elderly patients. The increasing disease burden must be addressed multidimensionally, incorporating screening and early detection, timely and sufficient treatment and appropriate prevention.**

**Keywords:** Age–period–cohort model, breast cancer, BRICS, disease burden, mortality.

BREAST cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths among females worldwide, which claimed about 6.9% of cancer-related deaths in 2020 globally<sup>1</sup>. Although the survival rate of breast cancer has improved in recent decades, its mortality is still

increasing and varies from country to country<sup>2,3</sup>. The disease is usually detected at an advanced stage due to a lack of early symptoms, and the outcomes are even poorer for breast cancer with metastasis<sup>4</sup>. A review and analysis of the disease burden trend would be beneficial in understanding the impact of this disease on public health.

Brazil, Russia, India, China and South Africa (BRICS) constitute the political and economic coalition of countries, accounting for nearly half of the world's population<sup>5</sup>. Global health is significantly affected by these five countries, which represent approximately 25% of global gross national income and account for around 40% of global disease burden<sup>6</sup>. Each country has its own culture, lifestyle and medical care system but shows huge inequities in healthcare delivery despite rapid economic growth. The lack of public spending on health has hindered progress towards universal health coverage, which hampered achievements in quality healthcare<sup>7</sup>.

These countries' efforts to reform their health systems were undermined by the growing burden of non-communicable diseases (NCDs)<sup>8</sup>. Previously there were studies conducted using data from the global burden of disease (GBD) database to illustrate and compare burdens of some diseases across the BRICS, including type-II diabetes mellitus<sup>9</sup>, cardiovascular diseases<sup>10</sup>, chronic respiratory diseases<sup>11</sup> and infectious diseases<sup>12</sup>, showing different trend patterns over a certain period in individual BRICS countries. For breast cancer, the incidence and mortality were projected to continue to increase in China<sup>13</sup>. The rising breast cancer burden in other BRICS countries was also noticed<sup>14</sup>. However, research comparing the disease burden in these five countries is lacking.

Furthermore, several of these countries are experiencing an ageing population, which may lead to increased mortality of breast cancer due to age-related physical changes or symptoms<sup>15</sup>. Analysing epidemiological data of diseases in these five countries is of significance to understanding the global disease burden and regional disparity with respect to their great contributions to the global population and public health.

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The GBD study provides epidemiological data on the prevalence, incidence, mortality, years lived with disability (YLD), disability-adjusted life years (DALYs) and years of life lost (YLLs) for 286 causes of death, 369 diseases and injuries, and 87 risk factors from specific groups, in 204 countries and territories by sex, age and year. In this study, we analyse the data from the GBD 2019 study with age–period–cohort (APC) model web tool<sup>16</sup> which is based on retrospective repeated measurement of cross-sectional data, systematically presenting the time trends of breast cancer mortality as well as their associations with age, period and birth cohort in the BRICS countries between 1990 and 2019.

## Methods

### Data sources

The population data, mortality and age-standardized mortality rates (ASMRs) data for age-standardized groups across BRICS were obtained from GBD 2019 study results, which systematically provided an estimation of the burden of 359 diseases and injuries and 87 risk factors across ages, sexes, regions, and 204 countries and territories, from 1990 to 2019 (refs 17, 18). All the estimated data were extracted from the website Global Health Data Exchange (GHDx) (<http://ghdx.healthdata.org/gbd-results-tool>), which was completely accessible online. The methodological details of GBD 2019 were described in previous studies<sup>17–19</sup>. In our study, ‘breast cancer’ was selected as the ‘cause’ with ‘deaths’ chosen as the ‘measure’. For ‘years’, data for every year between 1990 and 2019 were determined to precisely track the secular trends. As for ‘location’, data were extracted at the national level for each component of the BRICS countries respectively. Regarding ‘metrics’, the ‘number’ and ‘rate’ were selected for mortality data. For ‘age’, data for all ages and age-standardized rates were extracted, and both sexes were included for data analysis.

### Statistical analysis

ASMR and estimated annual percentage change (EAPC) were adopted to quantify the breast cancer mortality trends. The EAPC was calculated to estimate the ASMR trend over a specific period. A regression line,  $y = \alpha + \beta x + \varepsilon$ , was fitted to the natural logarithm of the mortality rates by taking  $\ln(\text{ASMR})$  and calendar year as dependent and independent variables respectively. The EAPC was calculated as  $100 \times (\exp(\beta) - 1)$  with its 95% confidence interval (CI) obtained from the linear regression model<sup>20</sup>. The ASMR was regarded to be in an increasing trend if the EAPC estimation and the lower boundary of its 95% CI were both larger than 0, while a decreasing trend was considered if the EAPC estimation and the upper boundary of its 95% CI were both smaller than 0. Otherwise, stable ASMR trends over time were considered.

APC model was adopted to evaluate the effect of age, period and birth control on breast cancer mortality<sup>16</sup>. Age effects refer to physiological changes and accumulated social experiences associated with ageing. Period effects describe changes in screening methods, medical technology applications, or disease classification standards over time. Cohort effects indicate the long-term trend of disease mortality among individuals born around the same time, which may be influenced by lifestyle, external factors and environmental exposure<sup>11,16</sup>. As an important parameter of the APC model, net drift represents the overall log-linear trend by period and birth cohort, presenting the overall annual percentage change of the ASMR over time, while local drift refers to the log-linear trend by period and birth cohort for specific age groups. The longitudinal age curve illustrates the expected age-specific rate in a reference cohort adjusted for period effects. The period rate ratios (RRs) are defined as the ratio of age-specific rates within a specific period relative to the reference period, while the cohort rate ratios (RRs) refer to the ratio of age-specific rates in each cohort relative to the reference cohort<sup>10,16</sup>.

For APC analysis, the population and mortality data were arranged into successive 5-year intervals from 1990 to 2019, forming consecutive 5-year age groups from 15 to 19 years, 80 to 84 years, and the corresponding successive 19 birth cohorts (1905–1909, 1910–1914, ..., 1995–1999), with 2000–2004 period and 1950–1954 cohort taken as reference. The age-period-cohort web tool provided by the National Cancer Institute was used to estimate the parameters (<http://analy-sistools.nci.nih.gov/apc/>)<sup>16</sup>, with Wald chi-square tests employed to test the statistical significance. A two-sided  $p$  value lower than 0.05 was considered statistically significant. Furthermore, the 95% uncertainty intervals (UIs), determined by the 2.5th and 97.5th percentiles, were calculated to quantify the effects of uncertainty on the estimated mortality, which primarily resulted from variations of data accessibility and sample size, as well as specifications of the cause-specific model<sup>21</sup>.

## Results

### Time trends of breast cancer mortality

According to the GBD 2019, breast cancer caused 0.23 million deaths across the BRICS countries in 2019, which accounted for 32.7% of the total deaths caused by breast cancer worldwide (0.70 (0.65 to 0.95) million). Table 1 presents the trends of breast cancer mortality in BRICS countries. The deaths from breast cancer varied among the BRICS. China had the largest number of deaths (96.3 (77.3 to 118.0) thousand), followed by India with a number of 83.5 (95% UI (64.6 to 106.0)) thousand in 2019. All five BRICS countries showed positive percentage changes of deaths from 1990 to 2019. The highest percentage change in deaths was observed in India which had increased by

**Table 1.** Mortality and ASMR with percentage changes of breast cancer in BRICS between 1990 and 2019

	Number of deaths			ASMR (per 100,000)		
	1990 (95% UI)	2019 (95% UI)	Change (95% CI)	1990 (95% UI)	2019 (95% UI)	EAPC (95% CI)
Brazil	8,883 (8,554–9,203)	20,121 (18,758–21,373)	1.27 (1.12–1.42)	9.66 (9.21–10.02)	8.43 (7.83–8.97)	–0.52 (–0.68–0.36)
China	41,804 (34,550–49,509)	96,306 (77,323–118,090)	1.3 (0.76–2.02)	4.74 (3.96–5.57)	4.85 (3.91–5.92)	0.06 (0–0.12)
India	26,924 (22,338–31,252)	83,510 (64,550–105,994)	2.1 (1.33–3.06)	5.56 (4.6–6.47)	7.12 (5.53–9.01)	0.75 (0.59–0.91)
Russia	16,692 (16,236–17,297)	23,778 (19,601–28,319)	0.42 (0.18–0.68)	9.46 (9.17–9.8)	10.4 (8.55–12.41)	–0.02 (–0.39–0.35)
South Africa	2,370 (2,078–2,744)	5,309 (4,671–6,033)	1.24 (0.98–1.58)	11.07 (9.61–13.06)	12.44 (11.05–14.02)	0.57 (0.3–0.84)

ASMR, Age-standardized mortality rate; EAPC, Estimated annual percentage change.

210%, followed by Brazil, with a percentage change of 127%.

However, the highest ASMR was seen in South Africa (12.44 per 100,000 people) in 2019. Russia also had a relatively high ASMR (10.40 per 100,000), but the EAPC of ASMR was slightly decreased (–0.02, 95% CI (–0.39 to 0.35)). Additionally, Brazil showed a decrease in ASMR from 9.66 per 100,000 in 1990 to 8.43 per 100,000 in 2019 with an EAPC of –0.52 (95% CI (–0.68 to –0.36)). In comparison, the ASMRs of breast cancer in India, South Africa and China presented increased trends, with India from 5.56 per 100,000 in 1990 to 7.12 per 100,000 in 2019, South Africa from 11.07 per 100,000 in 1990 to 12.44 per 100,000 in 2019 and China from 4.74 per 100,000 in 1990 to 4.85 per 100,000 in 2019 respectively.

#### Net drift and local drift in different age groups

Net drift represents the overall APC of ASMR over time across the whole study period (Figure 1). Similar overall net drift values were observed in China (–0.47%, 95% CI (–0.75 to –0.19)), Brazil (–0.45%, 95% CI (–0.58 to –0.31)), and South Africa (–0.42%, 95% CI (–0.91 to 0.06)), revealing the decline of breast cancer mortality during the study period. Additionally, Russia also presented a decreased mortality (–0.56%, 95% CI (–0.79 to –0.32)), whereas, India showed an elevated mortality rate (0.68%, 95% CI (0.52 to 0.85)). For females, the overall annual changes were similar to those shown in both sex groups (Figure 1 b), while the changes differed in males (Figure 1 c).

Local drift refers to the log-linear trend by period and birth cohort for specific age groups, presenting additional age variations in trends of breast cancer mortality. As illustrated in Figure 1, local drift values were below 0 for both sexes aged 15 to 44 in China, Russia and South Africa. However, for patients over 60 years of age, the local drift values were above 0, indicating worsened situations of breast cancer mortality for patients of older ages in these three countries. With regard to India, positive values were

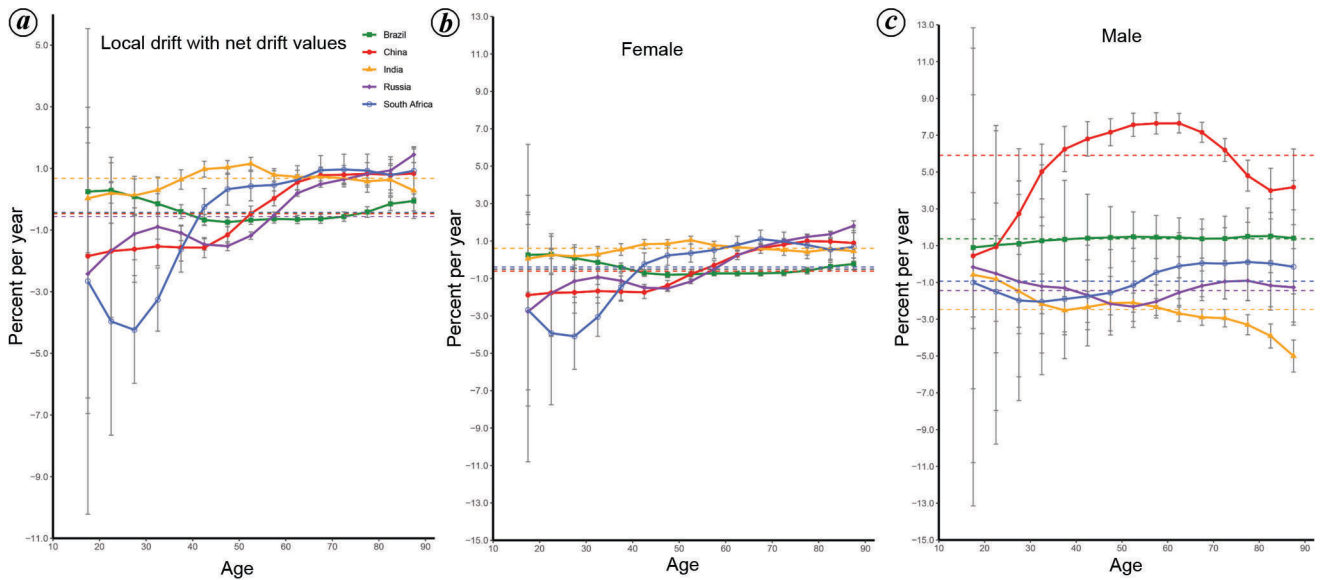
seen in all age groups from 15 to 84 for both sexes, but the corresponding values for specific age groups were all negative among Indian males, which demonstrated that the mortality rates for Indian females predominantly contributed to the overall age variations in the mortality trend. The discouraging thing was that Chinese males aged 35 to 69 rapidly increased mortality among the BRICS countries, especially for those aged 60 to 64 years (7.65%, 95% CI (7.12 to 8.18)).

#### Age–period–cohort effects on breast cancer incidence and mortality

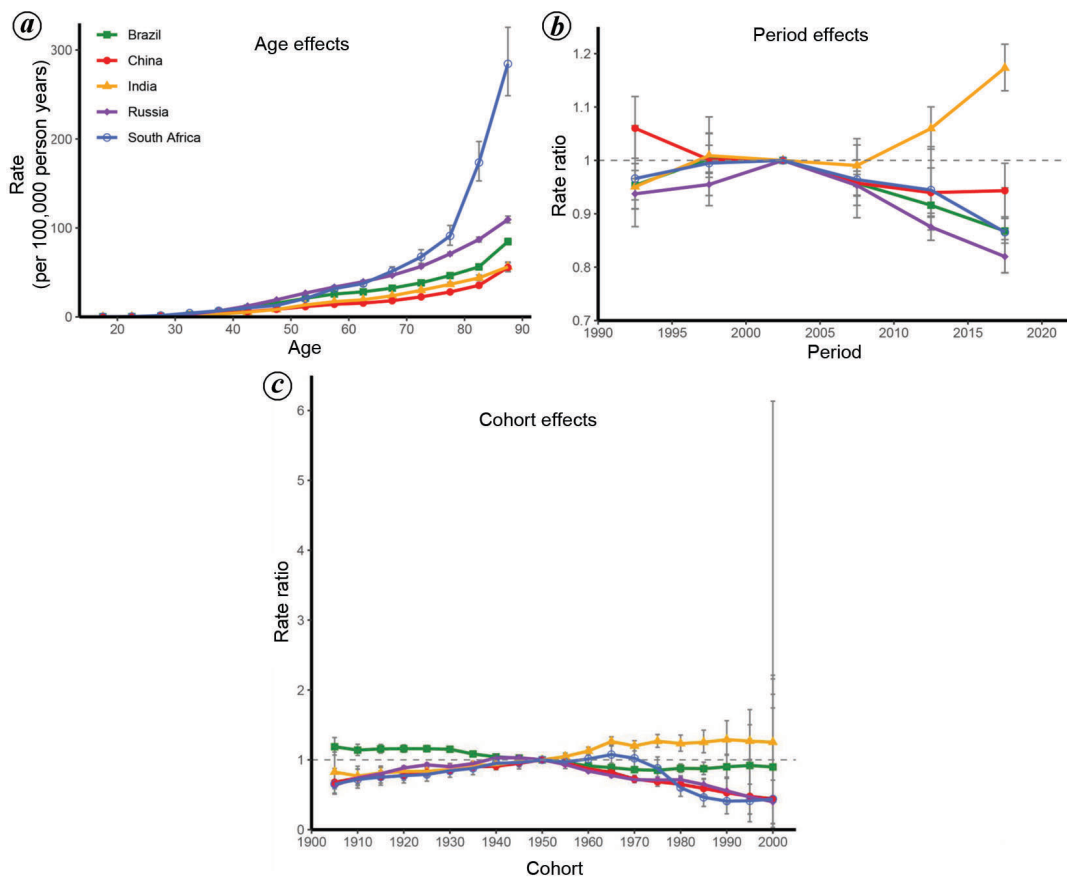
Figure 2 illustrates parameter estimates of age, period and cohort effects on breast cancer mortality in BRICS from 1990 to 2019. An expected exponential distribution for age effects across BRICS is shown in Figure 2 a. South Africa presented a rapid increase with age (0.10 to 284.56 per 100,000 person-years), followed by Russia.

By contrast, China and India showed similar and gentle increases in mortality trends, from 0.07 to 55.62 per 100,000 and from 0.07 to 56.35 per 100,000 person-years respectively.

Figure 2 b shows the estimated period effects on breast cancer mortality. Downward trends of period RRs could be observed in China, South Africa, Brazil and Russia. Particularly, more favourable trends were observed after 2005 in Russia (0.95 to 0.82), Brazil (0.96 to 0.87) and South Africa (0.96 to 0.87). In comparison, an upward trend was seen in India, with period RR increasing from 0.95 to 1.17, showing the unfavourable mortality trends in recent decades. For cohort effects (Figure 2 c), flat trends were observed in the five individual countries. Brazil showed improvements in mortality across birth cohorts from a RR of 1.19 in 1905 to 0.90 in 2000. On the contrary, India presented an increased RR from 0.83 in 1905 to 1.25 in 2000, suggesting the deterioration of mortality trends. For China, Russia and South Africa, improvements in breast cancer risk were not so obvious.



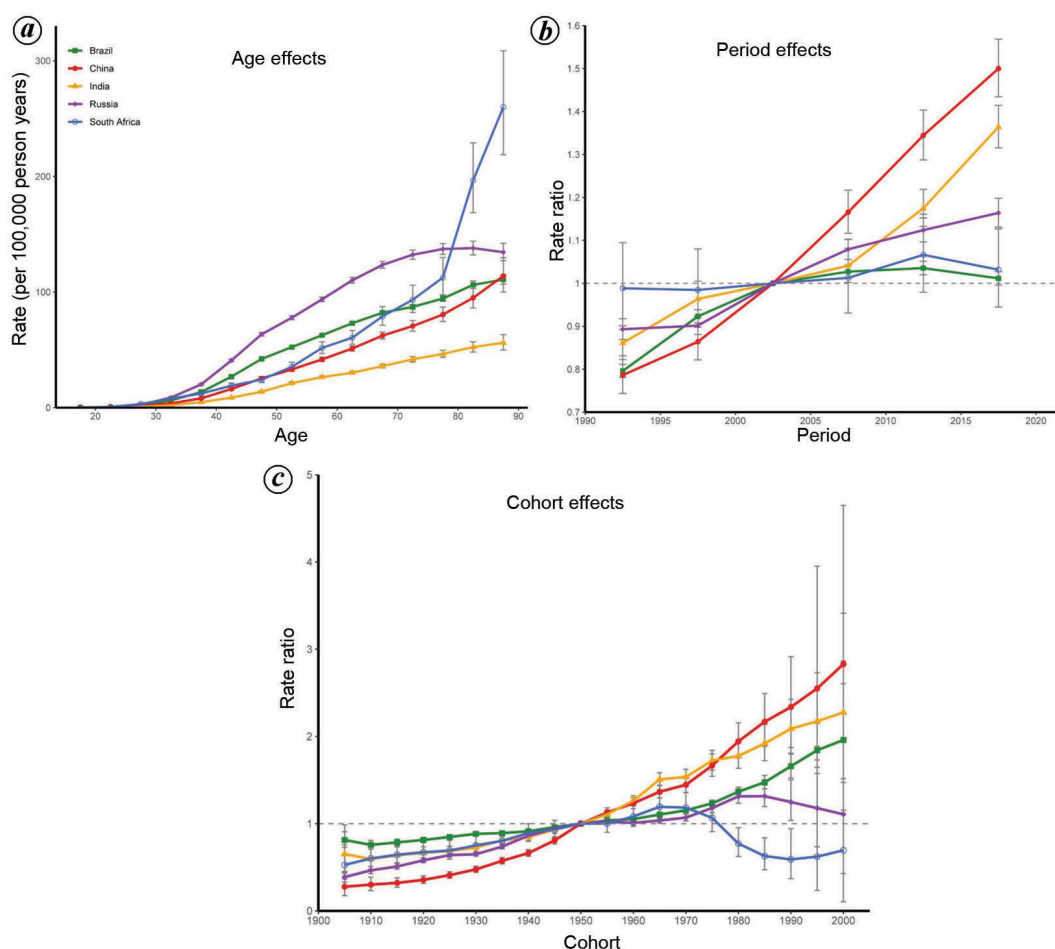
**Figure 1.** Local drift with net drift values for breast cancer mortality (a) and sex differences (b and c) in BRICS from 1990 to 2019.



**Figure 2.** Parameter estimates of age (a), period (b) and cohort (c) effects on breast cancer mortality in BRICS from 1990 to 2019.

To provide a more complete picture of the breast cancer burden in each population and help better interpret mortality rates, parameter estimates of age, period and cohort effects on breast cancer incidence in BRICS from 1990 to 2019

were also presented in Figure 3. As illustrated in Figure 3 a, breast cancer incidence in India gradually increased with age. South Africa presented the steepest increase for the 75–85 age group. Figure 3 b presents the estimated period



**Figure 3.** Parameter estimates of age (a), period (b) and cohort (c) effects on breast cancer incidence in BRICS from 1990 to 2019.

effects on breast cancer incidence. Prominent upward trends of period RRs were seen in China, India and Russia. For cohort effects (Figure 3 c), China, India and Brazil presented increased cohort RRs across the whole study cohort.

## Discussion

To our knowledge, this was the first study to identify and compare the secular trends of breast cancer mortality in the BRICS countries. According to GBD 2019, the BRICS accounted for approximately one-third of breast cancer deaths worldwide. The large proportion that the BRICS contributed to was partly due to BRICS comprising nearly half of the global population. Especially for the developing world's two giants, China and India, they gave rise to a large number of deaths across the BRICS. Since breast cancer incidence was much higher in females than males, the secular trends were predominantly determined by females, as shown in the local drifts in Figure 1.

Individual countries across the BRICS presented different mortality rates and time trends. All five BRICS countries showed positive percentage changes in deaths from 1990 to 2019. The highest ASMR of breast cancer was seen in

South Africa in 2019, and the ASMRs in India, South Africa and China presented increased trends. The APC model adopted to investigate the age, period and cohort effects on breast cancer mortality allows us to comprehensively detect the contributions of particular time period and series of birth cohorts exposed to risks. Results revealed similar net drift values in China, Brazil and South Africa. South Africa presented the fastest increased rate with age. Downward period trends were observed in China, South Africa, Brazil and Russia, while an upward trend was seen in India, with period RR increasing from 0.95 to 1.17.

According to a study on cancer survival in Africa, Central and South America and Asia (SURVCAN-3) published in *Lancet Oncology*<sup>22</sup>, negligible differences were shown in countries in Central and South America, while evident differences were observed in Asian countries. India had a lower median 3-year net survival rate of breast cancer than China and Brazil based on the diagnosis from 2008 to 2012 (ref. 22). To provide a complete picture of breast cancer outcomes, cancer mortality is discussed below.

China had the most breast cancer deaths, but its ASMR was the lowest among the BRICS. Additionally, China showed period improvements from 1990 to 2019. A previous

study also showed that the ASMR and DALYs decreased for Chinese females with breast cancer during 1990–2019 (ref. 13). The improvements in mortality might be accounted for by increased investment in health. During the study period, the development of screening techniques and early diagnosis, enhanced medical treatment technology, better availability to basic public health services, and access to cancer care were likely to have served their roles in the mortality improvements<sup>23</sup>. The use of mammography in diagnostic practices has enabled early detection of breast cancer, leading to timely treatment and better survival rates<sup>24</sup>. As more people underwent mammography screening, the number of breast cancer cases detected at earlier stages increased.

This shift towards an earlier stage at diagnosis has resulted in a decrease in breast cancer mortality rates over time. Additionally, increased awareness of breast cancer symptoms and risk factors led to quickly seeking medical attention and screening, which contributed to earlier detection of breast cancer and improved survival rates. However, it is important to note that the impact of changes in diagnostic practices and awareness of breast cancer mortality trends may vary across different countries and populations<sup>25,26</sup>. For example, in low-income countries, where access to mammography and other screening tools may be limited, changes in diagnostic practices may have a smaller impact on breast cancer mortality trends compared to high-income countries where mammography screening is more widely available. Further, though breast cancer occurrence in males is rare, attention should also be paid to this issue. Male breast cancer in different age groups in China was rather distinct from females. Chinese males aged 35 to 69 years had an extremely rapid increase in mortality among the BRICS countries. In a study conducted by Liu *et al.*<sup>13</sup>, it was found that China presented dramatically increasing incidence and mortality trends in male breast cancer in the past three decades, and it was predicted that the trends would continue to increase in the next 15 years. The higher mortality of male breast cancer compared with females was consistent with the poorer survival of breast cancer occurrence in males than females<sup>27</sup>. Therefore, enough attention should also be paid to Chinese male breast cancer cases in spite of their low incidence rate.

India had the highest percentage change of breast cancer deaths and the largest EAPC of ASMR from 1990 to 2019. Compared to females, gradual downward local drift values for Indian men indicated improvements in mortality among males in India. However, as illustrated in the result section, the overall age variations in the mortality were predominantly determined by Indian females, which showed a less optimistic trend than that for Indian males. One of the earlier studies presented a broader picture of breast cancer epidemiology and anticipated the disease burden to continue increasing in Indian women<sup>28</sup>. Furthermore, the period trend was in an upward direction, which to some extent reflected the insufficiency in the pathways to breast cancer care. A

possible factor might be the delayed diagnosis and treatment of breast cancer in India<sup>29</sup>. In some regions, illiteracy, lack of awareness and financial constraints might contribute to the late diagnosis of breast cancer, thus increasing the mortality rate<sup>28</sup>.

Improvements in ASMR were observed in Brazil from 1990 to 2019. It had the biggest reduction in EAPC among the BRICS. In the past decade, Brazil has shown a favourable period trend, which might be due to Brazil's investment in health as well as the reform of primary health care. A previous study has shown that the level of access to the health care system for cancer patients may, to some extent, determine breast cancer mortality in Brazil<sup>30</sup>.

Therefore, adequate and timely treatment is significant in reducing the disease burden. Although certain efforts have paid off, some challenges still exist, like the rapidly ageing population, decline in healthy diet and physical activity and so on<sup>31</sup>. In the future, policies should be developed to optimize age structure, and specific needs and priorities should be evaluated to tackle challenges that may occur in the path of reducing the growing burden of breast cancer<sup>32</sup>.

In 2019, Russia ranked second in ASMR of breast cancer among the BRICS countries. Breast cancer mortality increased with age for Russian patients aged over 60 years, with the second fastest increase across the BRICS. However, what was encouraging was that the period RRs were lower than 1 over the whole study period. Especially in recent decades, a promising downward trend has been observed. Meanwhile, although the trend for birth cohorts was flat, it was favourable. The downward mortality trend for breast cancer in our findings was consistent with previous studies based on available and reconstructed data<sup>33,34</sup>. Russia's reform in health care that had resulted in improving access and equality to health care was likely to have contributed to the encouraging trend<sup>7,35</sup>.

South Africa had the highest breast cancer mortality among the BRICS. Between 1990 and 2019, the EAPC of mortality was 0.57 (95% CI (0.30 to 0.84)), showing increased mortality trend. A previous study also reported increased ASMRs between 1997 and 2004 (ref. 36). An important factor for the discouraging mortality burden might be associated with a poor healthcare system. The quality of breast cancer care in sub-Saharan Africa should be promoted to help address the dismal cancer mortality<sup>37</sup>. With regard to the period trend, similar to the downward trend patterns in Brazil and Russia, South Africa, too has shown an impressive result in the past decade. Additionally, the rapid increase with age in South Africa was noted, which raised the concern of ageing situations that might result in significant changes in the patterns of disease burden in South Africa.

There are some limitations in our study. First, we only present an analysis of data and show the time trends of breast cancer mortality from 1990 to 2019 since there is a lack of GBD data prior to 1990, and data after 2019 have not yet been released. Second, the data that GBD studies provide are systematic, standardized estimates of the global burden of

breast cancer without taking the data on the primary cause of death identification into account. As illustrated in previous studies<sup>5,38</sup>, this may cause inconsistencies between prevalence data for selected causes and primary cause of death. Additionally, the estimates for breast cancer mortality in individual countries largely rely on the quality and quantity of data used during the GBD modelling process. Some missing and unusable data for some countries might affect the estimates of mortality. Third, the effects of migration on estimates will not be able to be considered. Fourth, the APC analysis is a method based on the population level, so it is possible for an ecological fallacy to occur.

Therefore, the study's interpretation should be cautiously handled while applying the analytical method at the individual level. Future research can include data before 1990, thus presenting mortality trends over a longer period. The primary cause of death should also be considered and identified to avoid potential inconsistencies.

## Conclusion

The BRICS countries accounted for approximately one-third of breast cancer deaths worldwide. All five BRICS countries showed positive percentage changes in deaths from 1990 to 2019. The disease burden of breast cancer was still heavy across the BRICS countries, although a decline in breast cancer mortality during the study period was observed in BRICS, except in India. The age effects indicated that more attention should be paid to elderly patients. Meanwhile, the period trends suggested that developing screening techniques and early diagnosis, enhanced medical treatment technology, better availability of basic public health services and access to cancer care are of great significance. Individual countries in the BRICS ought to appropriately learn from the experiences of effective efforts other countries have made, thus improving domestic disease management. The increasing disease burden requires to be addressed in a multi-dimensional manner incorporating screening and early detection, timely and sufficient treatment and appropriate prevention.

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*Data availability statement:* The database Global Burden of Disease (GBD) analysed for this study can be accessed at <http://ghdx.healthdata.org/gbd-results-tool>.

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