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Global, regional, and national time trends in mortality for breast cancer, 1992–2021: an age-period-cohort analysis for the global burden of disease 2021 study

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Abstract

Background Breast cancer remains a major global health concern. This study aims to assess the epidemiological trends of breast cancer, with a focus on mortality rates, primary risk factors, and their associations with age, time period, and birth cohort.

Methods Mortality data were obtained from the Global Burden of Disease Study 2021. An age-period-cohort model was employed to analyze trends in breast cancer mortality and its primary risk factors.

Results Globally, breast cancer outcomes remained poor between 1992 and 2021, with an estimated 660925.3 deaths in 2021. Mortality rates declined significantly in high and high-middle socio-demographic index (SDI) countries [-1.56%, 95% CI (-1.7 to -1.43)], [-1.03% (-1.11 to -0.94), respectively], but increases markedly in low-middle SDI countries [1.18% (1.13 to 1.23)], with little change in other regions. A global shift in breast cancer-related deaths from younger to older age groups was observed, and mortality increased sharply with advancing age. Positive period and cohort effects were primarily seen in high and high-middle SDI countries, whereas adverse effects were more common in lower-SDI regions. Diets high in red meat emerged as the leading risk factor for breast cancer mortality worldwide, although favorable trends were noted in high and high-middle SDI countries.

Conclusions Despite a global decline in breast cancer mortality, many countries continue to experience unfavorable period and cohort effects. A notable rise in mortality among individuals aged 80 and older was observed across all SDI quintiles, underscoring the urgent need to strengthen healthcare systems for aging breast cancer populations worldwide.

Keywords Breast cancer, Mortality, Age-period-cohort, Risk factor

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Introduction

Breast cancer is the most prevalent cancer among women, accounting for approximately one in every eight cancer diagnoses. In 2022, there were 2.31 million new cases globally, making up 11.6% of all cancers cases. It is also the leading cause of cancer-related deaths in women, with 0.67 million deaths, or 6.9% of all cancer deaths [1, 2].

Over the past three decades, advancements in early detection, treatment, and awareness have influenced the incidence, mortality, and survival rates of breast cancer [3]. However, these improvements are not uniform, with notable disparities observed between high- and low-to-middle-income countries [4, 5]. Understanding temporal trends in breast cancer mortality is crucial for evaluating the effectiveness of cancer control strategies, anticipating future healthcare demands, and informing evidence-based policymaking. In particular, the age-period-cohort (APC) analytical framework allows researchers to disentangle the independent contributions of biological aging (age effect) [6], historical and medical advancements (period effect) [7], and generational exposure to risk factors or interventions (cohort effect) [8]. Despite numerous reports on the global burden of breast cancer, few studies have provided a comprehensive analysis of long-term mortality trends using APC models at the global, regional, national and all-age levels [9, 10, 11, 12, 13]. Moreover, the implications of these epidemiological shifts for public health remain underexplored, particularly in light of emerging challenges such as declining fertility rates, population aging, and rising interest in personalized and precision medicine. The primary objective of this study is to (1) quantify long-term global, regional, and national mortality trends in breast cancer from 1992 to 2021 using APC modeling based on the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 dataset, (2) identify disparities by sociodemographic index (SDI) regions/age groups, and (3) evaluate the impact of modifiable risk factors (e.g., diet) to inform targeted interventions. By quantifying the effects of age, period, and cohort across diverse regions and sociodemographic contexts, this study aims to generate evidence that may guide future research, public health initiatives, and policy decisions in the era of demographic transition and precision oncology.

Materials & methods

Age-period-cohort modelling analysis of mortality data

This study employs an age-period-cohort (APC) model to examine mortality trends across age, period, and birth cohort. The APC model quantifies the contributions of age-related biological factors, as well as technological and social influences on disease patterns, extending beyond traditional epidemiological analyses [14]. It has been widely applied in descriptive epidemiology, particularly for chronic diseases such as cardiovascular and cancer conditions [13, 15].

The model fits a log-linear Poisson regression over a Lexis diagram to estimate the additive effects of age, period, and cohort. However, due to the exact linear dependency among these factors (birth cohort = period–age), their independent effects cannot be directly estimated, known as the "identification problem." To address this, we derive estimable APC parameters without imposing arbitrary constraints. The model is implemented in R using publicly available tools, following established methodologies [16].

Input data included GBD 2021 estimates of breast cancer deaths, along with population data for each region or country. Detailed input data, including 16 age groups (from 15 to 19 to 90–94) and 21 partially overlapping 10-year birth cohorts, are provided in Supplementary Table S1. The APC model outputs included: (1) net drift (overall temporal trend expressed as annual percentage change in death rate), (2) local drift (temporal trend within each age group), (3) age effect (longitudinal age-specific rates adjusted for period deviations), (4) period effect (relative risk of each period compared with the reference period), and (5) cohort effect (relative risk of each cohort compared with the reference cohort). The 2002–2006 period and 1948–1956 cohort were set as reference points in this study. Trend significance was assessed via Wald chi-squared tests.

Additional APC model outputs included fitted longitudinal age-specific rates adjusted for period deviations (age effects) and relative risks of mortality for each period and cohort. Relative risks were computed as the ratio of age-specific rates in each period (or cohort) to a reference period (or cohort), with the net drift fully incorporated. The choice of referent period or cohort was arbitrary and did not affect interpretation.

Statistical analysis

All statistical analyses were conducted using R (version 4.1.0), with p-values < 0.05 considered statistically significant. The detailed methods are available at supplemental material.

Results

Global and regional burden trends in breast cancer from 1992 to 2021

In 2021, the global estimated number of deaths from breast cancer was 660.93 thousand (95% UI 609.17 to 707.18, Table 1). Table 1 presents global and regional breast cancer mortality data for 2021, including all-age rates, age-standardized rates (ASRs), and net drifts from 1992 to 2021. Figure 1 and Supplementary Figure S1 illustrate mortality rates (both all-age and ASRs) in 2021

Table 1 Deaths for breast cancer in 2021 and net drift in age standardized rates (ASRs) per 100,000, by global burden of disease region, from 1992 to 2021. 95% UI, 95% uncertainty intervals; 95% CI, 95% confidence interval

Regions	Number (95% UI)	All-age rate per 100 000 (95% UI)	ASRs per 100 000 (95% UI)	Net drift (95% CI), %
Global	660925.3 (609171.34 to 707181.86)	16.81 (15.49 to 17.99)	14.55 (13.45 to 15.56)	-0.38 (-0.41 to -0.34)
Central Asia	6608.11 (5910.1 to 7374.62)	13.69 (12.24 to 15.27)	13.83 (12.41 to 15.37)	-0.81 (-1.02 to -0.6)
Central Europe	24869.17 (22633.13 to 26979.47)	42.08 (38.3 to 45.65)	20.26 (18.54 to 21.98)	-0.71 (-0.95 to -0.47)
Eastern Europe	35827.2 (31988.81 to 40502.03)	32.4 (28.93 to 36.63)	17.37 (15.49 to 19.72)	-1.04 (-1.26 to -0.83)
Australasia	4319.51 (3695 to 4877.2)	27.63 (23.63 to 31.19)	15.53 (13.68 to 17.26)	-2.03 (-2.57 to -1.48)
High-income Asia Pacific	20088.25 (16719.24 to 22018.71)	21.33 (17.75 to 23.38)	9.26 (8.26 to 9.86)	0.55 (0.32 to 0.78)
High-income North America	58937.35 (52684.31 to 62514.14)	31.32 (27.99 to 33.22)	17.02 (15.54 to 17.93)	-1.82 (-1.95 to -1.69)
Southern Latin America	9955.42 (8955.94 to 10829.89)	28.75 (25.86 to 31.27)	20.59 (18.69 to 22.27)	-0.97 (-1.18 to -0.76)
Western Europe	92828.52 (79697.52 to 100090.78)	41.73 (35.83 to 45)	18.01 (16.15 to 19.11)	-1.91 (-2.06 to -1.75)
Andean Latin America	4074.45 (3219.85 to 5146.16)	12.34 (9.75 to 15.59)	12.91 (10.2 to 16.33)	-0.22 (-0.48 to 0.05)
Caribbean	5593.57 (4716.78 to 6573.12)	23.32 (19.66 to 27.4)	19.62 (16.51 to 23.09)	0.2 (-0.05 to 0.45)
Central Latin America	19330.95 (16884.68 to 21775.01)	14.91 (13.02 to 16.79)	14.06 (12.28 to 15.82)	0.35 (0.21 to 0.48)
Tropical Latin America	23988.47 (22181.64 to 25488.33)	20.62 (19.06 to 21.91)	16.96 (15.7 to 18.02)	-0.08 (-0.2 to 0.04)
North Africa and Middle East	29522.68 (26059.3 to 33509.16)	9.85 (8.7 to 11.18)	12.2 (10.79 to 13.79)	2.12 (2.01 to 2.23)
South Asia	105497.03 (92006.39 to 121287.14)	11.65 (10.16 to 13.39)	13.24 (11.54 to 15.28)	1.02 (0.92 to 1.11)
East Asia	92961.69 (73229.73 to 115384.35)	12.91 (10.17 to 16.03)	8.38 (6.59 to 10.4)	-0.72 (-0.87 to -0.57)
Oceania	952.3 (780.07 to 1175.93)	14.13 (11.58 to 17.45)	22.22 (18.44 to 26.97)	0.49 (-0.01 to 0.99)
Southeast Asia	65437.37 (54265.99 to 79833.65)	18.76 (15.56 to 22.89)	17.72 (14.76 to 21.52)	0.69 (0.62 to 0.76)
Central Sub-Saharan Africa	6203.43 (4593.22 to 8211.54)	9.05 (6.7 to 11.98)	18.73 (14.12 to 24.76)	1.14 (0.9 to 1.37)
Eastern Sub-Saharan Africa	19591.01 (16711.13 to 23394.02)	9.12 (7.78 to 10.89)	20.18 (17.52 to 23.63)	0.79 (0.68 to 0.9)
Southern Sub-Saharan Africa	8412.02 (7611.22 to 9303.26)	20.47 (18.52 to 22.63)	24.93 (22.64 to 27.46)	1.44 (1.12 to 1.76)
Western Sub-Saharan Africa	25926.8 (20169.45 to 33021.25)	10.34 (8.04 to 13.17)	23.07 (18.69 to 28.77)	1.09 (0.98 to 1.19)

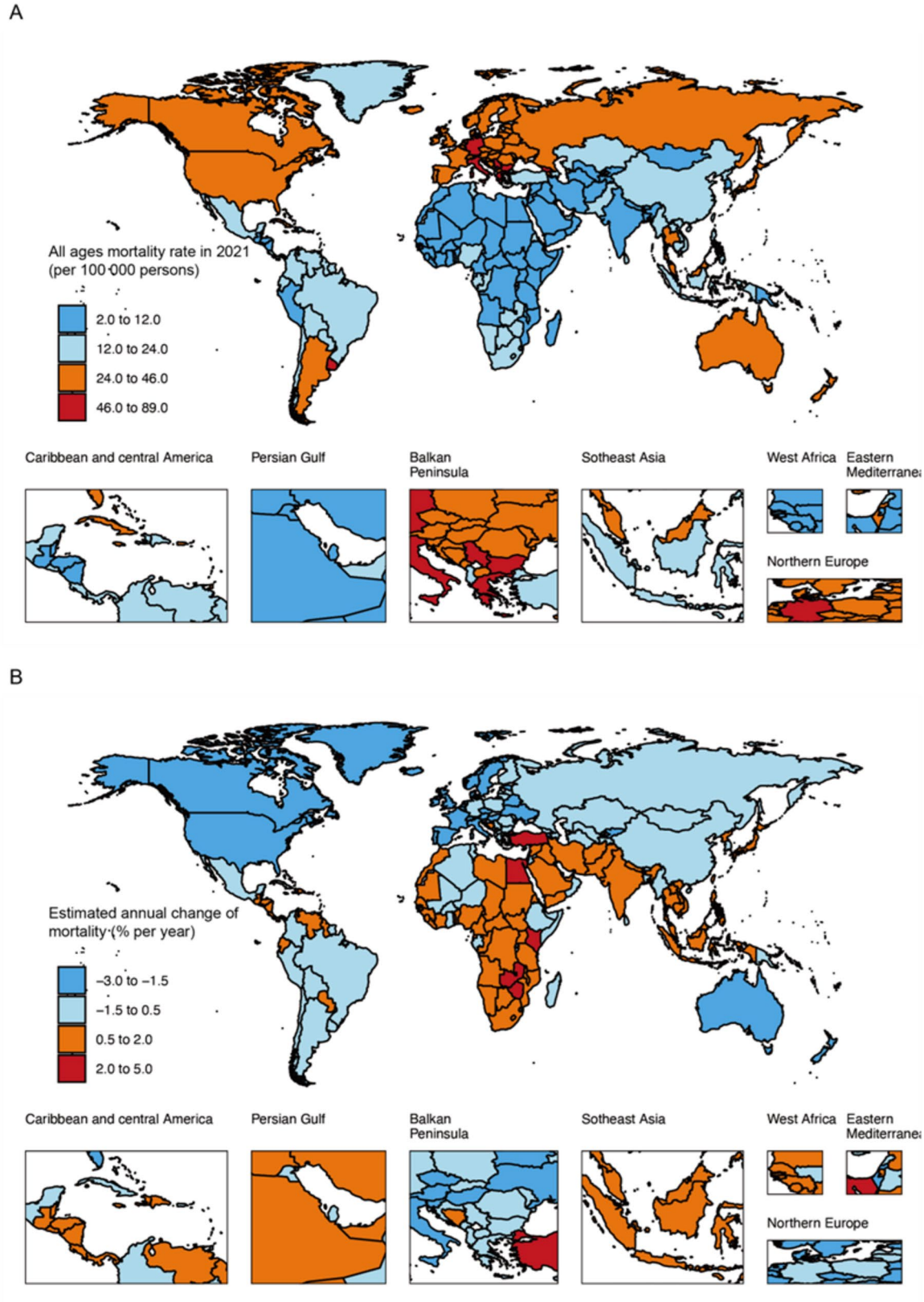

Fig. 1 All-age mortality in 2021 and net drift of mortality during 1992–2021 for breast cancer in 204 countries and territories. (**A**) World map of all-age mortality for breast cancer in 2021. (**B**) World map of net drifts (estimated annual percentage change of mortality from the age-period-cohort model) for breast cancer mortality

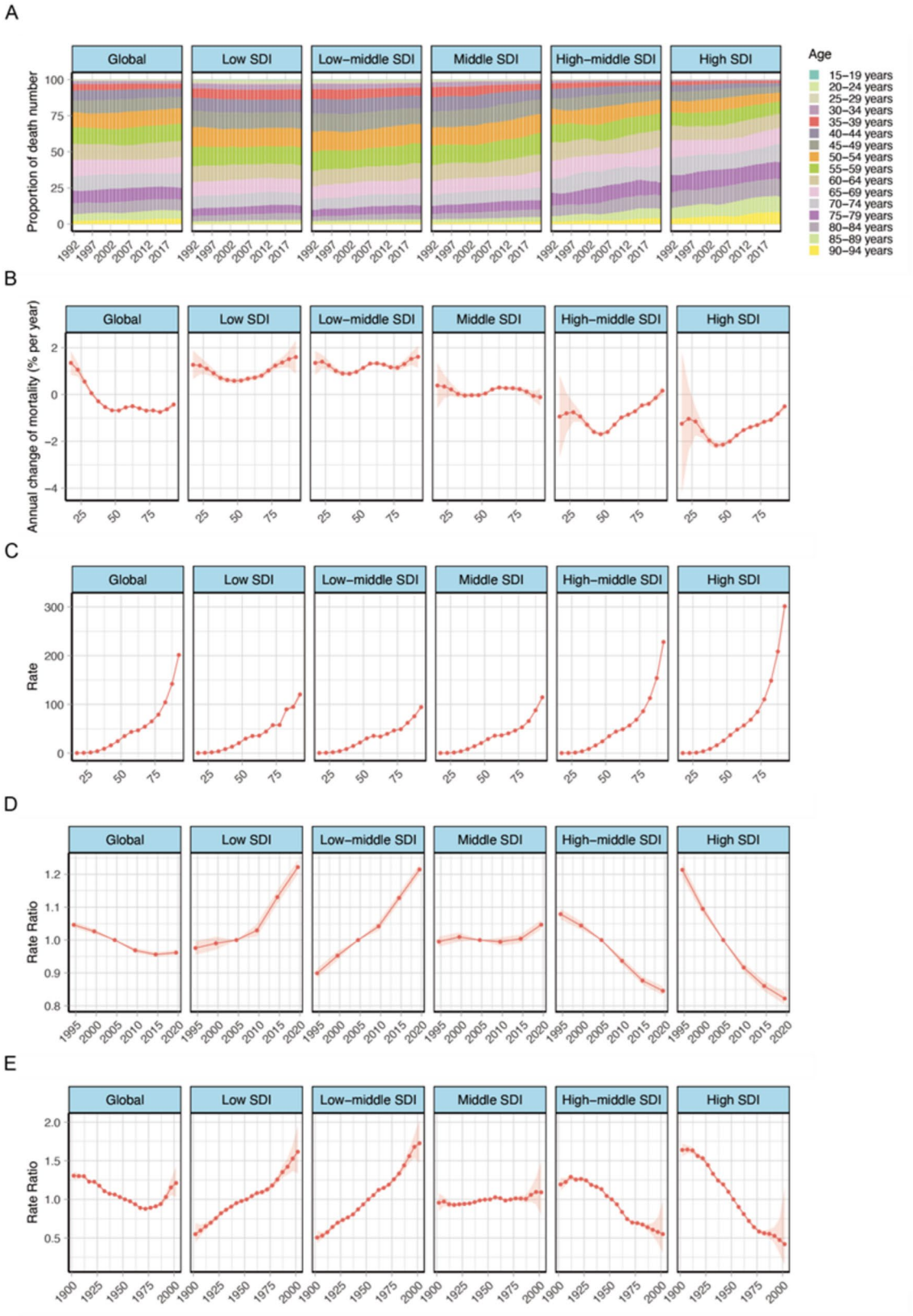

Fig. 2 (See legend on next page.)

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Fig. 2 Age distribution and APC-analysis of breast cancer mortality by SDI quintiles, 1992–2021. (**A**) Temporal change in the relative proportion of breast cancer deaths across 16 age groups, 1992–2021. (**B**) Age-period-cohort model-derived estimates of local drifts of breast cancer mortality for 16 age groups, 1992–2021. The dots indicate the annual percentage change of breast cancer mortality (% per year), and the shaded areas indicate the corresponding 95% CIs. (**C**) Age effects are represented by the fitted longitudinal age curves of breast cancer mortality (per 100 000 person-years) and the corresponding 95% CIs. (**D**) Period effects are represented by the relative risk of mortality of each period compared with the reference (period 2002–2006) adjusted for age and nonlinear cohort effects and the corresponding 95% CI. (**E**) Cohort effects are represented by the relative risk of mortality of each cohort compared with the reference (cohort 1948–1956) adjusted for age and nonlinear period effects and the corresponding 95% CI. SDI, socio-demographic index; CI, confidence interval

across countries, as well as their net drifts over 30 years. In 2021, the global all-age mortality rates per 100,000 were 16.81, with an ASR of 14.55. From 1992 to 2021, mortality has declined slightly {net drift = -0.38%, [95% confidence interval (CI): -0.41 to -0.34] (Table 1).

Breast cancer mortality has decreased modest in half of the regions, except in High-income Asia Pacific, Central Latin America, South Asia, Southeast Asia and Africa. North Africa and Middle East experienced the highest increase in mortality [2.12%, (2.01 to 2.23)], followed by Southern Sub-Saharan Africa [1.44%, (1.12 to 1.76)] and Western Sub-Saharan Africa [1.09%, (0.98 to 1.19)]. Regions such as Andean Latin America, Tropical Latin America, the Caribbean, Southeast Asia, and Oceania reported no improvement (Table 1), underscoring the need for better breast cancer management in these areas.

All-age mortality was higher than the ASR in high, high-middle, and middle SDI regions but reversed in other regions. These findings suggest that all-age mortality is a more accurate reflection of the true burden of breast cancer mortality in middle and high SDI regions. The APC model showed a global negative net drift, with significant declines in high SDI countries [-1.56% (-1.7 to -1.43)] and high-middle SDI countries [-1.03% (-1.11 to -0.94)], significant increases in low-middle SDI countries [1.18% (1.13 to 1.23)], and minimal change elsewhere (Supplementary Table S2).

National burden trends in breast cancer mortality

Among 204 countries and territories, 109 reported at least 500 breast cancer deaths in 2021. Detailed data for these countries, including total deaths, all-age mortality, age-standardized mortality, and APC-derived net drift, are provided in Supplementary Table S3. China [88,107 deaths, (95% UI 68,163 to 110,341)], India [78,879, (66,512 to 94,204)], and the USA [52,869, (47,359 to 56,161)] accounted for one-third of global breast cancer deaths. In 2021, 24 of these countries, predominantly high or high-middle SDI regions, had all-age mortality rates exceeding twice the global average. Additionally, 62 countries showed increasing trends (net drifts > 0.0% per year), with 24 countries exhibiting substantial increases (net drifts ≥ 1.0% per year). Turkey recorded the highest net drift [4.75%, (95% CI 4.33 to 5.18)] from 1992 to 2021. In contrast, countries like the Norway, Denmark, and United Kingdom demonstrated significant declines (net drifts ≤ – 1.0% per year) in mortality.

Time trends in breast cancer mortality across age groups

The time trends in breast cancer mortality across age groups over the past 30 years highlight a clear shift in the age distribution of breast cancer deaths. As shown in Fig. 2A, there has been a notable transition from younger to older populations, particularly in those aged ≥ 80 years. This trend is most pronounced in high and high-middle SDI countries. By 2021, individuals aged ≥ 70 years accounted for the largest proportion of breast cancer deaths across all SDI regions. However, in low, low-middle, and middle SDI regions, breast cancer mortality in individuals under 55 years remains significant and warrants attention. Detailed age distribution data for breast cancer deaths in each country are available in Supplementary Figures S2-S6.

Age, period, and cohort effects

The annual percentage change in breast cancer mortality across age groups was analyzed using the local drift derived from the APC model (Fig. 2B). The global trend showed an increase in breast cancer mortality in those aged ≤ 34 years, while mortality significantly decreased in those aged ≥ 35 years (Supplementary Table S4). The age groups 15–19 and 80–84 years exhibited the steepest increases [local drift = 1.35% (0.84 to 1.86)] and decreases [local drift = -0.75% (-0.80 to -0.69)], respectively. In all age groups, breast cancer mortality increased in low and low-middle SDI regions. However, in high and high-middle SDI countries (except for those aged 90–95), mortality decreased. Notably, high SDI regions experienced the greatest reductions in breast cancer mortality for age groups ≤ 64 years, with reductions ranging from – 2.17% (-2.31 to -2.03) in the 40–44 years group to -1.52% (-1.59 to -1.45) in the 60–64 years group (Supplementary Table S4). Detailed local drift data for breast cancer mortality in each country can be found in Supplementary Figures S7-S11.

Age effects reflect the natural progression of breast cancer mortality. Period and cohort effects illustrate its progression across different time periods and birth cohorts, respectively [15]. Similar age-related trends were observed globally and across SDI quintiles, indicating that the risk of breast cancer mortality increases with age.

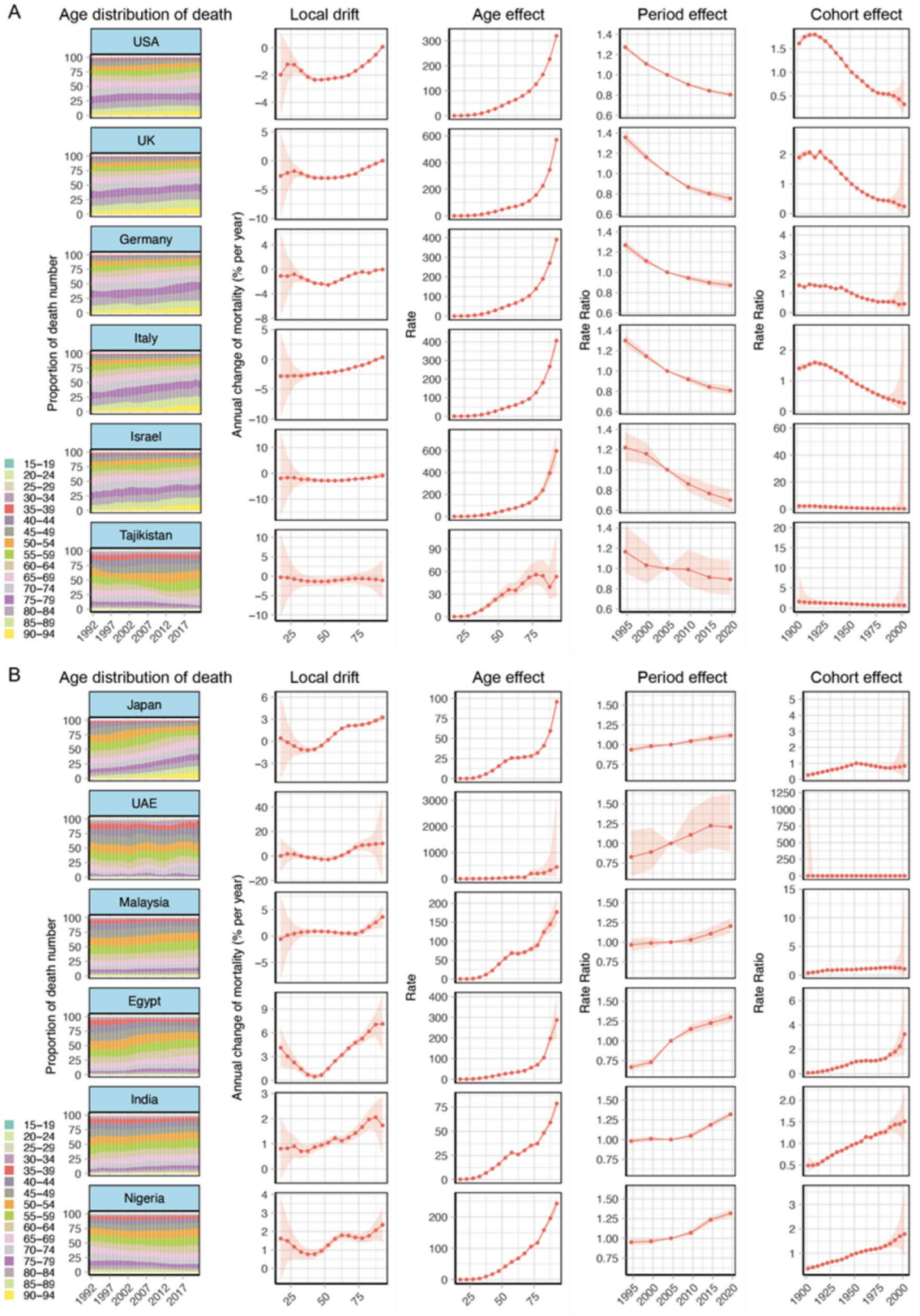

Fig. 3 (See legend on next page.)

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Fig. 3 Exemplar countries across SDI quintiles showing favorable (**A**) and unfavorable (**B**) age-period-cohort effects. Age distribution of deaths from 1992 to 2021 shows the relative proportion of breast cancer deaths across 16 age groups (15–19 to 90–94 years). Local drifts show the fitted longitudinal age curves of breast cancer mortality (per 100 000 person-years) across 16 five-year age groups (15–19 to 90–94 years) and the corresponding 95% CIs. Age effects show the fitted longitudinal age curves of breast cancer mortality (per 100 000 person-years) and the corresponding 95% CIs. Period effects show the relative risk of mortality of each period compared with the reference (period 2002–2006) adjusted for age and nonlinear cohort effects and the corresponding 95% CI. Cohort effects show the relative risk of mortality of each cohort compared with the reference (cohort 1948–1956) adjusted for age and nonlinear period effects and the corresponding 95% CI. SDI, socio-demographic index; CI, confidence interval

Notably, high SDI regions had the highest breast cancer mortality rates in those aged ≥ 55 years (Fig. 2C, Supplementary Table S4).

Global period effects showed a declining mortality risk before 2017, but this reduction reversed in the past 5 years (Supplementary Table S5). However, trends differed across SDI regions. In countries with middle SDI, period effects remained stable over the past 30 years, indicating limited improvement in breast cancer mortality. In high and high-middle SDI regions, a significant reduction in mortality was observed, with a relative period risk of 0.82 (0.80 to 0.84) and 0.85 (0.83 to 0.86) in 2017–2021, respectively. In contrast, low and low-middle SDI countries saw an increase in mortality risk [1.22 (1.20 to 1.24) and 1.21 (1.20 to 1.23) in 2017–2021, respectively] (Fig. 2D, Supplementary Table S5).

Globally, breast cancer mortality decreased for those born before 1968, but trends reversed in subsequent cohorts, indicating a lack of improvement in disease control. Different patterns were observed across countries with varying SDI levels. In high and high-middle SDI regions, improvements in disease control were evident. However, in low, low-middle, and middle SDI regions, no progress was made, underscoring the need for stronger efforts in these countries (Fig. 2E, Supplementary Table S6). Age, period, and cohort effects on breast cancer mortality for each country are shown in Supplementary Figures S12-S26.

Age, period, and cohort effects in exemplary countries

To explore breast cancer mortality trends, exemplary countries from different SDI quintiles were selected, and the age distribution of breast cancer deaths, local trends, and age/period/cohort effects were analyzed (Fig. 3).

Six countries from high, high-middle, and low-middle SDI regions were selected to illustrate favorable APC effects (Fig. 3A, B). The USA had the top high number of breast cancer deaths in 2021 (Supplementary Table S3), but mortality improved over the past 30 years, with reduced local drifts in those aged < 90 years, decreased period risks before 2021, and declining cohort risk for those born after 1919. UK, saw a great improvement in a net drift of -2.37% (-2.68 to -2.05). Germany, ranking seventh in global breast cancer deaths, mortality decreased in all age groups except those > 90 years, with period and cohort risks also showing a downward trend, particularly after 1914. Italy, the leading country in breast cancer deaths in European in 2021, showed favorable trends over the past three decades, with the age distribution shifting towards those > 90 years. Similarly, Israel and Tajikistan underwent an age distribution transition, with declining risks throughout the study period.

Unfavorable APC effects were clearly observed in two high-SDI and one high-middle SDI and three low-middle SDI countries (Fig. 3B). Japan was atypical high-SDI countries, with significantly increased breast cancer mortality, with significant increases in mortality across all age groups except for those aged < 50 years, along with worsening risks over the periods and in successive birth cohorts. The APC effects on the United Arab Emirates (UAE) was similar to Japan. Malaysia had the top worst breast cancer mortality rate globally (Supplementary Table S3), with a net drift of 0.84% (0.44 to 1.25), reflecting a 25.2% increase from 1992 to 2021. The other three low-middle SDI countries (Egypt, Nigeria, and India) exhibited similar transitions in the age distribution of breast cancer deaths and unfavorable APC effects, with a notable rise in breast cancer mortality among those aged > 40 years, along with worsening risks over the periods and in successive birth cohorts. Notably, all six countries with unfavorable APC effects were located in Asia and Africa, highlighting the need for enhanced breast cancer management in Asian and African countries.

Top leading risk factor and its age, period, and cohort effects

The top three risk factors for breast cancer deaths in 1992 and 2021 were examined, with diet in red meat consistently ranking first. From 1992 to 2021, the all-age mortality rate due to diet in red meat rose by 21.7% (21.0-29.3), while the age-standardized mortality rate dropped by 16.4 (-16.9 to -12.5) (Fig. 4A). This discrepancy may reflect changes in the population's age structure over time.

The APC model was applied to assess the annual percentage change in breast cancer mortality due to diet in red meat across different age groups, as well as the age, period, and cohort effects. Significant improvements were observed in those under 50 years of age, especially in high SDI regions, where the mortality rate due to diet in red meat decreased (local drift ≤ -1.0%) in most age groups. However, no such improvements were seen in lower SDI regions (Fig. 4B). Globally and across SDI quintiles, breast cancer mortality due to diet high

in red meat increased with age and was higher as age grew (Fig. 4C). Positive period and cohort effects were only noted in high and high-middle SDI regions, while other SDI quintiles showed no significant improvement (Fig. 4D, E), highlighting the need for better diet in red meat control in these regions.

Discussion

Breast cancer remains the leading cause of cancer-related deaths among women [1, 2]. Our analysis reveals that, in some countries, breast cancer mortality rates have either stagnated or worsened, particularly in Asian and African nations. Additionally, we observed a clear shift in breast cancer mortality from younger to older age groups, with this trend being more pronounced in higher SDI countries. Notably, the innovative use of the APC model in this study led to several important insights: (1) Traditional all-age rates and ASR may not align with the net drift observed through the APC model; (2) Breast cancer mortality generally increased exponentially with age; (3) Local drift, period effects, and cohort effects varied significantly (either favorable or unfavorable) across different SDI regions and countries; and (4) Diet in red meat emerged as the leading risk factor for breast cancer mortality, showing positive APC effects in high and high-middle SDI regions.

This study compared various metrics, including traditional all-age rates/ASRs and estimates derived from the APC model, to provide a comprehensive understanding of the disease burden of breast cancer. Notably, in economically advanced regions and countries, the all-age rates for breast cancer mortality were generally higher than the ASRs (Table 1, and Supplementary Table S2), which contribute the majority of breast cancer cases. These findings can be attributed to the older populations and improved access to healthcare interventions, which enhance survival rates. Consequently, the all-age rate likely provides a more accurate representation of breast cancer in these regions, while reliance on ASRs may be misleading. Furthermore, the breast cancer burden and its risk factors are influenced not only by physiological age (age effect) [6], but also by health policies, technological advances (period effect) [7], and early diagnosis or treatment (cohort effect) [8]. This highlights the importance of distinguishing between period and cohort trends when analyzing breast cancer mortality.

Breast cancer mortality exhibited an exponential increase with age (Fig. 2C), suggesting a strong correlation between a country's mortality rate and its degree of population aging. Typically, economically advantaged countries experience more advanced aging compared to economically disadvantaged countries, which may explain the higher breast cancer mortality observed in these regions (Supplementary Figure S5, S6), as well as the greater proportion of deaths among the aging population in higher SDI countries (Fig. 2A). However, breast cancer poses a significant health burden in lower SDI countries experiencing noticeable aging trends, particularly in populous nations like China (Supplementary Table S3). As the world's most populous country (1.42 billion), China is confronted with the challenges of an aging population, with the number of older adults growing exponentially. By 2050, the number of Chinese citizens aged over 65 is expected to reach 400 million, with 150 million of them aged over 80 years [17].

China's rapidly aging population, coupled with declining birth rates [18], underscores the urgency of adapting breast cancer management to demographic shifts. Our data showing increased mortality in those aged ≥ 70 years (Fig. 2A) suggest that geriatric oncology services must be expanded, including comorbidity management and palliative care integration. Simultaneously, rising mortality in younger women (< 55 years) in low- and middle-income countries (LMICs) demands policies to address disparities in access to HER2/HR testing and affordable trastuzumab biosimilars, as proposed in India's National Cancer Grid [19].

In light of the evolving landscape of breast cancer diagnosis and therapy, it is crucial to interpret our epidemiological findings not only in terms of incidence and mortality trends but also their implications for clinical practice, health system preparedness, and medico-legal responsibilities. As the population ages and fertility rates continue to decline [20], the burden of breast cancer in older and more comorbid patients increases, necessitating more nuanced, individualized therapeutic approaches.

Tailored treatment strategies are essential in reducing overtreatment and undertreatment, which may result in suboptimal outcomes or even potential malpractice claims if clinical decisions do not align with current prognostic knowledge. The integration of molecular insights with epidemiological trends opens new avenues for precision medicine and tailored treatment in breast cancer management. Our findings highlight several critical directions for future research. First, regarding molecular subtypes and epidemiological dynamics, the observed disparities in age-specific mortality may reflect variations in subtype prevalence. For example, triple-negative breast cancer (TNBC) disproportionately affects younger women in LMICs [21, 22]. This subtype's unique age distribution could amplify mortality trends in LMICs, where delayed diagnosis and limited access to targeted therapies exacerbate outcomes. Future studies should stratify APC analyses by molecular subtypes to clarify their interactions with age, period, and cohort effects, enabling subtype-specific prevention strategies. Second, regarding non-coding RNAs (ncRNAs) as emerging biomarkers,

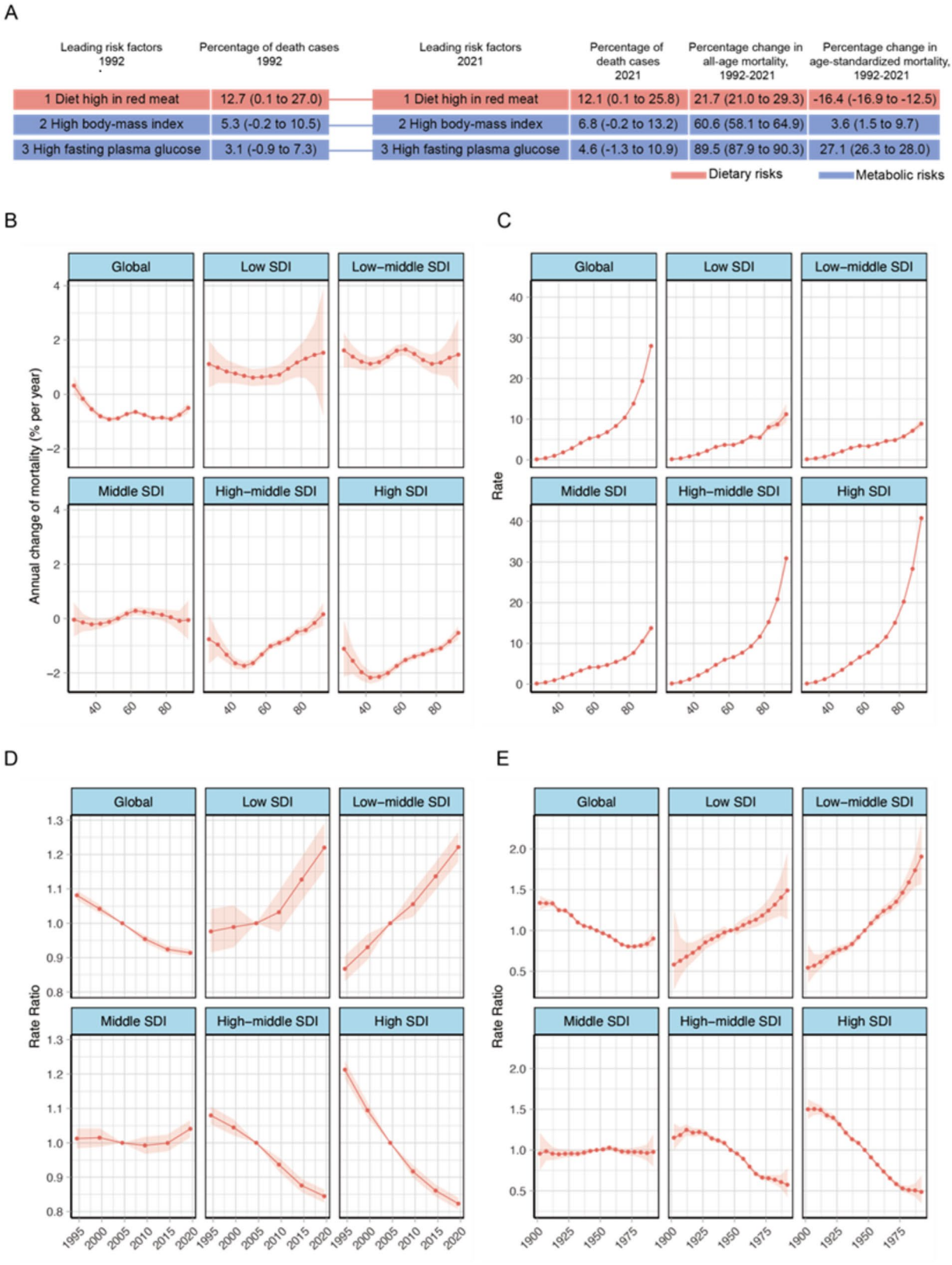

Fig. 4 (See legend on next page.)

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Fig. 4 Leading three risk factors for global breast cancer deaths and APC-derived parameters for mortality attributable to diet in red meat. (**A**) Leading three risk factors for global breast cancer deaths and percentage of total deaths (1992 and 2021), and percentage change in all-age and age-standardized mortality from 1992 to 2021. Risk factors are connected by lines between time periods. (**B**) APC model-derived estimates of local drifts of breast cancer mortality for 14 age groups (25–29 to 90–94 years), 1992–2021. The dots indicate the annual percentage change of CAVD mortality (% per year), and the shaded areas indicate the corresponding 95% CIs. (**C**) Age effects are represented by the fitted longitudinal age curves of breast cancer mortality (per 100 000 person-years) and the corresponding 95% CIs. (**D**) Period effects are represented by the relative risk of mortality of each period compared with the reference (period 2002–2006) adjusted for age and nonlinear cohort effects and the corresponding 95% CI. (**E**) Cohort effects are represented by the relative risk of mortality of each cohort compared with the reference (cohort 1948–1956) adjusted for age and nonlinear period effects and the corresponding 95% CI. Age, period, and cohort effects are stratified by sex. APC, age-period-cohort; SDI, socio-demographic index; CI, confidence interval

recent advances in genomics have identified ncRNAs—such as microRNAs (miRNAs) Y RNAs and long noncoding RNAs (lncRNAs)—as promising biomarkers for early detection, prognosis, and therapeutic response prediction [23, 24]. For example, Qian et al. demonstrated that circulating miRNAs (e.g., miR-21 and miR-155) are robustly associated with breast cancer aggressiveness and metastasis [25]. Similarly, Zhang et al. highlighted the role of lncRNAs (HOTAIR) in modulating treatment resistance [26]. Incorporating ncRNA profiling into population-level datasets could refine risk stratification and personalize screening protocols, particularly for high-risk cohorts identified through APC models. Third, regarding integrating genomic and population-level data, the APC framework traditionally relies on demographic and clinical variables, but integrating genomic data could unravel the biological underpinnings of observed trends. For instance, cohort effects may correlate with historical shifts in environmental exposures (e.g., endocrine disruptors) that interact with genetic susceptibility loci (e.g., BRCA1/2) [27]. Large-scale initiatives, such as the integration of whole-genome sequencing with national cancer registries, could elucidate how genetic variants modulate period- or cohort-specific risks. Furthermore, multi-omics approaches (e.g., epigenomics, proteomics) may enhance the APC model's capacity to predict emerging trends, such as the rising incidence of hormone receptor-positive cancers in aging populations.

Moreover, similar molecular approaches are being explored across a range of neoplastic conditions, including ovarian, lung, and colorectal cancers, underscoring their broader applicability [23]. Comparative analysis suggests that countries implementing evidence-based precision oncology guidelines are seeing earlier detection and better treatment alignment [28], which may translate into more favorable long-term epidemiological trajectories. These observations highlight the importance of aligning public health policies with rapidly evolving diagnostic technologies and individualized care frameworks.

While these innovations could mitigate mortality disparities by enabling early detection and personalized treatment, particularly in low-resource regions where late-stage diagnoses prevail. However, equitable access to such technologies remains a challenge, necessitating policy reforms to address cost barriers and infrastructure gaps. Collaborative efforts between epidemiologists, molecular biologists, and policymakers will be essential to translate these insights into actionable clinical guidelines, as exemplified by China's recent inclusion of HER2 testing in public health insurance to reduce financial barriers [29].

Furthermore, the implementation of personalized therapies raises complex ethical challenges [30]. A critical example is fertility preservation for premenopausal patients, where informed consent processes must account for cultural conflicts between individual autonomy and familial norms (e.g., East Asian collectivist societies prioritizing lineage continuity) [31, 32]. With global declines in birth rates and accelerated population aging, the psychosocial impact of treatment-induced infertility requires urgent attention [33]. LMICs should adapt fertility counseling guidelines from high-income settings, accounting for local resource constraints.

Failure to adopt tailored therapies (e.g., PARP inhibitors for BRCA-mutated patients) in LMICs (e.g., India) [34] not only worsens outcomes but may also trigger malpractice claims, as seen in litigation over delayed genetic testing in the USA [35]. To address this, we propose: (1) context-specific consent training for oncologists, incorporating legal risk scenarios; (2) leveraging telemedicine to expand genetic counseling access in LMICs. By integrating these molecular, clinical, and societal dimensions, our findings provide an essential epidemiological foundation to inform forward-looking breast cancer care strategies, not only in China but also in other countries facing similar demographic and health system challenges. In addition, diet in red meat has recently been identified as a risk factor for the development of various cancer diseases, including breast cancer [36]. As a result, there has been a significant increase in awareness regarding red meat diet control. In response, both countries and individuals have implemented measures that have contributed to the dieting high in red meat control rate, particularly in high SDI countries [37]. This trend aligns with the favorable effects observed in high SDI regions in the present study. However, the control rate in other regions, particularly in LMICs, remains relatively low and requires more stringent management [38].

This study had several limitations. First, primary data were scarce in LMICs, leading to broad uncertainty

bounds and affecting the precision of the APC-derived estimates. To enhance research accuracy, primary data collection in LMICs should be prioritized. Second, the analysis was conducted at the national level, without exploring subnational variations. Therefore, future studies should incorporate subnational data to capture more detailed differences, particularly in high-burden countries. Third, due to the 5-year age group data in the GBD 2021, the APC analysis was limited to 5-year intervals, potentially overlooking finer variations in age, period, and cohort effects.

This study provided a comprehensive analysis of breast cancer mortality, a growing concern in aging populations. In many countries, mortality rates have either stagnated or worsened, particularly among the older population, where mortality continues to rise. As the global population ages, the increasing burden of breast cancer mortality warrants urgent attention. These findings underscore the need for more effective and timely strategies to mitigate the growing impact of this disease.

Abbreviations

APC	Age-period-cohort
ASR	Age-standardized rates
SDI	Sociodemographic index

Supplementary Information

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Supplementary Material 1

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Author contributions

MF: Conceptualization, Methodology, Software, Data acquisition, Data analysis and interpretation, Writing- Original draft preparation and Editing, Visualization, Investigation. ZP: Visualization, Data analysis and interpretation, Writing- Reviewing and Editing. MW: Data acquisition. DL: Data analysis and interpretation. SL and XZ: Quality control of data and algorithms. YL: Supervision. HQ: Supervision, Writing- Reviewing and Editing. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available in the Global Health Data Exchange (https://vizhub.healthdata.org/gbd-results/). Further information is available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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