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Breast cancer epidemiology and sociodemographic differences in BRICS-plus countries from 1990 to 2019: An age period cohort analysis

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ABSTRACT

Background: Breast cancer (BC) is a major health concern in the BRICS-plus, a group of developing nations consisting of Brazil, Russia, India, China, South Africa, and 30 other Asian countries, with nearly half of the world's population. This study aims to identify potential risk factors contributing to the burden of BC by assessing its epidemiological and socio-demographic changes.

Methods: Data on BC outcomes were obtained from the 2019 Global Burden of Disease Survey. The age-period-cohort (APC) modeling technique was used to evaluate the nonlinear impacts of age, cohort, and period on BC outcomes and reported risk attributable mortality and disability adjusted life years (DALYs) rate changes between 1990 and 2019.

Results: In 2019, there were 0.90 million female BC cases and 0.35 million deaths in the BRICS-plus region, with China and India having the largest proportion of incident cases and deaths, followed by Pakistan. Lesotho experienced the highest annualized rates of change (AROC: 2.61%; 95%UI: 1.99–2.99) in the past three decades. Birth cohorts' impact on BC varies greatly between the BRICS-plus nations, with Pakistan suffering the largest risk increase in the most recent cohort. High body mass index (BMI), high fasting plasma glucose (FPG), and a diet high in red meat contributed to the highest death and DALYs rates in most BRICS-plus nations in 2019, and there was a strong negative link between SDI and death and DALYs rate.

Conclusions: The study found that the burden of BC varies significantly between BRICS-plus regions. Thus, BRICS-plus nations should prioritise BC prevention, raise public awareness, and implement screening efficiency measures to reduce the burden of BC in the future, as well as strengthen public health policies and initiatives for important populations based on their characteristics and adaptability.

1. Introduction

Breast cancer (BC), due to its high morbidity and mortality, has become a major health problem for women around the world. According to GLOBOCAN 2020 from the International Agency for Research on Cancer (IARC), which used data from 185 countries, new BC cases in women accounted for 11.7% of new cancer cases in 2020, overtaking lung cancer as the leading cause of cancer globally. BC ranked first in 159 countries for incidence, and first in 110 countries for mortality (Sung et al., 2021).

It was believed that the incidence of BC in high-income countries was higher than that in low-income countries in the past. However, with social development and economic growth, social culture and environment have changed dramatically, the prevalence gap of risk factors for BC among countries has gradually decreased, and BC incidence in low-income countries is growing rapidly. In sub-Saharan Africa (SSA), the incidence rate of BC in Malawi, Nigeria and other countries has increased by more than 5% per year (Joko-Fru et al., 2020). BC patients

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in low-income countries have a relatively poor prognosis compared to those in high-income countries, with approximately 60% of BC deaths occurring in developing countries (da Costa Vieira et al., 2017).

Despite the continuous development and progress of medical science, the lack of national BC screening programs, early diagnosis and treatment of BC in developing countries, especially low-income countries with limited resources, such as countries in SSA, has weak health infrastructure, leading to poor survival outcomes, with significant international differences. According to CONCORD program, the 5-year survival rate for BC in India was 66.1%, much lower than the 90.2% in the United States at the same time (Allemani et al., 2018). Other studies have also shown clear geographical differences in BC burden, particularly in countries with economies in transition, where BC mortality is significantly higher (Kashyap et al., 2022). Without new interventions, the burden of BC will continue to rise, especially in low- and middle-income countries. A study in SSA countries suggests that BC deaths could be reduced by 28%–37% with early diagnosis and treatment (Birnbaum et al., 2018).

BRICS is an informal financial group comprising four emerging market countries: Brazil, Russia, India, China and South Africa. The BRICS-plus, which adds more than 30 other Asian countries on the basis of BRIC, has roughly half the world's population, which greatly raises the global burden of disease and healthcare. Studies suggest that many BRICS-plus countries have not been able to implement well-organized BC screening programs, and with large variations across countries (Basu et al., 2020; Vieira et al., 2015). Currently, many emerging nations lack a consistent assessment of their health systems. The accompanying epidemiological variations of the load and their link with age groups, birth cohorts, and socioeconomic status, as well as the evaluation of its improvement, have not been exhaustively researched. To address the rising burden of BC and regional disparities and inequalities, it is essential to conduct relevant evaluation studies.

This study aims to utilise data from the Global Burden of Disease Study 2019 (GBD 2019) to investigate the existing condition and changing patterns of breast cancer in BRICS-plus nations and globally. To investigate the independent effects of age, period, and cohort across diverse economies, as well as the possible causes of the link between SDI and these health outcomes. To offer evidence for the optimal use of health resources across economies in order to reduce breast cancer morbidity and mortality and to promote health equality and social justice.

2. Material and methods

2.1. Data source

The Global Burden of Diseases (GBD) study, which is considered the most comprehensive epidemiological research assessment, investigated 359 diseases and injuries, 84 risk factors, and 282 documented causes of death across 195 nations, 21 regions, and seven super-regions. Utilizing unique estimating methods and supporting materials from earlier studies (Gakidou et al., 2017; James et al., 2018; Kyu et al., 2018; Roth et al., 2018). The GBD provides updated data from 1990 to 2019. Breast cancer (BC) data, on the other hand, was obtained through the Global Health Data Exchange (GHDx) online data collection tool (http://ghdx.healthdata.org/gbd-results-tool), with all pertinent information regarding the data sources found in the "Availability of data and materials" section.

2.2. Study population and variables

The BRICS-plus countries were divided into five regions, namely Mercosur (including core and new members), SAARC (comprising SAFTA members), China-ASEAN FTA, Eurasian Economic Union (EEU), and a separate subdivision for the 35 countries listed below. These subdivisions were SAARC (Afghanistan, Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, Sri Lanka), China-ASEAN FTA (China, Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei, Vietnam, Laos, Myanmar, Cambodia), Mercosur (Brazil, Argentina, Paraguay, Uruguay, Bolivia, and Venezuela), SACU (Botswana, Lesotho, Namibia, South Africa, and Swaziland), and EEU (Russia, Kazakhstan, Belarus, Armenia, Kyrgyzstan).

We collected data on the annual incidence of breast cancer (BC), mortality, disability-adjusted life years (DALY), and age-standardised rates (ASR) of BC by age group from 1990 to 2019, using the GBD study 2019 as a baseline. The data were collected for all 35 BRICS-plus nations and the entire world. To categorize the countries based on their degree of development, we created the sociodemographic index (SDI) that ranked them into five quintiles using national per capita income, average years of education for those over 15, and general fertility rate. The SDI indicator ranges from 0 to 1, representing the level of development.

2.3. Estimation of outcome variables

According to GBD research, the incidence of BC is estimated using integrated cancer registry databases or individual cancer registries. To determine these estimates, four unique inputs from DisMod-MR2.1 were used, based on the literature review data obtained (Vos et al., 2017). DisMod-MR2.1 employs Bayesian meta-regression to calculate the prevalence and incidence of 354 injuries and disorders across 195 nations and territories.

Breast cancer in female study participants was diagnosed using the ICD-10 code C50 (Organization WH, 2021). To estimate population figures for the BRICS-plus nations by age group (20–24 to 80–84) and year (1990–2019), information from the online Global Health Data Exchange (GHDx) was utilized (Wang et al., 2020). The Ministry of Health's Mortality Information System is the primary source of statistics for Brazil (Ribeiro et al., 2016), while the Russian Institute for Demographic Research at the New Economic School monitors death rates by age, gender, area, and causes (Starodubov et al., 2018). Similarly, India's mortality database is maintained by the Registrar General of India and the Indian Sample Registration System (Jha et al., 2006), and China's database of health statistics is managed by the Chinese Center for Disease Control and Prevention, Disease Surveillance Points, Maternal and Child Surveillance System, and Cause of Death Reporting System (Zhao et al., 2019). The South African Department of Home Affairs tracks data on general mortality by age, gender, region, and cause of death. Other BRICS-plus countries used their current methods for registering patients in health databases to assess breast cancer figures. The GBD estimates were based on complex statistical modeling to handle sparse and occasionally discordant data due to a lack of knowledge about various illnesses, injuries, and risk factors from different countries (Murray & Lopez, 2013). Data from the vital registry system and mortality forecasts were used to perform CODEm (Death Ensemble Model) for breast cancer (Foreman et al., 2012). The CODEm utilizes data and variables such as education, SDI, lagged distribution income, smoking, and alcohol use to estimate mortality rates. The CodCorrect method was used to separately account for all-cause mortality and modify the single-cause estimates (Wang et al., 2017; Zhou et al., 2019). The GBD article series includes certain computing techniques (Kyu et al., 2018; Murray, 1994; Murray & Acharya, 1997; Salomon et al., 2015).

To calculate the disability-adjusted life years (DALYs) caused by breast cancer (BC), we first determined the years lived with disability (YLDs) by multiplying the disability weight of each sequela with its prevalence, and adding the clinical morbidity of BC diagnosis. The years of life lost (YLLs) attributable to BC were computed by considering the global average life expectancy and the number of deaths in each age group. These YLDs and YLLs were then combined to obtain the DALYs caused by BC (Wang et al., 2016).

2.4. Attributable risk factors to breast cancer

The GBD 2019 study employed a framework known as comparative risk assessment (CRA) to estimate the burden of disease attributable to various risk factors. This approach assumes that reducing exposure to a particular risk factor to a theoretical minimum risk exposure level (TMREL) would lead to a decrease in disease burden. The GBD 2019 risk factors research (Murray et al., 2020). Provides a comprehensive description of the method used to evaluate these risk factors. After establishing the relationship between the risk factors and the health outcome, the relative risk value was calculated using reliable literature sources. This study will examine seven significant risk factors, namely alcohol consumption, high body mass index (BMI), high fasting plasma glucose (FPG), a diet high in red meat, poor physical activity (PA), exposure to secondhand smoke, and smoking.

2.5. Statistical analysis

2.5.1. Measuring the regular trends in BC incidence, death and DALYs

We conducted a geographic evaluation of changes in BC using a graphical representation, stratified by time and age. To measure trends over the last 29 years, we calculated the annualized rate of change (AROC) by taking the ratio of the natural logarithms of the rate in 1990 and 2019 and multiplying by 100 [i.e., $100 \times \ln(2019\ \text{Rate}/1990\ \text{Rate})$/ (Naghavi et al., 2017)]. A positive AROC indicates an increase in BC mortality or incidence over the 29-year period, while a negative AROC implies a slowing or declining trend/slope. We estimated uncertainty for each outcome (Foreman et al., 2012; Naghavi et al., 2017) using 1000 posterior distribution bootstrap samples and measured this uncertainty using uncertainty intervals (UIs). We calculated point estimates and uncertainty intervals (UIs) by taking the mean and the 25th and 975th posterior distribution values of 1000 simulations. The 95% UI of the percentage change did not contain 0, indicating statistical significance.

Our analysis assessed the percent change in age-standardised BC mortality, DALYs, and incidence rates between 1990 and 2019 for 35 BRICS-plus nations and the entire world. We reported 2019 estimates for these 35 countries, accompanied by a 95% UI. To explore the relationship between SDI and BC outcomes, we used the Spearman correlation coefficient (r).

2.5.2. Measuring the age period and cohort effects on BC outcome

We organized data on population, incidence, mortality, and DALYs related to breast cancer into 19 cohorts spanning from 1905 to 2019. The cohorts consisted of individuals born between 1905 and 1909 (median, 1907), from 1995 to 1999 (median, 1997), from 1990 to 1994 (median, 1992), and from 2015 to 2019 (median, 2017). To fit an APC model with age, time, and cohort as continuous variables, we used the "apc.fit" command in R. In line with Carstensen et al.'s recommendation (2021) (Carstensen et al., 2021), we used five-year intervals for age (20–84 years) and period (1990–2019) in our Lexis diagram since we had yearly data available for both breast cancer outcomes and population data. We used a Poisson distribution with a log-link function to model the number of breast cancer outcomes, using the logarithm of associated person-years as the offset. We utilized functions for age, period, and cohort as independent variables in the model, which were derived using limited cubic (natural) splines. Matrix transformations were applied to the spline basis vectors for period and cohort effects (Carstensen, 2007). We fitted models for age only (A), age with a linear temporal trend (Ad), age with cohort (AC), age with period (AP), and the full age + period + cohort (APC) model.

The non-identifiability issue is a well-known challenge for APC models, as age and year of diagnosis can be used to estimate the birth year or cohort (Clayton & Schifflers, 1987a, 1987b; Holford, 1983). To address this issue and prevent excessive parameterization, an additional restriction is necessary to obtain a unique set of parameters. In this study, we used the Holford technique (Holford, 1992) and set the median year of diagnosis as the reference period and the median year of birth as the reference cohort. We calculated the rate ratio (RR) for incidence, mortality, and DALYs using this approach.

To analyze the non-linear impact of birth cohorts on the incidence, mortality, and DALYs trends, we constrained the period slope to zero on average (on the log scale), assuming that any linear change in these outcomes is due to the effect of the birth cohort. The relative risks (RR) of cohort effects were presented with respect to the reference cohort, which served as a baseline for the cohort function. We employed the same method to evaluate the effects of time.

To evaluate the goodness-of-fit of the models, we followed the approach previously described by Clayton and Schifflers (Clayton and Schifflers, 1987a, 1987b), and analyzed the deviation of nested models. We used the likelihood ratio test to assess the significance of nonlinear (NL) period and cohort effects in these models, with p-values below 0.05 considered statistically significant. Our APC analysis was performed using the R package (Epi, version 4.2.1) developed by Carstensen et al. (Carstensen et al., 2021).

For the BRICS-plus countries, we depicted the age-standardised rates (ASR) of BC incidence and mortality over time. We presented rates by age group over time to illustrate the impact of age and period on mortality trends. Additionally, we displayed rates by age group for each birth cohort to demonstrate the effect of age and birth cohorts on death trends. Finally, we used graphs of the relative risk (RR) through cohort and period to illustrate the influence of age, period, and cohort on the incidence, mortality, and DALYs trends of BC based on our final model findings.

2.5.3. Ethical considerations

The Institute for Health Metrics and Evaluation offers public access to all de-identified data through their website http://ghdx.healthdata.org/gbd-results-tool. The GBD study utilized this compiled data, which was also de-identified. Due to this, the Institutional Review Board at the University of Washington conducted a review and granted a waiver for informed consent.

3. Results

3.1. Number of cases and age-standardised rate of incidence, death and DALYs

In 2019, there were 0.90 million female BC cases and 0.35 million deaths in the entire BRICS-plus region. Among the BRICS-plus countries in 2019, China and India had the largest percentage of incident cases and deaths, followed by Pakistan (Figs. 1 and 2). Age-standardised death rate (ASDR) for the SACU in the BRICS-plus region increased by 7.38% between 1990 and 2019 (%AROC Range: 0.29–2.61). Among the BRICS-plus countries, Lesotho had the greatest AROC from 1990 to 2019 (ASDR: 2.61% (95%UI: 1.99, 2.99). In 13 of the 35 BRICS-plus countries, the ASDR decreased between 1990 and 2019. Most of the BRICS-plus countries had higher AROCs than the global average. All of the BRICS-Plus countries saw an increase in the age-standardised incidence rate (ASIR) over the past three decades, from 1990 to 2019, with the exception of Myanmar and Kyrgyzstan, where it fell by 1.98% (95%UI: 1.53, −2.29) and 1.19% (95%UI: 1.48, −0.94), respectively. Across the BRICS-Plus countries, DALY trends were equivalent to those of the ASDR; the only difference was the magnitude (Table 1).

3.2. Time and age specific trends in mortality rate

Fig. 3 shows the trends in the global and BRICS-plus countries' BC mortality rates over time by age group. The results demonstrate that, with age group, the BC mortality rate has increased over time in the majority of the BRICS-plus regions. Myanmar, the Philippines, Singapore, Thailand, Armenia, Belarus, Kazakhstan, and Kyrgyzstan saw the biggest reductions in BC mortality during the past few years ($P <$

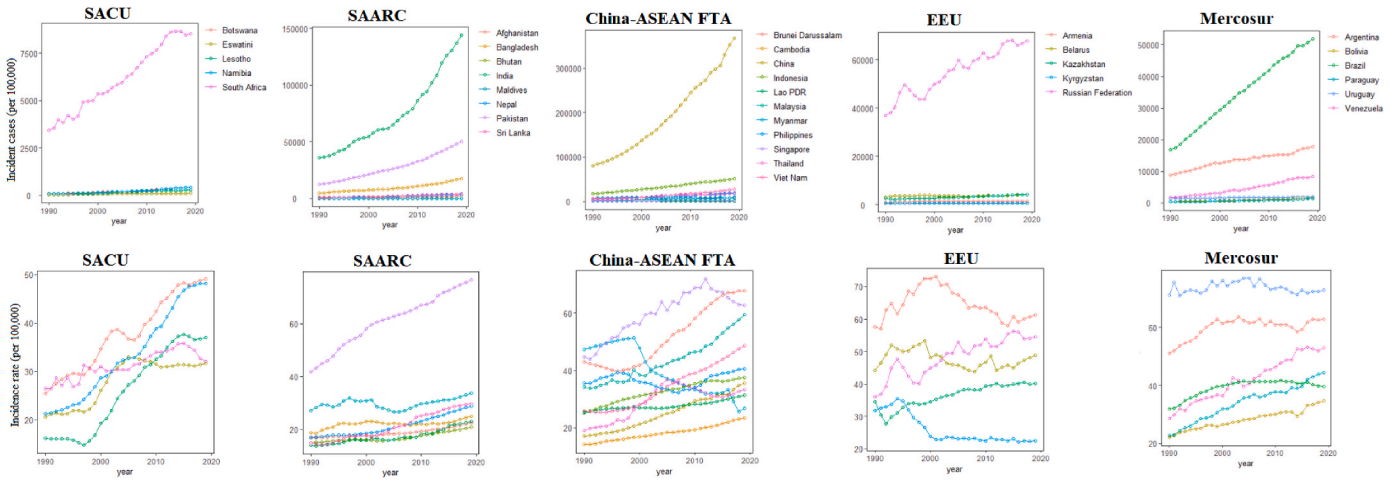

Fig. 1. Total number of incident cases and age-standardised incidence rate by years across BRICS-plus countries.

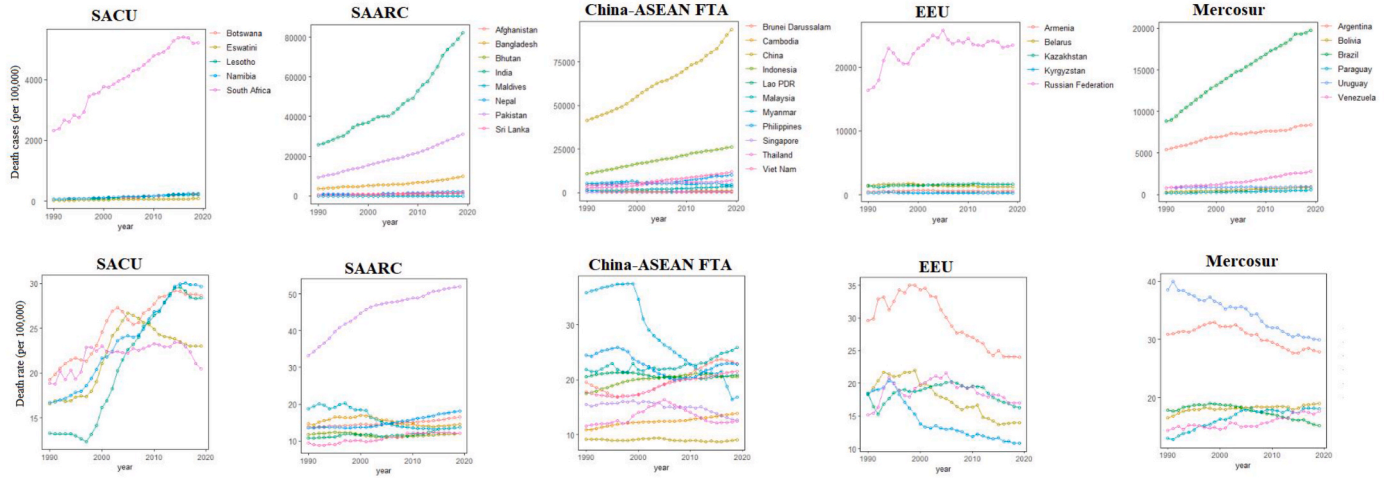

Fig. 2. Total number of death cases and age-standardised death rate by years across BRICS-plus countries.

0.01 for all) (Supplementary Fig. S1).

Fig. 4 shows that the global BC death rate declined for all birth cohorts between 1905 and 1999. Contrarily, across all birth cohorts, BC mortality rates increased in the majority of BRICS-plus countries. Eswatini, South Africa, Bangladesh, India, Maldives, Sri Lanka, Malaysia, Philippines, Singapore, Thailand, Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russia, Argentina, and Uruguay all saw BC mortality rates rise exponentially at the oldest birth cohorts, followed by a decline in all age groups ($p < 0.001$ for all). For instance, those under 50 consistently exhibited lower BC mortality than those over 50 compared to subsequent birth cohorts (Supplementary Fig. S2).

3.3. APC analysis on incidence, mortality and DALYs

The findings of the APC study indicated that the entire APC model was the best-fitting model for breast cancer incidence, death, and disability-adjusted life years (DALY) in all BRICS-plus countries and for the global BC outcome (Supplementary Table S1, Table S2 and Table S3). The impacts of age (as rates per 100,000) as well as cohort and period (as RR, rate ratio) on the incidence, mortality, and DALYs trends of BC are shown in Figs. 3, figure 4, and Fig. 5 and Supplementary Table S4, Table S5 and Table S6 respectively.

A consistent increase in incidence rate ratio (IRR) of BC across successive birth cohorts was observed starting with the oldest birth cohort (1905) through to the most recent cohort born in 1999 in all BRICS-plus regions, except for Myanmar and Kyrgyzstan which experienced a decline after the birth cohort 1945. In particular, Lesotho, Sri Lanka, Vietnam, and Venezuela displayed a high IRR of cohort-related risks. The effect difference between BRICS-plus regions was more significant for cohorts older than 50 and those born between 1940 and later. Our results indicate a slightly decreasing or stable risk in BC incidence across periods of diagnosis until 2019 almost in all BRICS-plus regions (Fig. 3, Table S4).

Age-related effects on BC mortality are seen to have a significant impact in each BRICS-plus area. The SACU, SAARC, and Mercosur regions have the highest age-related risk in Botswana, Eswatini, South Africa, Pakistan, Uruguay, and Argentina. We found that the birth cohort effects differ significantly amongst the BRICS-plus countries. In the majority of BRICS-plus nations, the mortality rate ratio (MRR) trend was increasing as birth cohorts grew from the cases' median birthdate. With the exception of the EEU and a few other nations from other regions, the mortality risk increased in each of the BRICS-plus regions. As high cohort-risk countries, Lesotho, Pakistan, Burnie, and Venezuela were identified. The age and cohort associated mortality risk of BC has increased overall as a result of the risk value being greater than the global impact. The temporal effect during the study period was either slightly declining or stable, and age and cohort impacts on disability adjusted life years rate ratio (DALYRR) were equivalent to mortality trends (Figs. 4 and 5, and Table S5 and Table S6).

Table 1
Age-standardised incidence rate, death rate and disability adjusted life years (DALYs) rate due to breast cancer and Annualized rate of change (AROC%) from 1990 to 2019, Globally and across BRICS-plus regions.

	Age-standardised incidence rate (per 100,000 person-years) and AROC from 1990 to 2019		Age-standardised death rate (per 100,000 person-years) and AROC from 1990 to 2019		Age-standardised DALYs rate (per 100,000 person-years) and AROC from 1990 to 2019	
	IR_2019 (95%UI)	%AROC (95%UI)	MR_2019 (95%UI)	%AROC (95%UI)	DALYs_2019 (95%UI)	%AROC (95%UI)
Global	45.86 (41.91,49.76)	0.46(0.27,0.64)	15.88 (14.66,17.07)	−0.38(-0.28, 0.5)	473.83(437.3510.51)	−0.35(-0.47,-0.26)
SACU						
Botswana	49.02 (31.66,72.18)	2.26(1.89,2.49)	28.63 (19.05,41.04)	1.36(1.03,1.55)	792.45 (503.91,1179.15)	1.32(0.95,1.57)
Eswatini	31.61 (19.22,47.07)	1.46(0.92,2.0)	23.03 (14.59,33.51)	1.14(0.72,1.6)	614.44(366.53,943.38)	1.02(0.43,1.63)
Lesotho	37(23.32,55.81)	2.85(2.24,3.27)	28.37 (18.11,41.78)	2.61(1.99,2.99)	783.95 (477.69,1202.31)	2.62(1.98,3.03)
Namibia	48.17 (33.07,70.08)	2.81(2.5,3.31)	29.68 (20.88,41.74)	1.98(1.71,2.39)	866.43 (581.94,1283.12)	1.84(1.59,2.34)
South Africa	32.08 (27.82,36.95)	0.66(0.60,0.67)	20.48 (18.08,23.22)	0.29(0.17,0.35)	529.91(461.82,609.3)	−0.12(-0.16,-0.06)
SAARC						
Afghanista	22.28 (16.83,29.07)	0.92(0.8,10)	16.47 (12.51,21.29)	0.59(0.45,0.68)	506.19(380.93,663.44)	0.43(0.37,0.5)
Bangladesh	25.03 (19.56,31.81)	0.97(0.95,1.09)	14.54 (11.51,18.15)	−0.05(-0.11,0.12)	450.24(352.39,570.27)	−0.28(-0.35,-0.08)
Bhutan	20.87 (14.61,28.78)	1.16(1.05,1.39)	12.02(8.53,16.35)	0.05(0.07,0.29)	347.9(236.86,482.29)	−0.31(-0.36,-0.18)
India	23.04 (17.79,28.97)	1.74(1.57,1.94)	13.67 (10.57,17.35)	0.81(0.64,1.06)	416.38(321.04,530.26)	0.83(0.6,1.14)
Maldives	33.75 (26.91,40.94)	0.74(0.08,1.67)	13.65 (11.14,16.51)	−1.09(-1.66,-0.24)	373.42(299.67,455.79)	−1.55(-2.19,-0.51)
Nepal	28.81(21.2,38.35)	1.83(1.66,2.22)	18.08 (13.41,23.83)	0.99(0.81,1.47)	549.94(401.77,738.00)	0.8(0.64,1.14)
Pakistan	76.49 (56.07,102.5)	2.08(1.95,2.21)	51.94 (39.03,69.76)	1.54(1.41,1.79)	1570.06 (1177.2,2135.47)	1.5(1.5,1.63)
Sri Lanka	29.78 (21.86,40.03)	2.35(1.77,2.91)	12.14(8.99,16.07)	0.85(0.31,1.38)	345.01(252.16,463.13)	0.67(0.08,1.23)
China-ASEAN FTA						
Brunei Darussalam	67.73 (55.46,82.13)	1.58(1.55,1.61)	22.9(19.26,27.04)	0.55(0.49,0.61)	737.82(612.52,882.27)	0.32(0.23,0.42)
Cambodia	23.52 (17.91,29.43)	1.75(1.59,1.79)	13.86 (10.73,17.11)	0.84(0.67, 0.96)	442.69(336.45,558.71)	0.62(0.46,0.65)
China	35.61 (28.07,44.81)	2.54(2.39,2.73)	9.02(7.19,11.1)	−0.06(-0.2,0.09)	277.98(224.35,339.93)	−0.19(-0.28,-0.09)
Indonesia	37.42 (28.96,48.59)	1.34(0.99,1.67)	20.47 (15.89,25.94)	0.55(0.2,0.8)	704.7(549.24,905.84)	0.44(0.1,0.7)
Lao People's Democratic Republic (Lao PDR)	31.24(22.4,44.28)	0.73(0.57,0.97)	20.79(15.1,29.08)	0.04(-0.11,0.25)	650.11(460.16,932.94)	−0.15 (-0.29,0.17)
Malaysia	59.48 (45.19,75.15)	1.91(1.38,2.27)	25.81 (19.83,32.54)	0.57(0.08,0.9)	757.24(581.12,952.13)	0.43(-0.08,0.78)
Myanmar	26.64 (21.39,33.54)	−1.98(-2.29,-1.53)	16.78 (13.87,20.84)	−2.61(,-2.89,-2.18)	505.69(404.83,640.96)	−3.12(-3.4,-2.59)
Philippines	40.63 (30.52,52.96)	0.47(-0.04,0.95)	22.85 (17.39,29.48)	−0.24(-0.71,0.25)	711.69(534.07,924.42)	0.02(-0.5,0.52)
Singapore	62.72(49.6,78.06)	1.17(0.64,1.63)	12.66 (11.44,13.77)	−0.7(-0.6,-0.85)	386.85(351.21,429.7)	−0.85(-0.97,-0.68)
Thailand	33.31(23.94,44.6)	1.94(1.31,2.44)	12.41(9.08,16.35)	0.25(-0.35,0.72)	394.58(283.96,529.03)	0.22(-0.41,0.75)
Viet Nam	48.65 (36.57,63.02)	2.18(2.06,2.31)	21.54 (16.39,27.78)	0.67(0.52,0.83)	653.36(492.18,848.61)	0.56(0.45,0.68)
EEU						
Armenia	61.17 (49.78,73.72)	0.21(-0.27,0.63)	23.95 (19.86,28.52)	−0.74(-1.18,-0.32)	704.48(576.74,849.33)	−1.08(-1.56,-0.64)
Belarus	48.88 (36.92,64.83)	0.35(-0.38,1.11)	14.01 (10.77,18.08)	−0.93(-1.68,-0.22)	433.52(329.21,573.12)	−1.18(-1.96,-0.39)
Kazakhstan	40.07 (33.62,47.05)	0.52(0.19,0.83)	16.3(13.96,18.85)	−0.43(-0.73,-0.15)	486.4(411.22,572.5)	−0.65(-0.99,-0.32)
Kyrgyzstan	22.43 (19.09,26.21)	−1.19(-1.48,-0.94)	10.8(9.36,12.47)	−1.82(-2.08,-1.6)	317.43(272.24,370.97)	−2.15(-2.42,-1.87)
Russian Federation	54.39 (44.01,66.87)	1.42(0.78,1.97)	17.02 (13.91,20.46)	0.4(-0.19,0.91)	509.29(419.52,618.33)	0.14(-0.42,0.65)
Mercosur						
Argentina	62.72 (48.36,80.34)	0.71(-0.02,1.4)	27.92 (25.85,30.04)	−0.35(-0.47,-0.24)	749.03(694.47,808.06)	−0.49(-0.62,-0.36)
Bolivia	34.52 (26.16,45.81)	1.56(1.47,1.67)	18.98 (14.75,24.35)	0.49(0.44,0.50)	536.09(398.87,707.72)	0.23(0.14,0.29)
Brazil	39.64(37.1,42.28)	0.74(0.66,0.85)	15.13(14.1,16.08)	−0.57(-0.66,-0.49)	449.44(422.78,478.81)	−0.54(-0.62,-0.44)

(*continued on next page*)

Table 1 (*continued*)

	Age-standardised incidence rate (per 100,000 person-years) and AROC from 1990 to 2019		Age-standardised death rate (per 100,000 person-years) and AROC from 1990 to 2019		Age-standardised DALYs rate (per 100,000 person-years) and AROC from 1990 to 2019	
	IR_2019 (95%UI)	%AROC (95%UI)	MR_2019 (95%UI)	%AROC (95%UI)	DALYs_2019 (95%UI)	%AROC (95%UI)
Paraguay	44.33 (32.75,57.04)	2.3(1.8,2.64)	18.04 (13.71,23.01)	1.15(0.74,1.49)	528.37(392.15,686.1)	1.05(0.57,1.43)
Uruguay	72.65 (55.79,92.57)	0.07(-0.60,0.68)	29.97 (27.54,32.27)	−0.87(-0.98, −0.75)	810.49(746.22,884.55)	−1.06(-1.19,-0.91)
Venezuela	53(39.43,70.51)	2.15(1.34,2.9)	17.65 (13.43,23.06)	0.73(-0.01,1.48)	537.71(402.12,721.94)	0.73(-0.09,1.56)

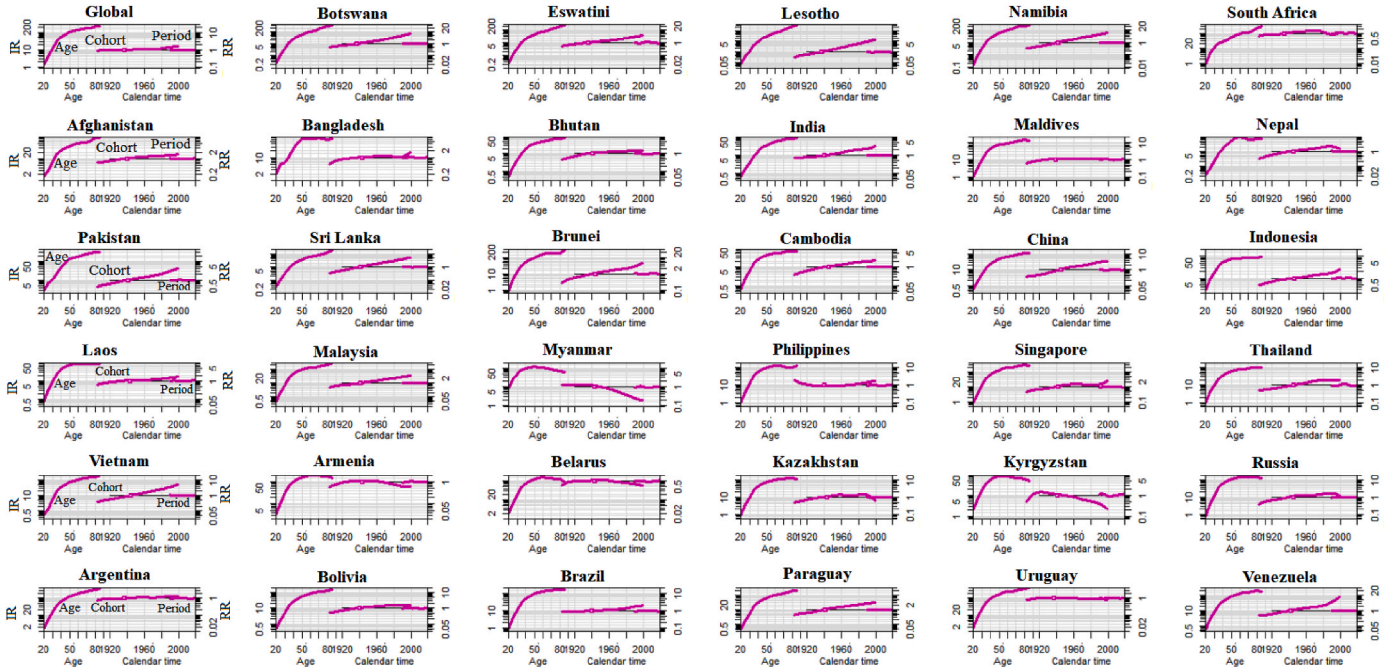

Fig. 3. Age period cohort effects on BC incidence rate (IR) from 1990 to 2019 with ages 20–84 year. Rate ratio (RR) was estimated using ML of APC-model Poisson with log(Y) based on natural-spline function, for each BRICS-plus country separately. ML, maximum likelihood; APC, age-period-cohort; Reference cohort for age-effects was chosen as the median date of birth among cases; and Median date of diagnosis among cases was selected as reference period.

3.4. Changes in mortality rate and DALYs attributable to modified risk factors, 1990–2019

Significant variations in age-standardised mortality rate (ASMR) and DALYs patterns were seen among the BRICS-plus countries, indicating that the risk factors for BC may have differing effects on mortality and DALYs in these countries' female populations. In 2019 among the BRICS-plus countries, high fasting plasma glucose (FPG), high body mass index (BMI), alcohol usage, a diet high in red meat, and active smoking were the risk factors associated with the greatest death and DALY rates (per 100 k). Namibia, South Africa, Pakistan, Malaysia, Russia, Brazil, Kazakhstan, Argentina, and Uruguay had relatively high rates of these risk factors. The top 10% of BC death and DALY rates in 2019 were correlated with high BMI and high FPG, a diet high in red meat, and alcohol intake in almost all BRICS-plus countries. Alcohol consumption, high BMI, high FPG, a diet high in red meat, and secondhand smoke were the main causes of the high positive annual rate of change in BC deaths and DALYs between 1990 and 2019 across the majority of BRICS-plus countries. The age group of female BC patients with the highest risk for this increase was 50 years and older (Figs. 6 and 7, Supplementary Fig. S3 and Fig. S4).

3.5. Sociodemographic variations in incidence, mortality, and DALYs

Fig. 8 for the year 2019 displays bivariate relationships for age-standardised incidence rates (ASIR), mortality rates (ASMR), disability-adjusted life years (DALYs), and countries' SDI. The bivariate correlation plot revealed a statistically significant positive link between the higher incidence rate and SDI ($r_{ASIR} = 0.64$, $p < 0.001$). ASIR eventually increases along with SDI, growing more swiftly in countries with higher SDI values. Further, the countries that increased their SDI in 2019 also had decreases in ASMR and DALYs ($r_{\text{ASMR}} = -0.34$, $p = 0.04$; $r_{\text{ASDALYs}} = -0.24$, $p = 0.04$). Pakistan and Lesotho, two nations with low SDIs in 2019, have high ASMR and DALY rates.

4. Discussion

As the major global health challenge, BC is the leading cause of morbidity and mortality among women, especially in countries such as SSA. However, there is still a lack of comprehensive and unified analysis among low-income and developing countries, and BRICS-plus offers us new opportunities. BRICS-plus is an open and inclusive multilateral cooperation platform, comprising more than 30 countries. As the representation of emerging and developing countries to participate in global governance, BRICS-plus aims to form a common position and collective will of developing countries and further achieve win-win

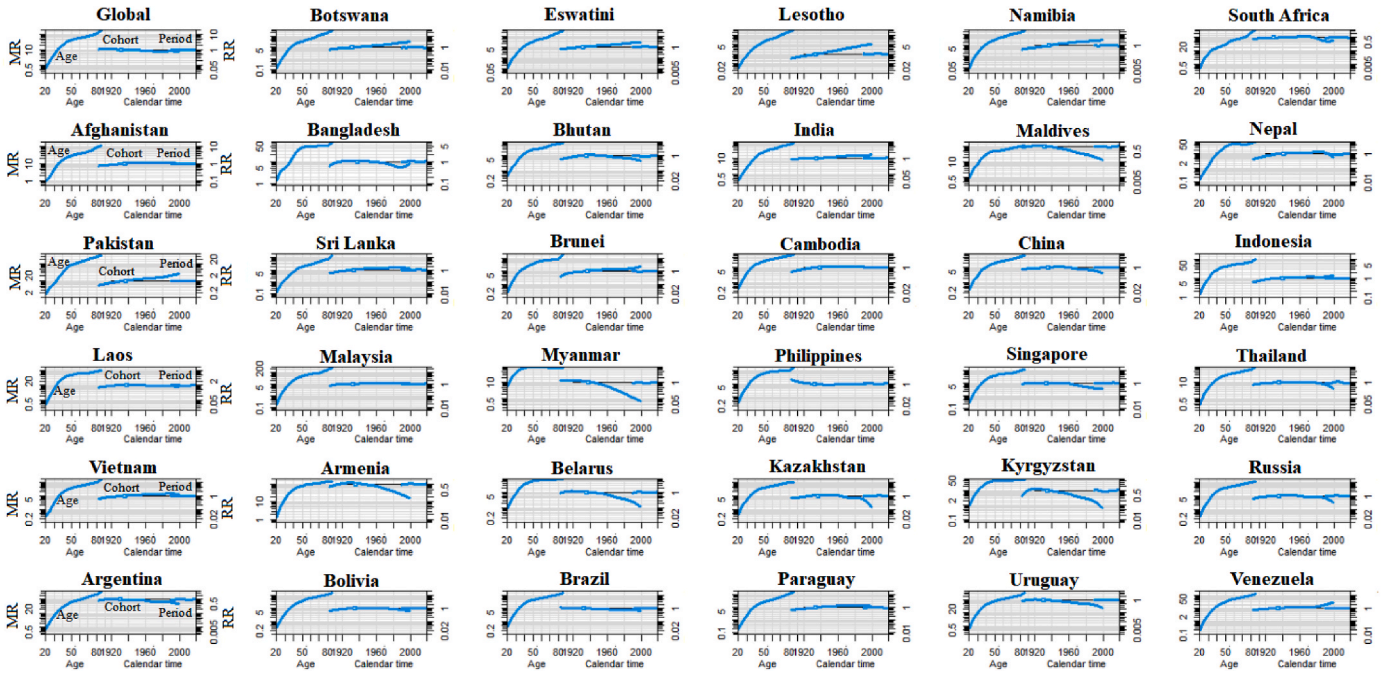

Fig. 4. Age period cohort effects on BC mortality rate (MR) from 1990 to 2019 with ages 20–84 year. Rate ratio (RR) was estimated using ML of APC-model Poisson with log(Y) based on natural-spline function, for each BRICS-plus country separately. ML, maximum likelihood; APC, age-period-cohort; Reference cohort for age-effects was chosen as the median date of birth among cases; and Median date of diagnosis among cases was selected as reference period.

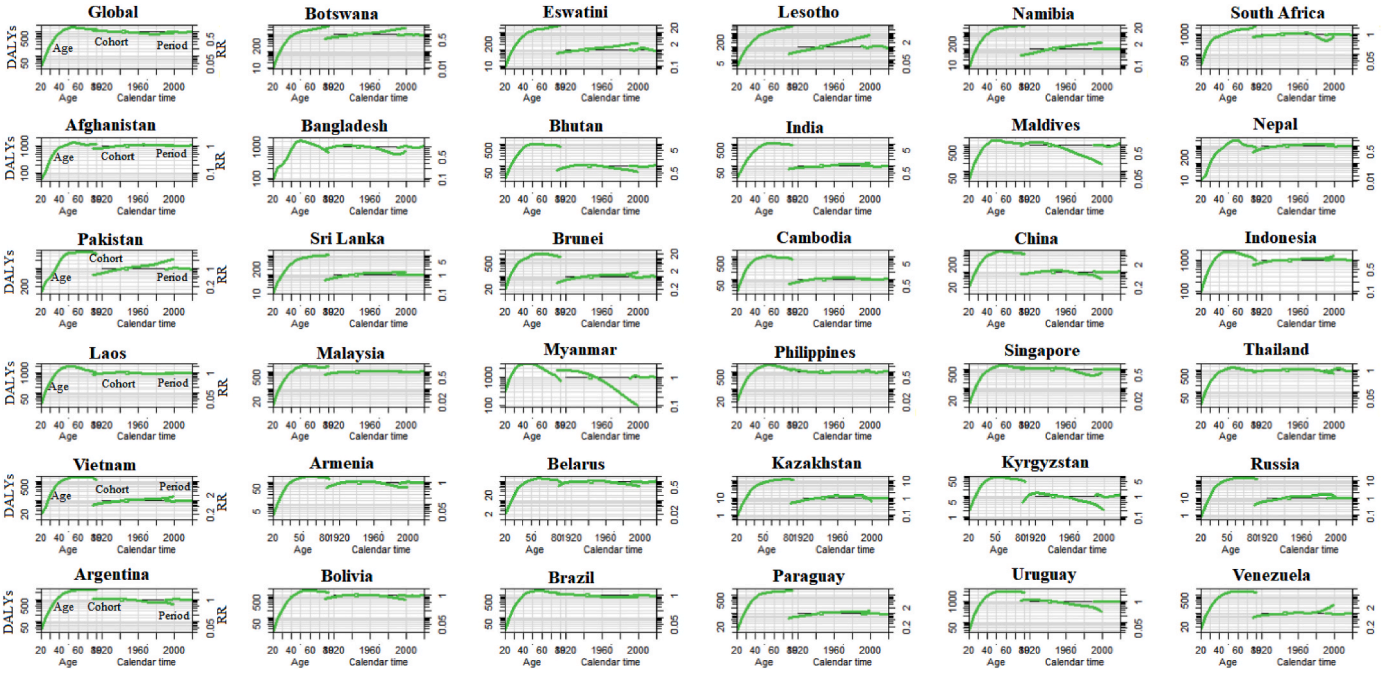

Fig. 5. Age period cohort effects on BC disability adjusted life years (DALYs) from 1990 to 2019 with ages 20–84 year. Rate ratio (RR) was estimated using ML of APC-model Poisson with log(Y) based on natural-spline function, for each BRICS-plus country separately. ML, maximum likelihood; APC, age-period-cohort; Reference cohort for age-effects was chosen as the median date of birth among cases; and Median date of diagnosis among cases was selected as reference period.

cooperation. In view of the growing burden of BC in low- and middle-income countries, as well as regional differences, we study the current situation in BRICS-plus countries and its changing trends, explore and identify risk factors that may affect BC burden in resource-limited settings, so as to help policy-makers better address this huge public health challenge and further promote health equity and social justice.

We found that there were 0.90 million female BC cases and 0.35 million deaths in the BRICS-plus countries in 2019. Overall, BC mortality rates have increased over time in most BRICS-Plus countries, although ASR of BC mortality have declined. Age contributes significantly to BC mortality, the birth cohort effects varied among different BRICS-plus countries. BC risk is associated with SDI, but incidence and mortality seem to show different directions.

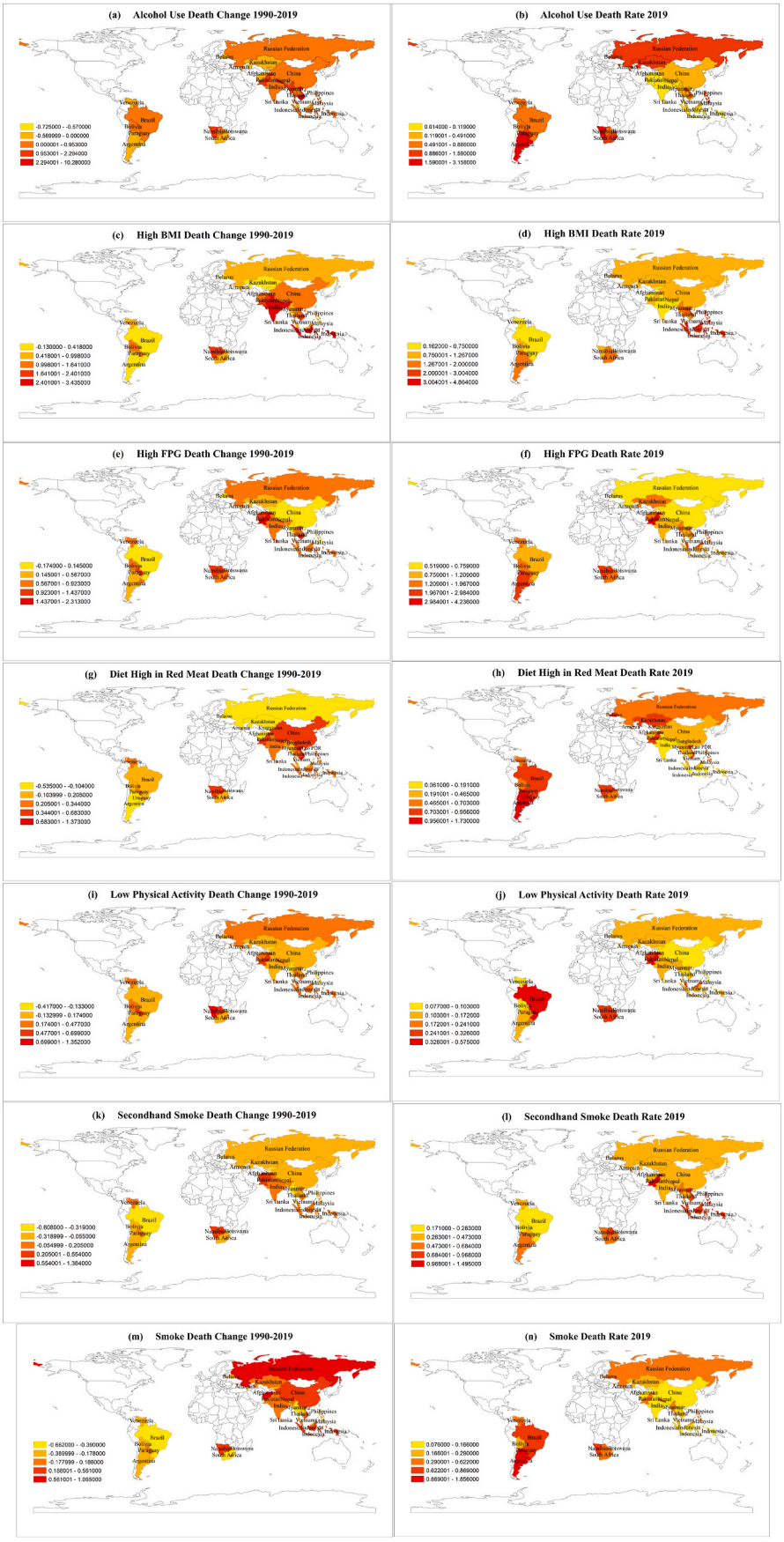

Fig. 6. Annual rate of change in breast cancer death rate from 1990 to 2019 (left panel), and age-standardised death rate in 2019 (right panel) attributable to modified risk factors across BRICS-plus countries.

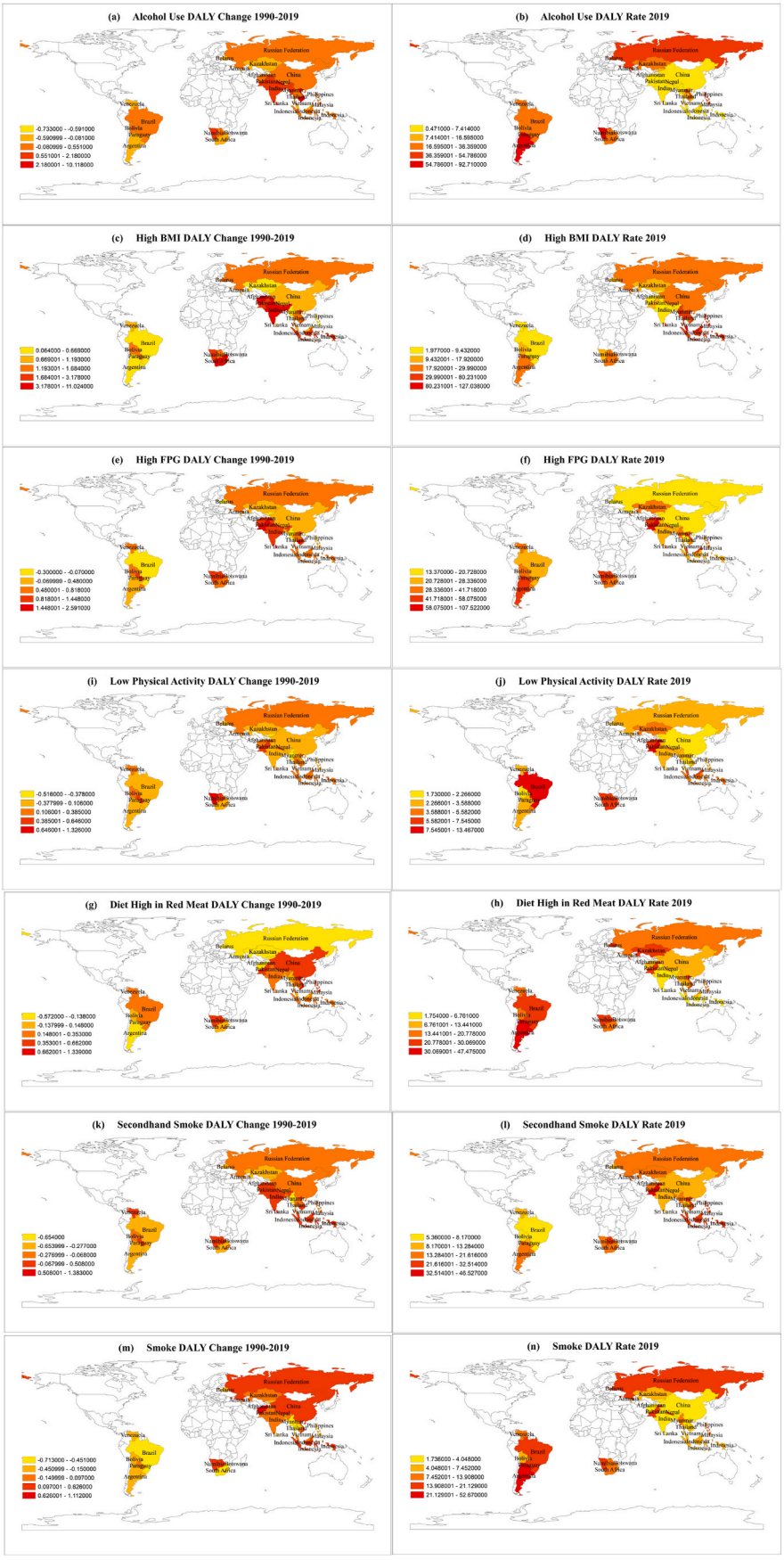

Fig. 7. Annual rate of change in disability adjusted life years (DALY) from breast cancer, 1990 to 2019 (left panel), and age-standardised rate of DALY in 2019 (right panel) attributable to modified risk factors across BRICS-plus countries.

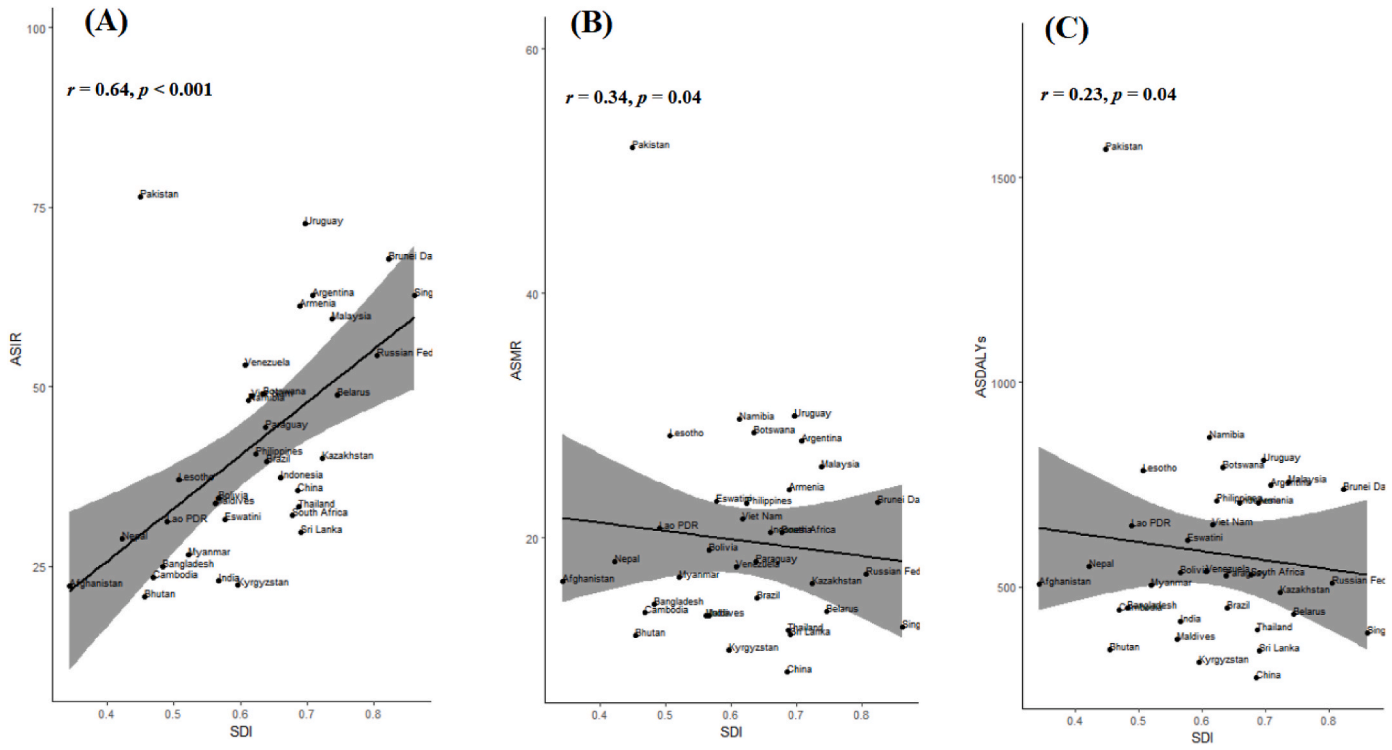

Fig. 8. Country wise correlation between age-standardised BC rate (per 100,000 person-years) and country's sociodemographic index (SDI) in 2019 across BRICS-plus; **(A)** age-standardised incidence rate (ASIR) **(B)** age-standardised mortality rate (ASMR) **(C)** age-standardised disability adjusted life years (ASDALYs); SDI ranges from 0 (less developed) to 1 (most developed).

4.1. Age effect

Age is one of the important risk factors for BC. We found that age had a greater impact on BC mortality regardless of the BRICS-plus countries. BC mortality was lower in younger people than in those older than 50 years in all birth cohorts, suggesting that advanced age is one of the most important risk factors for BC mortality and DALY. Contrary to common belief, studies have reported that young women under the age of 40 have a worse prognosis than older women, younger age is an independent determinant of poor prognosis in BC (Shoemaker et al., 2018). Younger women with BC are more likely to be diagnosed with advanced or higher-grade, tumor tend to be more aggressive and invasive, but this pattern varies according to the diagnosis time, histologic type, race, and geographic region (Chen et al., 2016). After controlling for above adverse factors such as race, histologic type, TNM stage, hormone receptor status, studies suggest that advanced age is an independent risk factor for poor survival and BC specific survival rate, and older women face worse prognosis than younger patients. Balabram et al. found that the cancer-specific survival rate of women aged 70 and older and under 35 was worse than that of other age groups in Brazil from Mercosur (Balabram et al., 2015). Places such as China, India and Pakistan, where the proportion of older women is relatively higher, also show the largest percentage of incident cases and deaths. Age 60 or above is independent predictor of poor prognosis (Joko-Fru et al., 2020). This may provide some basis for determining the optimal screening age for women in different regions. These are generally consistent with our results.

4.2. Alcohol and tobacco use

Although the ASDR and DALY rates of BC attributable to alcohol usage have been declining from 1990 to 2019, alcohol consumption remains the important identifiable risk factors for BC, as well as active smoking. Per capita alcohol consumption has declined and drinking prevalence has shown a significant decrease in countries such as Europe and the United States with high SDI, particularly in Eastern Europe, while alcohol consumption is still rising in Asian countries such as China, India, and Vietnam, as well as many BRICS-plus countries in SSA (Safiri et al., 2022). The harmfulness of alcohol has been demonstrated in enhancing DNA damage, interfering with mitochondrial function, affecting DNA methylation status/histone modification/lipid change, oxidative stress, and hormone levels, etc (Li et al., 2019; Singletary & Gapstur, 2001). Moreover, studies also suggest that there may be a dose-response relationship between alcohol consumption and breast cancer, which further aggravate adverse BC outcomes (Li et al., 2019). In SSA, alcohol-attributed cases due to alcoholism make a significant contribution, and we found that only one third of countries have enacted national/subnational alcohol strategies (Ferreira-Borges et al., 2015).

Evidence suggests that there is a synergistic effect between alcohol consumption and smoking, in addition to causing cancer development through multiple biological pathways, ethanol can also be used as a solvent for chemicals in tobacco (Singletary & Gapstur, 2001), indirectly promoting cancer development and increasing disease burden. In the world, there are more than 1 billion smokers, 80% of whom reside in low- and middle-income countries. In Indonesia, Myanmar and the Philippines, women have the highest cancer mortality due to smoking (Kristina et al., 2019). According to WHO estimates, there are 246 million smokers and 290 million smokeless tobacco users in ASEAN countries, making Southeast Asia one of the regions with the largest tobacco consumption, which also contributes to a heavy BC burden (Kristina et al., 2019). Studies suggested that alcohol and tobacco are the main causes of premature deaths among Russian adults (Zaridze et al., 2009), and we also found that the BC burden caused by smoking and alcohol risk factors in Russia was at a high level among BRICS-plus countries (Barchuk et al., 2018; Rumgay et al., 2021).

4.3. Metabolic and dietary risks

The progression of breast cancer development involves a complex

interplay of genetic, environmental, socio-economic, and lifestyle risk factors. In addition to alcohol consumption and active smoking, risk factors associated with BC in BRICS-plus countries also included high FPG, high BMI, and high red meat diet. In most BRICS-plus countries, these three factors led to the highest BC mortality and DALY rates in 2019. These risks used to be more present in high and high-middle SDI areas, while social development over time showed a very different scenario. Driven by significant period and cohort effects, a heavier burden of BC was observed in the elderly and the recent birth cohorts (Shwe et al., 2022). With social development and initial increases in national wealth, diet conditions have unexpectedly worsened, leading to higher calorie intake and high FPG. Therefore, the prevalence of obesity and high BMI has also increased in low- and middle-income countries from BRICS-plus (The Lancet, 2022). These conditions will only improve as further increase of income and people's health awareness.

In high-income Asia-Pacific countries, obesity rates have decreased through healthy lifestyles (Li et al., 2019). Excess cholesterol may accelerate tumor formation, and further increase the disease burden. Individuals with a high BMI or obesity have altered systemic metabolism, which may increase the risk of BC (Engin, 2017; Singh et al., 2011). It has been shown that obesity is an independent adverse prognostic factor for BC mortality in postmenopausal patients with a high BMI, and 50% of deaths can be attributed to obesity (Iyengar et al., 2019). Results from the National Family Health Survey in India showed that the proportion of married women who were overweight or obese had increased to 18% by 2015–2016, which may further lead to the increase in BC incidence (Vennu et al., 2019), also validating our findings. In addition, studies have linked high BMI to an increased risk of triple negative breast cancer (TNBC), and in countries such as South Africa and India, the detection rate of TNBC is relatively high (Malvia et al., 2017), which also indicates the regional differences in breast cancer subtypes.

4.4. Regional variation

Breast cancer risk and outcomes vary by country and race (Anyigba et al., 2021). In many BRICS-plus countries, people are plagued by infectious diseases, governments are focusing more on other health priorities, making NCDs including BC, a neglected healthcare issue in these countries. In the past, BC incidence was high in most developed countries. With the period effect and the continuous improvement of medical level, early diagnosis enabled BC patients to receive more timely and effective treatment, which reduced the mortality of BC in these regions, and continued to increase the survival rate (Martei et al., 2022). As we summarized earlier, SDI is negatively correlated with the adverse prognosis and positively correlated with incidence of BC.

Among BRICS-plus countries, the EEU and Mercosur countries with relatively high SDI showed relatively better performance in decreasing the risk of death and DALY rate of breast cancer. For example, in Russia, a member of the EEU, the BC incidence remained stable in several generations after World War II. In SSA countries, the incidence of BC has increased since 1990, and is associated with higher mortality. Considering the reasons, it is related to the increasing urbanization in these countries in recent years. With the implementation of various measures, the gradual development of the country has reduced social poverty, increased per capita purchasing power, and medical diagnosis level, showing a high incidence of BC(2). For example, in China, with the increase of BC screening rate, the number and effectiveness of national cancer registries were significantly improved from 2003 to 2011, the proportion of population covered has significantly increased, and the quality of the data collected has also improved, showing an increase in incidence (Li et al., 2016).

However, in SSA countries with lower SDI, more than half of the countries lack radiotherapy facilities, which can only meet about 18% of the expected demand (Anyigba et al., 2021; Brinton et al., 2014). In addition, there is a shortage of training personnel and testing equipment (Anyigba et al., 2021). The detection and identification of different types of BC is limited. A population survey of Lesotho showed that only 10% of local women were screened for BC (Ramathebane et al., 2022). Targeted therapy methods and drug supply are insufficient, which affect the prognosis of BC patients. In some areas, cultural beliefs and possible stigma associated with BC treatment may also discourage patients from seeking and early diagnosis (Akuoko et al., 2017). Due to the inconvenience of diagnosis and the difference in concept, many patients in these regions are already in advanced stage when they are discovered, 80% patients have local metastasis at the time of diagnosis, resulting in poor prognosis and high mortality (Anyigba et al., 2021). In addition, distance to medical centres and limitations on treatment costs will further hinder patients from seeking treatment. Thus, although the BC burden in SSA appears to be relatively low, the mortality was disproportionately high due to the low survival rate. Many countries are still in poverty, despite improvements in economic levels. It has been estimated that 9 out of every 10 people in SSA countries will still be living in extreme poverty in 2030, which may further increase the burden of BC. In developing countries with limited resources, it seems unrealistic to imitate policy measures of BC diagnosis and treatment in high-income countries. Clinical breast examination and breast self-examination (Black & Richmond, 2019; Mittra et al., 2021) for example, may be more suitable and practical for BRIC-Plus countries, although these tests are less effective than clinical X-ray examination.

Our study has certain limitations. First, the estimated incidence of breast cancer was generated from population-based cancer registries. Most of the BRIC-plus countries concerned in this study are low- and middle-income countries, the quantity and quality of the cancer registry data are generally relatively low, especially among Africans with genetic diversity, which hinders the estimates of the local actual disease burden and may affect our findings. Secondly, in SSA countries such as South Africa, Cameroon, and Malawi, many BC patients were not detected until the advanced stage due to the lack of diagnostic capacity, but it does not mean that there are more advanced patients than early patients in the local area. Combined with the multi-hierarchical estimation pattern makes it impossible to avoid or balance differences in data collection, coding, and the quality of data sources across countries.

5. Conclusion

In summary, we systematically assessed the burden of BC in BRICS-plus countries, as well as its associated major risk factors. From 1990 to 2019, the BC burden of female in BRIC-plus countries has still increased. Although BRICS-plus countries have made some achievements in their efforts to control BC, the overall progress lags behind the global level. Therefore, BRICS-plus countries should pay more attention to BC prevention, strengthen the public's awareness, and formulate corresponding policies to improve screening efficiency, so as to better prevent BC and reduce the burden in the future. Given the gaps in BC diagnosis and treatment among different countries, directly use the prevention measures implemented in high-income countries should be avoided. Specific public health policies and strategies for different key populations should be further strengthened according to the characteristics of each BRICS-Plus country and its adaptability.

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Availability of data and materials

The dataset analyzed during the current study are available in the Institute for Health Metrics and Evaluation (IHME): http://ghdx.healthdata.org/gbd-results-tool.

Ethics approval

Not applicable.

Conflict of interest and authorship conformation form

Please check the following as appropriate:

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

The following authors have affiliations with organizations with direct or indirect financial interest in the subject matter discussed in the manuscript.

Compliance for ethical requirement

All anonymized data are accessible online at http://ghdx.healthdata.org/gbd-results-tool, the Institute for Health Metrics and Evaluation. The deidentified, compiled data was used in the GBD investigation. As a result, the University of Washington Institutional Review Board examined and approved a waiver of informed consent.

CRediT authorship contribution statement

Sumaira Mubarik: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Fang Wang:** Formal analysis, Investigation, Software, Visualization, Writing – review & editing. **Adeel Ahmad Nadeem:** Formal analysis, Investigation, Data curation. **Muhammad Fawad:** Writing – review & editing, Validation, Visualization, Data curation. **Chuanhua Yu:** Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation.

Declaration of competing interest

All authors declare that no conflict of interest exists.

Data availability

The dataset analyzed during the current study are available in the Institute for Health Metrics and Evaluation (IHME): http://ghdx.healthdata.org/gbd-results-tool.

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Abbreviations

BC	breast cancer
GBD	global burden of diseases
SDI	sociodemographic index
DR	death rates
IR	incidence rates
ASIR	age-standardised incidence rates
ASMR	age-standardised mortality rates
APC	age-period-cohort
BRICS	Brazil, Russia, India, China, South Africa
SSA	sub-Saharan Africa

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2023.101418.

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