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Global Patterns and Trends in Breast Cancer Incidence and Mortality according to Socio-demographic Index

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Abstract:

Objectives: Disparities existed in the global burden of breast cancer. We aimed to figure the recent patterns and trends in incidence and mortality from breast cancer, and to assess breast cancer associated health inequalities according to development.

Methods: Estimates of breast cancer incidence and mortality data from 1990 to 2016 were obtained from the Global Health Data Exchange database. Patterns in 2016 were described with age-standardized and age-specific incidence, mortality and mortality-to-incidence ratio (MIR) according to socio-demographic index (SDI) levels. Trends were assessed via the annual percent change using joinpoint regression. The between-country health inequalities were measured with the Gini coefficients and concentration indexes.

Results: Countries with higher levels of SDI were shown to have worse incidence burdens in 2016, though the health inequality in breast cancer incidence, in terms of Gini coefficients and concentration indexes decreased since 1990. In keeping with the opposite trends in mortality rates between high and low SDI countries, the concentration indexes for mortality also declined and even turned negative in 15-49 and 50-69 years age groups, pointing towards increasing concentration in mortality burdens of undeveloped regions. Conversely, both the overall inequality and the part related to socioeconomic development in MIR increased. In 2016, MIRs showed distinct gradients from the high to low SDI regions for all age groups.

Conclusions: Patterns and trends in breast cancer incidence and mortality closely correlated with SDI levels. Our findings highlighted that primary prevention of breast cancer in high SDI countries with high incidence and developing of cost-effective detection and treatment interventions in low SDI countries with poor MIRs are two pressing needs in future decades.

Keywords: breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini coefficient, concentration index

Article summary

Strengths and limitations of this study：

To our knowledge, this study was a first overview about the global patterns and trends in breast cancer incidence and mortality in relation to levels of SDI. Limitations should also be considered when interpreting the results of our investigation. Firstly, this study was subject to the limitations of the GBD 2016 study, such as data sources and statistical assumptions, which were detailed in the GBD 2016 reports. Secondly, joinpoint analysis is sensitive to parameter settings. The pattern groupings of trends in incidence and mortality may change if parameters are set differently or more data are involved in the analysis. Thirdly, district data within each country, information on disease stage or histopathological characteristics were unavailable in GBD 2016 database. In the United States, for example, nationwide distributions and trends in breast cancer burdens differed by ethnicity, state, disease stage and intrinsic subtype. More studies are needed to further understand disparities due to these biases worldwide.

Introduction

Breast cancer is the most common cancer and the first leading cause of cancer death among women, with an estimated 2.4 million new cases and 523 thousand deaths worldwide in 2015[1]. Where and in which socioeconomic status a woman lives can significantly affect her odds of developing breast cancer and whether she will ultimately survive[1]. Breast cancer is not confined to high-income countries, however, it more often occurred in developed regions, where the incidence rates were multifold higher compared with those in low- and middle-income countries (LMICs)[1-3]. The cancer-related mortality rates in those LMICs were not fit in their low incidence rates[3-5]. Along with better awareness of risk factors, regular mammography screening and sufficient and effective medical services, the mortality rates in many high-income countries significantly declined in recent decades, and their incidence rates also stabled or even decreased since around 2000. Rather, in many resource-poor settings or countries undergoing rapid transition, both the incidence and mortality rates from breast cancer have been increasing, partially attributed by changes in reproductive patterns, increases in awareness but backward detections or treatments[6, 7].

Disparities do exist in the global burden of breast cancer, especially among counties and regions with different levels of development. Understanding the exact correlations between the disease burden and socioeconomic status are critical for the world's health policymakers to formulate appropriate measures adapted to local conditions. Socio-demographic Index (SDI) was first introduced in the Global Burden of Disease Study 2015 (GBD 2015) by the Institute for Health Metrics and Evaluation to quantificationally measure the development of a country or region[8]. The aims of our study were to describe the current patterns and trends in breast cancer incidence and mortality according to the country-level wellbeing, and to further explore distributions and changes in the breast cancer associated health inequality according to the spectrum of development, by combining the latest updated SDI data with breast cancer incidence and mortality data during 1990 and 2016 available at the GBD 2016 database.

Material and Methods

Patient and Public Involvement

Breast cancer was defined by the International Classification of Disease - Revision 10 with code C50. Incidence and mortality data from 195 individual countries and predefined five SDI groups between 1990 and 2016 were collected from the Global Health Data Exchange database[5]. Annual incidence and mortality rates by a 5-year age bracket from age 15 to 95+ years were obtained for each involved country. Detailed methods pertaining to estimation of age-standardized incidence and mortality rate (ASIR and ASMR) per 100,000 population had been previously described in the GBD 2016 reports[3, 4]. Because women aged 50-69 years were the major population participating in regular screening programs, we further calculated age-specific incidence and mortality rates per 100,000 population into three subgroups by age: 15-49, 50-69 and 70+ years, which were adjusted within age groups according to the new world population age-standard[3]. Mortality-to-incidence ratio (MIR) was calculated by dividing the breast cancer mortality rate for a given year, age-group, country or SDI group by its corresponding incidence rate.

Socio-demographic index

SDI is a comparable metric of overall development achieved by using an equal weighting of lag-distributed income per capita, average years of education in the population over 15 years, and total fertility rate[9]. SDI values on a scale of 0 to 1. A greater value of SDI implies higher level of development. SDI data for the involved 195 countries from 1990 to 2016 were obtained from the Global Health Data Exchange database[5]. Countries were grouped into quintiles based on their SDI values in 2016: high, high-middle, middle, low-middle and low SDI groups. Detailed methods describing computation of the SDI as well as choosing of the quintile cutoffs were reported elsewhere[1, 3].

Gini coefficient and concentration index

Gini coefficient and concentration index drawn from the field of economics were used to measure breast cancer associated health inequality in our study[10, 11]. Gini coefficient was calculated based on the Lorenz curve, and it ranged from 0 to 1, 0 representing perfect equality and 1 total inequality[11]. Annual ASIRs, ASMRs, age-specific incidence and mortality rates and MIRs of breast cancer for 195 countries were used to calculate the Gini coefficients, to find out the trends in between-country health inequality during 1990 and 2016. Concentration index was derived from the concentration curve and commonly used to measure socioeconomic-related health inequality[12]. Concentration indexes were computed by relating the above breast cancer metrics to corresponding national SDIs. The value of this index varies between -1 and +1. Positive (negative) values of the concentration index indicated the disease burden owing to the occurrence or death of breast cancer were more concentrated in countries with high (low) levels of development measured by SDI[12]. The absolute value demonstrates the degree of a "pro-developed" or "pro-underdeveloped" distribution in health limitations, and zero means an absence of inequality associated to the socioeconomic gradient instead of absence of inequality.

Statistical analyses

For a normal distribution but heterogeneity in variances of incidence, mortality and MIR data, one-way ANOVA was performed to determine the statistical significance of differences in incidence rates, mortality rates and MIRs across SDI-based country groups, followed by pairwise comparisons using Tamhane T2 test[13]. Liner regression model was used to test for the correlation between breast cancer indicators and SDI values. Joinpoint piecewise linear regression analysis was performed to identify time points when significant changes occurred as well as temporal trends in age-standardized and age-specific incidence and mortality rates during 1990 and 2016[14]. Default parameters were used, except for setting the minimum number of data points between two joints and at either end of the data to 5. To avoid over-fitting at the truncating points, maximum number of joinpoints was defined as 2. The best-fit point where the rate had changed prominently was decided by means of a permutation test, and the *P* value for each permutation test was estimated using Monte Carlo methods[14]. Statistics on annual percent change (APC) for each segment and average annual percent change (AAPC) for the overall period were summarized using the optimal joinpoint model. All joinpoint trend analyses were undertaken via the joinpoint statistical software (Version 4.5.0.1) from the surveillance research program of the United States National Cancer Institute[15]. The Gini coefficient was computed by the AINEQUAL module[16], and the concentration index by the CONIDEX module[17] using Stata 14.0 software (Stata Corp, Texas, USA). Other statistical analyses were performed with SPSS 20.0 (IBM Corp, Chicago, USA).

Results

Current profiles in breast cancer incidence and mortality according to SDIs

Figure 1 showed distinct distributions of counts and proportions of new cases and deaths due to breast cancer in five SDI groups in 2016. There were 719 thousand new cases in high SDI countries, about 20 times of that of 37 thousand in low SDI groups. Death number in these two groups were 162 and 32 thousand, respectively. About half of the new cases were occurred in women aged 50-69 years across all SDI groups. In countries belonging to middle, low-middle or low SDI group, more than one third new cases happened in young ages between 15 and 49 years, along with more proportion of deaths in this age group. Deaths in age 70 years or elder, by contrast, made up 50.9% of total breast cancer deaths in high SDI countries.

One-way ANOVA suggested significant differences in both age-standardized and age-specific incidence rates and MIRs ($P < 0.01$), but not mortality rates among countries in different SDI groups. Pairwise comparisons indicated lower MIRs in countries representing the higher level of development based on SDI, where the mortality rates were not proportional to their high incidence rates (Figure 2). The Incidence rates in all age groups were shown to have a positive dose-response relationship with SDIs, otherwise than a negative dose-response relationship between MIRs and SDIs (Figure 3). Besides, the rate ratios exhibited well-fitting linear relationships in all age groups, whereas the incidence and mortality rates in elder age groups were more scattered across countries with varied SDIs.

Temporal trends in breast cancer incidence and mortality across SDI groups

According to the joinpoint trend analyses (Table 1), the ASIRs in high and high-middle SDI groups plateaued after a quick increase at early 1990s. The ASIRs in high SDI group even displayed a declining trend by 0.1% per year since 2000. However, significant increases were found in middle, low-middle and low SDI groups through the whole period from 1990 to 2016 (Supplementary figure 1A). The AAPC in ASIR for the middle SDI group was 2.1%, far ahead of increases in other groups. Trends of incidence rates in 15-49, 50-69 and 70+ years age groups were comparable with those of ASIRs across SDI groups (Supplementary table 1 and figure 1B).

Changes in ASMRs were contradictory among SDI groups as shown in table 2 and supplementary figure 2A. In high SDI group, the ASMR continuously decreased from 24.2 in 1990 to 17.6 in 2016, with an AAPC of -1.3%. The ASMR in high-middle SDI group began to decline in 1994, and an accelerated decrease (APC: -1.9%) was witnessed between 2004 and 2016. The ASMR in middle SDI group also slightly diminished in 2002 to 2016 with an average decrease of 0.5% per year. Opposite trends were displayed in the low-middle (2002-2016, APC: 0.7%) and low SDI groups (2009-2016, APC: 0.8%), especially in recent years. Patterns of change in three age groups were similar with those of ASMR in each SDI group, however, the spectrum of change differed (Supplementary table 2 and figure 2B). For example, our results showed a much less decreasing in more developed regions and more increasing in less developed regions in the mortality for 70+ years age group compared with other age groups, which was much less-than-ideal.

Health inequality in worldwide breast cancer

The Gini coefficients for the incidence of breast cancer decreased continuously from 1990 to 2016 (Figure 4A), the values of which computed from ASIRs and incidence rates in 15-49, 50-69 and 70+ years age groups had dropped to 0.33, 0.30, 0.34 and 0.38 by 2016, compared with those of 0.38, 0.35, 0.39 and 0.43 in 1990, respectively. Similarly, the Gini coefficients calculated with mortality rates in all age groups except the 15-49 years age group showed markedly declining trends during the same period. Though the between-country inequalities due to both breast cancer incidence and mortality decreased, the Gini coefficients according to the distribution of MIRs conversely increased. For instance, the Gini coefficients derived from age-standardized MIRs reached up to 0.29 in 2016 from a base of 0.23 in 1990.

The concentration indexes according to breast cancer age-standardized and age-specific incidence and mortality rates were all above zero in 1990, suggesting that the inequalities associated with socioeconomic development were more concentrated in countries with higher level of development measured by SDI. Moreover, the concentration indexes for the 70+ years age group were much greater than those in other age groups. As can be seen in Figure 4B, both the concentration indexes of incidence and mortality rates decreased between 1990 and 2016, and the rates of descent sped up since late 1990s. The concentration indexes computed with mortality rates in 15-49 and 50-69 years age groups inclined to zero and became negative in 1998 and 2013, respectively. In contrast, the concentration indexes based on age-standardized and age-specific (15-49, 50-69 and 70+ years age group) MIRs were below zero, with values of -0.21, -0.22, -0.22 and -0.18 in 1990, and by 2016, the values of which had decreased to -0.28, -0.31, -0.30 and -0.25, respectively.

Discussion

The socioeconomic development associated inequality in global incidence of breast cancer has been decreasing since 1990. Still, countries with higher levels of development on the basis of SDIs were shown to have worse incidence burdens by 2016. In keeping with the opposite trends for mortality rates between countries with high and low SDIs, the concentration indexes by mortality fell and even turned to be negative in 15-49 and 50-69 years age groups in recent years, pointing towards a transition in the concentration of mortality burdens from the developed to undeveloped regions. Conversely, both the overall inequality and the part correlated with socioeconomic development in MIR - a health measure derived from the rate ratio of mortality and incidence - increased from 1990 to 2016. In 2016, MIRs showed distinct gradients from the high to low SDI regions in all age groups.

With epidemiological data reported for specific countries, it has been a prevailing perception that inequalities existed in breast cancer incidence worldwide, especially between the high-income countries and LMICs[18-21]. However, evidence about the quantitative relationship between the breast cancer burdens and national socioeconomic development was still limited. On the basis of GLOBOCAN 2012 estimates, incidence burden due to breast cancer distributed with obvious disparities among countries in different levels of human development index (HDI)[2], which was in accordance with our results in the light of data from the GBD 2016 study and SDI-a newly developed indicator for socioeconomic status of a given country. The overall inequality in breast cancer incidence had not yet been eliminated and was still more concentrated in countries with higher levels of SDI. The prevalence of breast cancer is somewhat associated with a so-called western lifestyle (ie, specific reproductive patterns and excess body weight)[22, 23], making it a marker for the extent of development. Trend analyses in our study demonstrated a quick increasing in breast cancer incidence in countries belonging to the middle SDI group. This fact might suggest that countries with middle levels of SDI were undergoing rapid social and economic transitions[24]. In many LMICs, burden of infection-related cancers, such as cervical, gastric and liver cancer, remained top ranking, instead of breast cancer[1, 2]. Mammographic screening programs were generally implemented in high-income countries, for women aged 50-69 years[25-27]. Our subgroup analysis based on age conformed transient rises in incidence of women at this age group and subsequent falls in those elder than 70 years in high SDI countries.

The mortality rates from breast cancer did not differ significantly from the low to high SDI regions. Inequalities in breast cancer caused deaths were possibly offset by better outcomes in more developed countries with early detections and advanced treatments, and small scale of incidence but limited access to health cares in most LMICs[28, 29]. Therefore, mortality rates could not well represent the exact trends and current status of cancer caused death burdens. Cancer survival was another important indicator for death burden of malignancies. According to data from 59 countries in CONCORD-2 study[30], five-year survival for patients diagnosed with breast cancer during 2005-09 in the North America, Australia, Israel, Brazil, and most Northern and Western European countries had reached up to 85% or higher, while it remained 60% or lower in many LMICs, such as India, Mongolia, Algeria and South Africa. However, comprehensive survival data were scarce in most countries, especially in those with limited resources. It remained an important issue to conclude the extent of socioeconomic development associated inequalities in the survivorship of breast cancer and to compare the current survival status in each country across the world. Here in our study, we analyzed the trends of inequalities in breast cancer MIRs, which evaluated the departure of mortality in relation to incidence from expectation and was suggested as an approximation for cancer survival[31-33]. Our results indicated widening disparities in the MIRs of breast cancer among countries with different levels of development.

HDI was a metric composed by life expectancy at birth, mean and expected years of schooling and gross national income per capita[34], and was used by a few researches to investigate how macro-socioeconomic determinants correlated with national disease burdens[2, 28, 35]. Nevertheless, it could be confusing when a measure of overall health (life expectancy at birth) was one important component of the index used to evaluate how socioeconomic development influences health. In the GBD 2015 study, SDI was first developed to identify where countries or geographic areas sit on the spectrum of societal development[8]. As reproductive patterns were proved to be risk factors for breast cancer[22], SDI, a yardstick constructed based on measures of income, education, and fertility rate, might be more appropriate to weigh the influence of socioeconomic status on the global patterns and trends in health inequality due to breast cancer.

To our knowledge, this study was a first overview about the global patterns and trends in breast cancer incidence and mortality in relation to levels of SDI. Limitations should also be considered when interpreting the results of our investigation. Firstly, this study was subject to the limitations of the GBD 2016 study, such as data sources and statistical assumptions, which were detailed in the GBD 2016 reports[3, 4]. Secondly, joinpoint analysis is sensitive to parameter settings. The pattern groupings of trends in incidence and mortality may change if parameters are set differently or more data are involved in the analysis. Thirdly, district data within each country, information on disease stage or histopathological characteristics were unavailable in GBD 2016 database. In the United States, for example, nationwide distributions and trends in breast cancer burdens differed by ethnicity, state, disease stage and intrinsic subtype[36, 37]. More studies are needed to further understand disparities due to these biases worldwide.

Conclusions

The socioeconomic development associated health inequality in breast cancer incidence has been declining since 1990. Countries undergoing an economic and lifestyle transition were experiencing growing prevalence of breast cancer. Nonetheless, the incidence burden was still more concentrated in countries with higher SDIs by 2016. These findings highlighted that public health clinicians and cancer control specialists should pay more attention to primary prevent of breast cancer especially in these high-incidence countries. Breast cancer mortality, in less developed countries, deviated from expectation seriously in relation to their low incidence. This situation even deteriorated with ever-increasing between-country inequalities for rate ratios from 1990 until 2016. Planners should try to carry out more sensitive and cost-effective detection and treatment interventions, particularly in low and low-middle SDI settings with limited healthcare resources, to combat premature deaths due to breast cancer.

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Competing interests

The authors declare that they have no conflict of interest.

Data sharing statement

No additional data available.

Authors' contributions

Kaimin Hu designed the study, acquired and analyzed the data and prepared the figures. Peili Ding and Yinan Wu interpreted the results and wrote the first draft of the manuscript. Tao Pan and Wei Tian interpreted the results and supported the research funding. Suzhan Zhang was the principle investigator and designed the study. All authors commented on manuscript drafts, approved the final version and declared no conflict of interest.

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Figure legend:

Figure 1. Distribution of breast cancer incidence and mortality counts and proportions by age at the global level and SDI quintiles in 2016.

Figure 2. Patterns for breast cancer, in terms of age-standardized and age-specific (A) incidence rates, (B) mortality rates and (C) MIRs by SDI group in 2016. Black squares represent the medians of all rates from the countries included in each SDI level. Lines denote the interquartile ranges. $^{*}P < 0.05$, $^{***}P < 0.001$.

Figure 3. Relationship between the incidence rates, mortality rates, MIRs and SDI levels by age. The best-fitted line according to linear regression analysis was showed.

Figure 4. Trends in (A) the Gini coefficients and (B) concentration indexes computed from health metrics of breast cancer, in terms of age-standardized and age-specific incidence rates, mortality rates and MIRs, across countries worldwide during 1990 and 2016.

Table

Table 1. Breast cancer age-standardized incidence rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	815.4	41.0	39.8-43.1	1681.9	45.6	43.6-48.2	1990-1995	1.5*	1995-2000	0.2*	2000-2016	0.1*	0.4*
High SDI	463.0	83.6	82.0-85.1	719.4	88.9	86.5-93.0	1990-1995	1.3*	1995-2000	0.2*	2000-2016	-0.1*	0.2*
High-middle SDI	153.1	37.1	36.0-38.6	329.0	46.5	42.9-50.5	1990-1995	3.2*	1995-2016	0.4*			0.9*
Middle SDI	116.0	19.3	18.1-22.1	408.8	33.2	30.4-36.0	1990-2000	2.6*	2000-2009	2.0*	2009-2016	1.5*	2.1*
Low-middle SDI	69.7	17.7	14.9-21.9	187.0	23.1	21.1-27.8	1990-1999	1.3*	1999-2010	0.4*	2010-2016	1.8*	1*
Low SDI	15.6	16.3	13.6-20.9	37.0	18.8	17.1-20.8	1990-1995	0.9*	1995-2010	0.3*	2010-2016	0.8*	0.5*

95% UI, 95% uncertainty interval; ASR, age-standardized rate; APC, annual percent change; AAPC, average annual percent change. *P < 0.05.

Table 2. Breast cancer age-standardized mortality rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	336.9	17.2	16.4-18.8	535.3	14.6	13.8-15.6	1990-1994	0.8*	1994-2002	-0.6*	2002-2016	-1.1*	-0.7*
High SDI	141.1	24.2	23.8-24.7	162.1	17.6	16.9-18.3	1990-1995	-0.6*	1995-2010	-1.6*	2010-2016	-1*	-1.3*
High-middle SDI	65.5	15.9	15.2-17.0	97.9	13.7	12.2-15.7	1990-1994	2.9*	1994-2004	-0.4*	2004-2016	-1.9*	-0.6*
Middle SDI	65.5	11.6	10.7-13.7	138.5	11.8	10.8-12.7	1990-2002	0.8*	2002-2016	-0.5*			0.1*
Low-middle SDI	50.7	13.6	11.4-17.3	104.5	13.8	12.1-17.2	1990-1999	0.7*	1999-2012	-0.6*	2012-2016	0.7*	0
Low SDI	13.9	15.7	13.0-20.2	31.9	17.6	15.7-19.9	1990-1996	0.9*	1995-2009	0	2009-2016	0.8*	0.5*

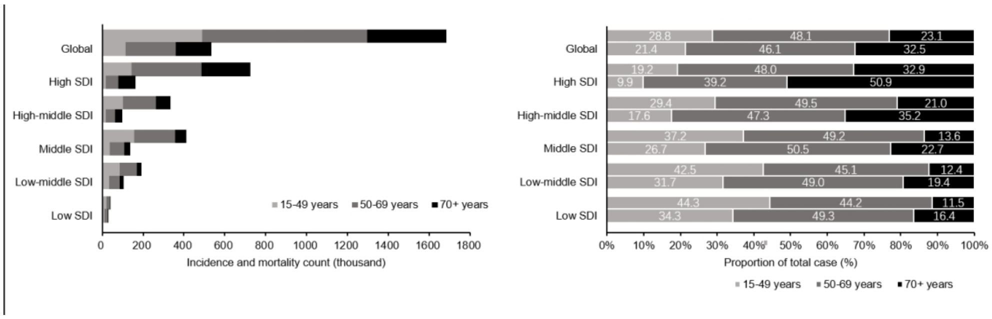

Figure 1

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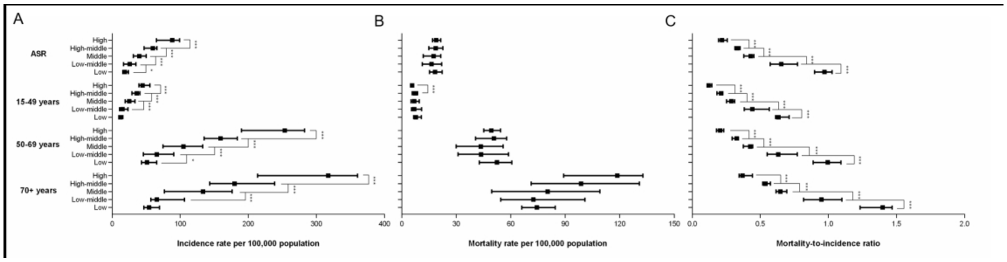

Figure 2

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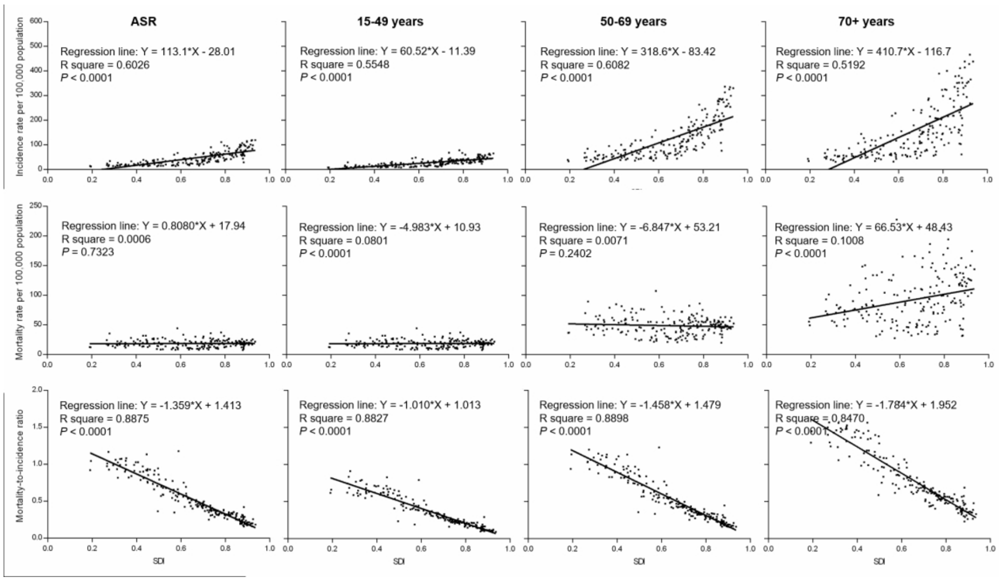

Figure 3

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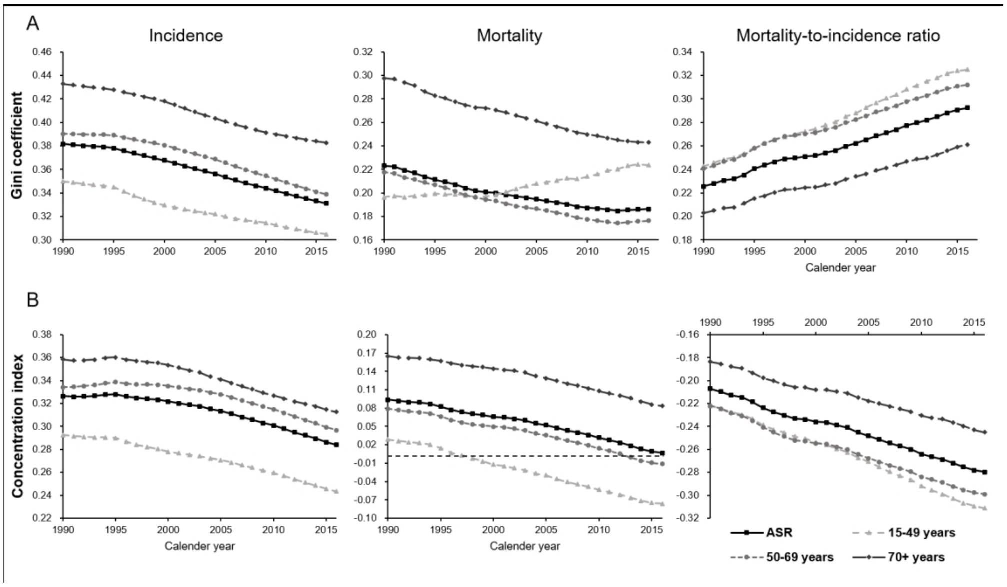


Figure 4

283x163mm (150 x 150 DPI)

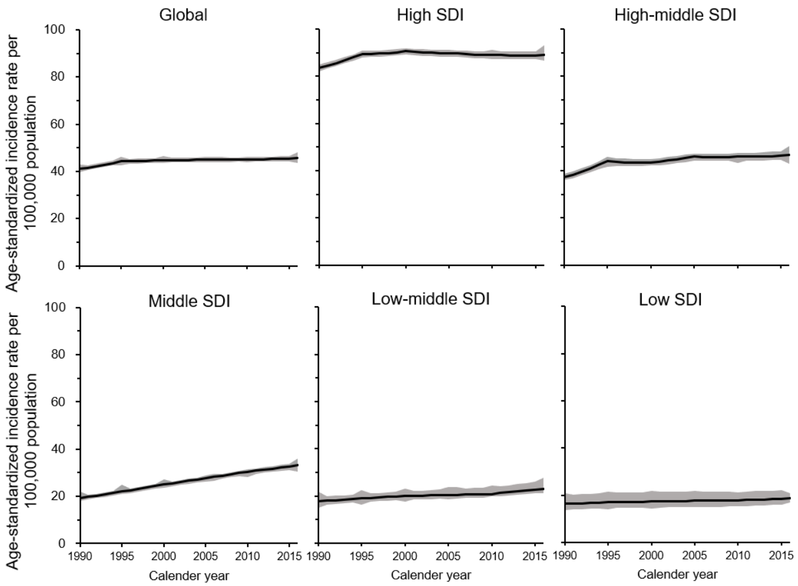
Supplementary figures and tables

Supplementary table 1. Breast cancer age-specific incidence rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

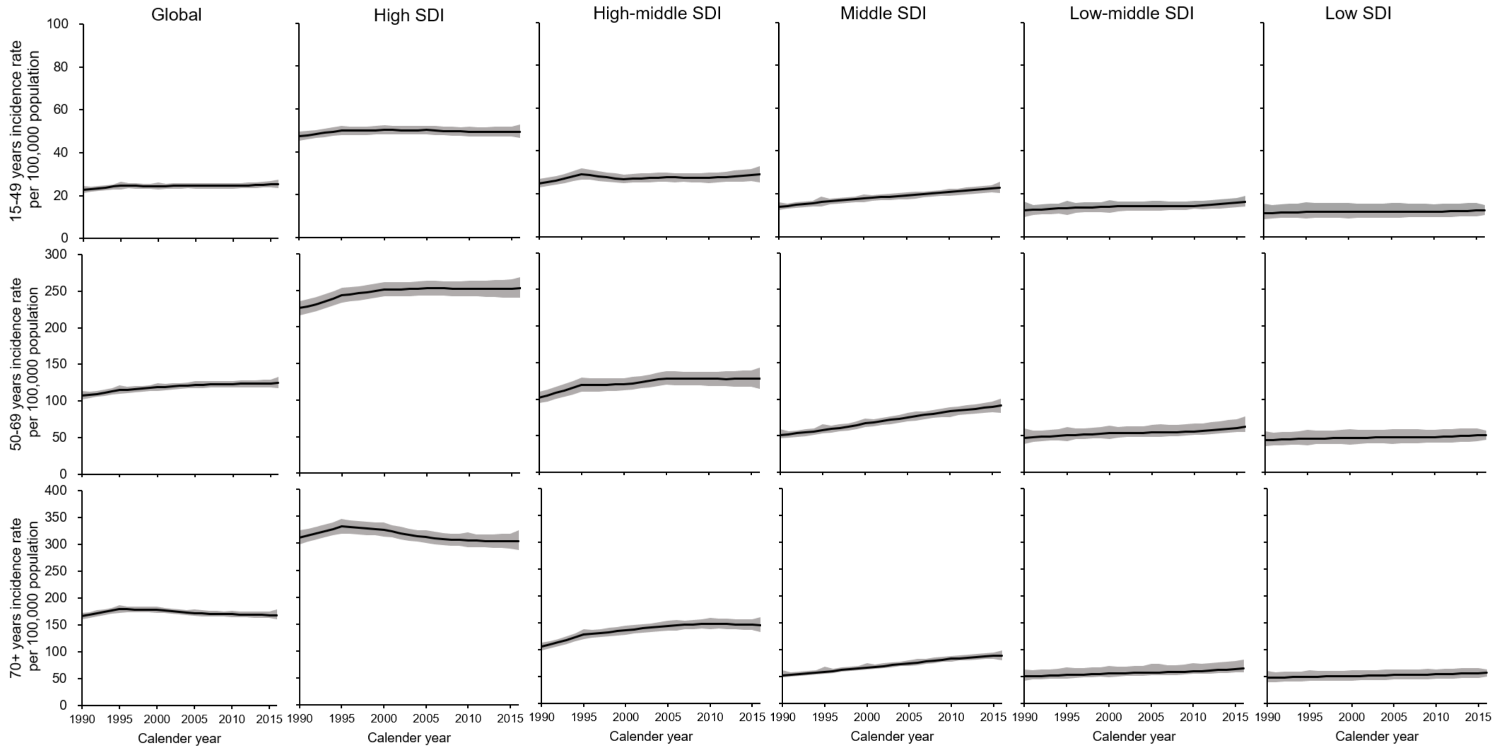
		1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Age	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	248.2	22.7	21.0-24.6	484.0	25.4	23.6-27.5	1990-1995	1.6*	1995-2011	0	2011-2016	0.7*	0.4*
	50-69 years	372.8	107.0	102.4-113.5	809.6	124.4	117.4-132.8	1990-1995	1.4*	1995-2005	0.6*	2005-2016	0.2*	0.6*
	70+ years	194.4	165.8	159.8-172.8	388.3	167.8	159.8-178.5	1990-1995	1.7*	1995-2008	-0.4*	2008-2016	-0.2*	0.1*
High SDI	15-49 years	111.6	47.3	45.3-49.4	137.8	49.4	46.6-52.6	1990-1995	1.0*	1995-2000	0.2	2000-2016	-0.1*	0.2*
	50-69 years	208.8	225.6	216.1-235.4	345.1	252.7	239.8-268.1	1990-1995	1.5*	1995-2000	0.8*	2000-2016	0*	0.5*
	70+ years	142.7	310.7	297.6-324.2	236.5	303.7	287.7-324.7	1990-1995	1.4*	1995-2008	-0.6*	2008-2016	-0.1*	-0.1*
High-middle SDI	15-49 years	48.8	24.8	23.0-26.9	96.9	29.0	25.3-33.0	1990-1995	3.3*	1995-2000	-1.5*	2000-2016	0.4*	0.6*
	50-69 years	76.1	101.6	94.5-110.0	163.0	128.1	113.7-143.2	1990-1994	3.5*	1994-2006	0.8*	2006-2016	0	0.9*
	70+ years	28.2	106.1	99.1-114.0	69.2	146.0	133.2-161.1	1990-1995	4.0*	1995-2007	1.2*	2007-2016	-0.1*	1.3*
Middle SDI	15-49 years	51.0	14.0	12.2-16.2	152.2	22.9	20.4-25.6	1990-1995	2.9*	1995-1999	2.2*	1999-2016	1.6*	1.9*
	50-69 years	50.5	50.8	46.2-59.0	201.0	91.0	81.0-100.8	1990-2004	2.7*	2004-2010	2.0*	2010-2016	1.5*	2.3*
	70+ years	14.4	52.8	48.5-62.3	55.6	89.8	80.8-98.7	1990-2000	2.4*	2000-2010	2.2*	2010-2016	1.2*	2.1*
Low-middle SDI	15-49 years	30.6	12.4	9.2-16.2	79.5	16.0	14.2-19.1	1990-2000	1.3*	2000-2010	0.2*	2010-2016	1.8*	1.0*
	50-69 years	31.4	47.1	38.9-59.8	84.4	61.9	54.7-76.1	1990-1999	1.3*	1999-2010	0.4*	2010-2016	1.9*	1.0*
	70+ years	7.6	50.6	42.9-63.7	23.1	65.2	57.8-82.6	1990-2000	1.0*	2000-2010	0.7*	2010-2016	1.4*	1.0*
Low SDI	15-49 years	7.0	10.9	8.1-15.5	16.4	12.2	10.2-14.6	1990-1995	1.1*	1995-2010	0.1*	2010-2016	0.8*	0.4*
	50-69 years	7.0	43.9	35.5-56.2	16.4	50.7	44.2-57.4	1990-1998	0.8*	1998-2010	0.3*	2010-2016	0.8*	0.5*
	70+ years	1.6	48.5	39.8-60.8	4.3	57.3	50.5-63.5	1990-2010	0.6*	2010-2016	0.8*			0.6*

Supplementary table 2. Breast cancer age-specific mortality rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

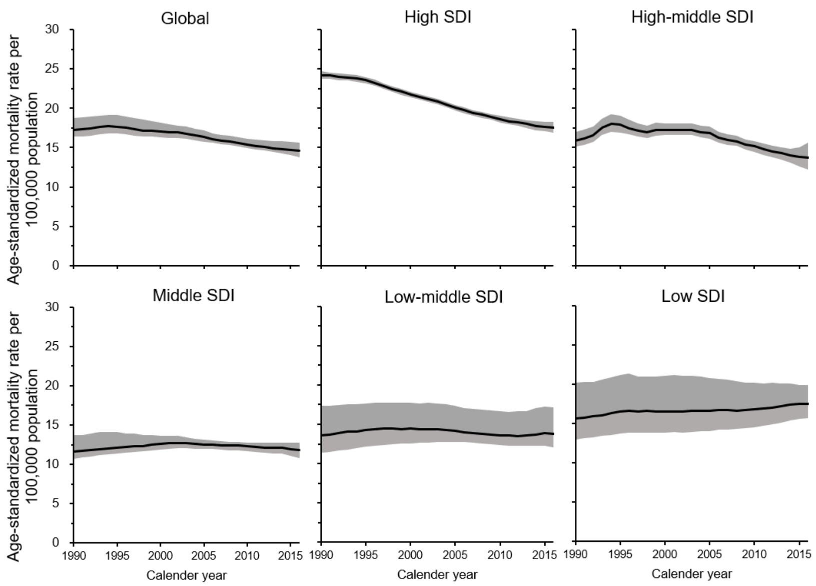
	Age	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
		Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	80.7	7.4	6.6-8.4	114.3	6.0	5.6-6.6	1990-1995	0.8*	1995-2012	-1.4*	2012-2016	-0.3*	-0.8*
	50-69 years	156.5	44.9	42.2-49.4	246.9	38.0	35.6-41.4	1990-1994	0.5*	1994-2003	-0.5*	2003-2016	-1.1*	-0.7*
	70+ years	99.6	85.6	81.8-92.2	174.1	74.5	69.9-80.5	1990-1994	0.9*	1994-2002	-0.5*	2002-2016	-1.0*	-0.5*
High SDI	15-49 years	20.9	8.9	8.6-9.1	16.0	5.7	5.4-6.0	1990-1994	-1.1*	1994-2012	-2.1*	2012-2016	-0.4	-1.7*
	50-69 years	59.8	64.2	62.2-66.3	63.5	46.2	43.9-48.5	1990-1995	-0.8*	1995-2012	-1.5*	2012-2016	-0.7*	-1.3*
	70+ years	60.4	128.9	123.9-134.0	82.6	99.5	93.2-106.4	1990-1995	0	1995-2009	-1.3*	2009-2016	-1.0*	-1.0*
High-middle SDI	15-49 years	14.5	7.5	6.9-8.2	17.2	5.2	4.5-5.9	1990-1994	2.7*	1994-2016	-2.2*			-1.5*
	50-69 years	33.0	43.9	40.7-48.0	46.2	36.5	31.4-43.2	1990-1994	2.7*	1994-2004	-0.4*	2004-2016	-2.1*	-0.7*
	70+ years	17.9	67.9	63.2-74.0	34.4	71.1	62.6-82.0	1990-1994	3.5*	1994-2003	0.9*	2003-2016	-1.2*	0.2*
Middle SDI	15-49 years	22.5	6.3	5.6-7.3	37.0	5.6	5.0-6.2	1990-2002	0.3*	2002-2008	-1.8*	2008-2016	-0.7*	-0.5*
	50-69 years	30.9	31.1	28.2-37.1	70.0	31.8	28.8-34.7	1990-2002	0.8*	2002-2012	-0.2*	2012-2016	-0.9*	0.1*
	70+ years	12.1	45.8	41.6-57.5	31.5	51.7	46.8-56.7	1990-2002	1.1*	2002-2011	0.2*	2011-2016	-0.7*	0.5*
Low-middle SDI	15-49 years	17.7	7.3	5.5-9.7	33.1	6.7	5.8-8.2	1990-1999	0.5*	1999-2012	-1.2*	2012-2016	0.6	-0.4*
	50-69 years	25.8	38.9	31.4-50.6	51.2	37.9	32.7-48.1	1990-1999	0.7*	1999-2012	-0.8*	2012-2016	0.5	-0.1*
	70+ years	7.2	47.8	37.8-66.7	20.2	57.5	47.8-74.6	1990-2001	0.9*	2001-2011	0.3*	2011-2016	1.0*	0.7*
Low SDI	15-49 years	5.0	7.9	5.8-11.4	10.9	8.3	6.7-10.3	1990-1995	1.2*	1995-2010	-0.3*	2010-2016	0.7*	0.2*
	50-69 years	7.0	44.4	35.7-58.2	15.7	49.1	42.1-56.5	1990-1996	1.0*	1996-2009	0	2009-2016	0.7*	0.4*
	70+ years	1.9	59.9	48.7-76.3	5.2	72.6	62.3-82.3	1990-1995	1.0*	1995-2009	0.5*	2009-2016	1.1*	0.8*



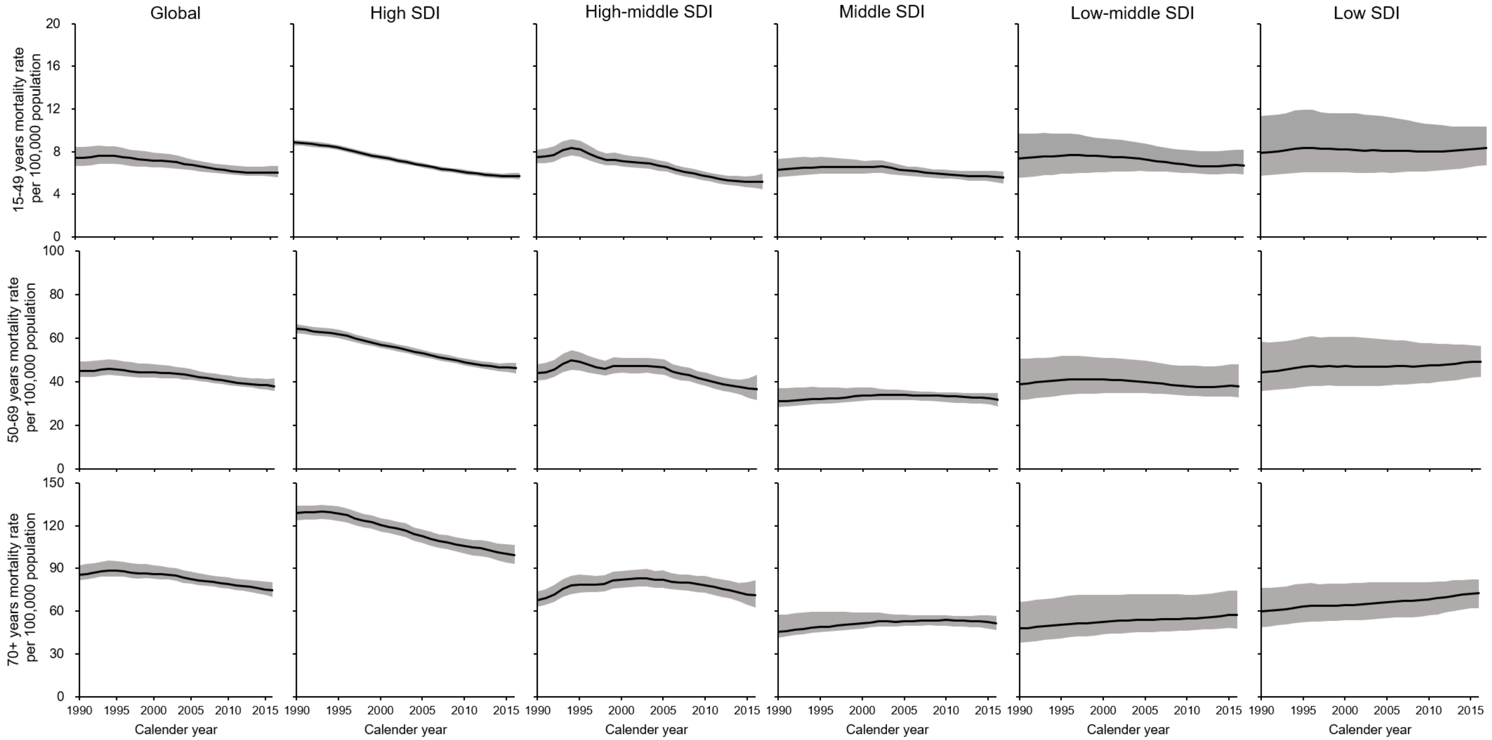
Supplementary figure 1A. Trends in breast cancer age-standardized incidence rate (ASIR) according to SDI settings, 1990-2016. The black lines represent the estimated ASIRs, and areas shaded in gray denote 95% uncertainty intervals.



Supplementary figure 1B. Trends in incidence rate for 15-49, 50-69 and 70+ years age groups according to SDI settings, 1990-2016. The black lines represent the estimated age-specific rates adjusted within each group by the new world population age-standard, and areas shaded in gray denote 95% uncertainty intervals.



Supplementary figure 2A. Trends in breast cancer age-standardized mortality rate (ASMR) according to SDI settings, 1990-2016. The black lines represent the estimated ASMRs, and areas shaded in gray denote 95% uncertainty intervals.



Supplementary figure 2B. Trends in mortality rate for 15-49, 50-69 and 70+ years age groups according to SDI settings, 1990-2016. The black lines represent the estimated age-specific rates adjusted within each group by the new world population age-standard, and areas shaded in gray denote 95% uncertainty intervals.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	**Item #**	**Recommendation**	**Reported on page #**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#4
Objectives	3	State specific objectives, including any prespecified hypotheses	#4
Methods			
Study design	4	Present key elements of study design early in the paper	#5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	#5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#5-6
Bias	9	Describe any efforts to address potential sources of bias	#5-6
Study size	10	Explain how the study size was arrived at	#5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#6-7
		(*b*) Describe any methods used to examine subgroups and interactions	#6-7
		(*c*) Explain how missing data were addressed	#6-7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	#6-7
		(*e*) Describe any sensitivity analyses	#6-7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#7-9
		(b) Give reasons for non-participation at each stage	#7-9
		(c) Consider use of a flow diagram	#7-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#7-9
		(b) Indicate number of participants with missing data for each variable of interest	#7-9
Outcome data	15*	Report numbers of outcome events or summary measures	#7-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#7-9
		(*b*) Report category boundaries when continuous variables were categorized	#7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	#9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	#11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	#9-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#12-13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Global Patterns and Trends in Breast Cancer Incidence and Mortality according to Socio-demographic Index: An Observational Study Based on the Global Burden of Diseases

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Title page:

Global Patterns and Trends in Breast Cancer Incidence and Mortality according to Socio-demographic Index: An Observational Study Based on the Global Burden of Diseases

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Abstract:

Objectives: Disparities existed in the global burden of breast cancer. We aimed to figure out the recent patterns and trends in incidence and mortality from breast cancer, and to assess health inequalities related to breast cancer according to socioeconomic development.

Methods: Estimates of breast cancer incidence and mortality data from 1990 to 2016 were obtained from the Global Health Data Exchange database. Patterns in 2016 were described with age-standardized and age-specific incidence, mortality and mortality-to-incidence (MI) ratio according to socio-demographic index (SDI) levels. Trends were assessed via the annual percent change using joinpoint regression. The between-country health inequalities were measured with the Gini coefficients and concentration indexes.

Results: Countries with higher levels of SDI were shown to have worse incidence burdens in 2016, though the health inequality in breast cancer incidence, in terms of Gini coefficients and concentration indexes, decreased since 1990. In keeping with the opposite trends in mortality rates between high and low SDI countries, the concentration indexes for mortality also declined and even turned negative in the age of 15-49 and 50-69 groups, pointing towards increasing concentration in mortality burdens of undeveloped regions. Conversely, both the overall inequality and the part related to socioeconomic development in MI ratio increased. In 2016, MI ratios showed distinct gradients from high to low SDI regions for all age groups.

Conclusions: Patterns and trends in breast cancer incidence and mortality closely correlated with SDI levels. Our findings highlighted that the two pressing needs in the following decades are 1) the primary prevention of breast cancer in high SDI countries with high incidence and 2) the development of cost-effective detection and treatment interventions in low SDI countries with poor MI ratios.

Keywords: breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini coefficient, concentration index

Article summary

Strengths and limitations of this study：

Patterns and trends of breast cancer burden worldwide was evaluated in relation to levels of socio-demographic index in this study.

Gini coefficient and concentration index revealed the extent, trend and concentration of health inequality caused by breast cancer.

The findings might be limited by the fact that secondary estimated data from the Global Burden of Disease database was used in this study and estimates for some countries with poor-quality law data could be biased.

Introduction

Breast cancer is the most common cancer and the first leading cause of cancer death among women, with an estimated 2.4 million new cases and 523 thousand deaths worldwide in 2015[1]. Where and in which socioeconomic status a woman lives can significantly affect her odds of developing breast cancer and whether she will ultimately survive[1]. Breast cancer is not confined to high-income countries. However, it often occurred in developed regions, where the incidence rates were multifold higher compared with those in low- and middle-income countries (LMICs)[1-3]. The cancer-related mortality rates in those LMICs were not fit in their low incidence rates[3-5]. Along with better awareness of risk factors, regular mammography screening and sufficient and effective medical services, the mortality rates in many high-income countries significantly declined in recent decades, and their incidence rates also kept stable or even decreased since around 2000. In many resource-poor settings or countries undergoing rapid transition, both the incidence and mortality rates from breast cancer have been increasing, partially attributed by changes in reproductive patterns and delayed detections or treatments regardless of the increase in awareness[6, 7].

Disparities do exist in the global burden of breast cancer, especially among counties and regions with different levels of development. Understanding the exact correlations between the disease burden and socioeconomic status is critical for the world's health policymakers to formulate appropriate measures according to local conditions. Socio-demographic Index (SDI) was first introduced in the Global Burden of Disease Study 2015 (GBD 2015) by the Institute for Health Metrics and Evaluation to quantificationally measure the development of a country or region[8]. Through combining the latest updated SDI data with breast cancer incidence and mortality data during 1990 and 2016 available at the GBD 2016 database, this study aimed to describe the current patterns and trends in breast cancer incidence and mortality according to the country-level wellbeing, thus further exploring distributions and changes in the breast cancer associated health inequality according to the spectrum of development.

Material and Methods

Breast cancer was defined by the International Classification of Disease - Revision 10 with code C50. Incidence and mortality data from 195 individual countries and predefined five SDI groups between 1990 and 2016 were collected from the Global Health Data Exchange database[5]. Annual incidence and mortality rates by a 5-year age bracket from age 15 to 95+ were extracted for each involved country. Detailed methods pertaining to estimation of age-standardized incidence and mortality rate (ASIR and ASMR) per 100,000 population had been previously described in the

GBD 2016 reports[3, 4]. Women aged between 50 to 69 constituted the major population participating in regular screening programs. We further calculated age-specific incidence and mortality rates per 100,000 population into three subgroups by age: 15-49, 50-69 and 70+, which were adjusted within age groups in terms of the new world population age-standard[3]. Mortality-to-incidence (MI) ratio was calculated by dividing the breast cancer mortality rate for a given year, age-group, country or SDI group by its corresponding incidence rate.

Patient and Public Involvement

Patients or public were not involved in the recruitment and conduct of this study.

Ethics approval

Ethical approval was not obtained because the data included in this study were publicly available.

Socio-demographic index

SDI is a comparable metric of overall development achieved by using an equal weighting of lag-distributed income per capita, average years of education in the population over 15 years, and total fertility rate[9]. SDI values on a scale of 0 to 1. A greater value of SDI implies higher level of development. SDI data for the involved 195 countries from 1990 to 2016 were obtained from the Global Health Data Exchange database[5]. Countries were grouped into quintiles based on their SDI values in 2016: high, high-middle, middle, low-middle and low SDI groups. Detailed methods describing computation of the SDI as well as the choice of the quintile cutoffs were reported elsewhere[1, 3].

Gini coefficient and concentration index

Gini coefficient and concentration index drawn from the field of economics were used to measure breast cancer associated health inequality in our study[10, 11]. Gini coefficient was calculated based on the Lorenz curve, and it ranged from 0 to 1, 0 representing perfect equality and 1 total inequality[11]. Annual ASIRs, ASMRs, age-specific incidence and mortality rates and MI ratios of breast cancer for 195 countries were used to calculate the Gini coefficients and to find out the trends in between-country health inequality during 1990 and 2016. Concentration index was derived from the concentration curve and commonly used to measure socioeconomic-related health inequality[12]. Concentration indexes were computed by relating the above breast cancer metrics to corresponding national SDIs. The value of this index varies between -1 and +1. Positive (negative) value of the concentration index indicated the disease burden owing to the occurrence or death of breast cancer was more concentrated in countries with high (low) levels of development measured by SDI[12]. The absolute value demonstrates the degree of a "pro-developed" or "pro-underdeveloped" distribution in health limitations. Zero means an absence of inequality associated to the socioeconomic gradient instead of the absence of inequality.

Statistical analyses

For a normal distribution but heterogeneity in variances of incidence, mortality and MI ratio data, one-way ANOVA was performed to determine the statistical significance of differences in incidence rates, mortality rates and MI ratios across SDI-based country groups, followed by pairwise comparisons using Tamhane T2 test[13]. Liner regression model was used to test for the correlation between breast cancer indicators and SDI values. Joinpoint piecewise linear regression analysis was performed to identify time points when significant changes occurred as well as temporal trends in age-standardized and age-specific incidence and mortality rates during 1990 and 2016[14]. Default parameters were used, except for setting the minimum number of data points between two joints and at either end of the data to 5. To avoid over-fitting at the truncating points, maximum number of joinpoints was defined as 2. The best-fit point where the rate had changed prominently was decided by means of a permutation test, and the *P* value for each permutation test was estimated using Monte Carlo methods[14]. Statistics on annual percent change (APC) for each segment and average annual percent change (AAPC) for the overall period were summarized using the optimal joinpoint model. All joinpoint trend analyses were undertaken via the joinpoint statistical software (Version 4.5.0.1) from the surveillance research program of the United States National Cancer Institute[15]. The Gini coefficient was computed by the AINEQUAL module[16], and the concentration index by the CONINDEX module[17] using Stata 14.0 software (Stata Corp, Texas, USA). Other statistical analyses were performed with SPSS 20.0 (IBM Corp, Chicago, USA).

Results

Current profiles in breast cancer incidence and mortality according to SDIs

Figure 1 showed distinct distributions of counts and proportions of new cases and deaths due to breast cancer in five SDI groups in 2016. There were 719 thousand new cases in high SDI countries, about 20 times of that of 37 thousand in low SDI groups. Death number in these two groups were 162 and 32 thousand, respectively. About half of the new cases occurred in women aged 50 to69 across all SDI groups. In countries belonging to middle, low-middle or low SDI group, more than one third new cases happened in young ages between 15 and 49, along with more proportion of deaths in this age group. Deaths in the age of 70 or elder, by contrast, made up 50.9% of total breast cancer deaths in high SDI countries.

One-way ANOVA suggested significant differences in both age-standardized and age-specific incidence rates and MI ratios ($P < 0.01$), but did not imply discrepancies of mortality rates among countries in different SDI groups. Pairwise comparisons indicated lower MI ratios in countries representing the higher level of development based on SDI, where the mortality rates were not proportional to their high incidence rates (Figure 2). The Incidence rates in all age groups were shown to have a positive dose-response relationship with SDIs, otherwise than a negative dose-response relationship between MI ratios and SDIs (Figure 3). Besides, the rate ratios exhibited well-fitting linear relationships in all age groups, whereas the incidence and mortality rates in elder age groups were more scattered across countries with varied SDIs.

Temporal trends in breast cancer incidence and mortality across SDI groups

According to the joinpoint trend analyses (Table 1), the ASIRs in high and high-middle SDI groups plateaued after a quick increase at early 1990s. The ASIRs in the high SDI group even displayed a declining trend by 0.1% per year since 2000. However, significant increases were found in middle, low-middle and low SDI groups through the whole period from 1990 to 2016 (Supplementary figure 1A). The AAPC in ASIR for the middle SDI group was 2.1%, far ahead of increases in other groups. Trends of incidence rates in groups of 15-49, 50-69 and 70+ years old were comparable with those of ASIRs across SDI groups (Supplementary table 1 and figure 1B).

Changes in ASMRs were contradictory across SDI groups as shown in table 2 and supplementary figure 2A. In the high SDI group, the ASMR continuously decreased from 24.2 in 1990 to 17.6 in 2016, with an AAPC of -1.3%. The ASMR in high-middle SDI group began to decline in 1994, and an accelerated decrease (APC: -1.9%) was witnessed between 2004 and 2016. The ASMR in the middle SDI group also slightly diminished from 2002 to 2016 with an average decrease of 0.5% per year. Opposite trends were displayed in the low-middle (2002-2016, APC: 0.7%) and low SDI groups (2009-2016, APC: 0.8%), especially in recent years. Patterns of change in three age groups were similar with those of ASMR in each SDI group, but the spectrum of change differed (Supplementary table 2 and figure 2B). For example, our results showed a much less decrease in more developed regions and more increase in less developed regions in the mortality among the group aged 70+, which was much less-than-ideal.

Global health inequality related to breast cancer

The Gini coefficients for the incidence of breast cancer decreased continuously from 1990 to 2016 (Figure 4A), the values of which computed from ASIRs and incidence rates in the age groups of

15-49, 50-69 and 70+ had dropped to 0.33, 0.30, 0.34 and 0.38 by 2016, compared with those of 0.38, 0.35, 0.39 and 0.43 in 1990, respectively. Similarly, the Gini coefficients calculated with mortality rates in all age groups except the 15-49 group showed markedly declining trends during the same period. On the contrary, the Gini coefficients, according to the distribution of MI ratios, increased, which reached up to 0.29 in 2016 from a base of 0.23 in 1990.

The concentration indexes according to breast cancer age-standardized and age-specific incidence and mortality rates were all above zero in 1990, suggesting that the inequalities associated with socioeconomic development concentrated in countries with a higher level of development measured by SDI. Moreover, the concentration indexes for the 70+ group were much greater than those in others. As can be seen in Figure 4B, both the concentration indexes of incidence and mortality rates decreased between 1990 and 2016, and the rates of descent sped up since late 1990s. The concentration indexes computed with mortality rates in the age groups of 15-49 and 50-69 inclined to zero and became negative in 1998 and 2013, respectively. In contrast, the concentration indexes based on age-standardized and age-specific MI ratios were below zero, with values of -0.21, -0.22, -0.22 and -0.18 in 1990, and by 2016, the values of which had decreased to -0.28, -0.31, -0.30 and -0.25, respectively.

Discussion

The socioeconomic development associated inequality in global incidence of breast cancer has been decreasing since 1990. Still, countries with higher levels of development on the basis of SDIs were shown to have worse incidence burdens by 2016. In keeping with the opposite trends for mortality rates between countries with high and low SDIs, the concentration indexes of mortality fell and even turned to be negative in the age groups of 15-49 and 50-69 in recent years, pointing towards a transition in the concentration of mortality burdens from the developed to undeveloped regions. Conversely, both the overall inequality and the part correlated with socioeconomic development in MI ratio - a health measure derived from the rate ratio of mortality and incidence - increased from 1990 to 2016. In 2016, MI ratios showed distinct gradients from the high to low SDI regions among all age groups.

With epidemiological data reported for specific countries, it has been a prevailing perception that inequalities existed in breast cancer incidence worldwide, especially between the high-income countries and LMICs[18-21]. However, evidence about the quantitative relationship between the breast cancer burdens and national socioeconomic development was still limited. On the basis of GLOBOCAN 2012 estimates, incidence burden due to breast cancer distributed with obvious disparities among countries in different levels of human development index (HDI)[2], which was in accordance with our results in the light of data from the GBD 2016 study and SDI-a newly developed indicator for socioeconomic status of a given country. The overall inequality in breast cancer incidence had not yet been eliminated and still concentrated in countries with higher levels of SDI. The prevalence of breast cancer is somewhat associated with a so-called western lifestyle (ie, specific reproductive patterns and excess body weight)[22, 23], making it a marker for the extent of development. Trend analyses in our study demonstrated a quick increasing in breast cancer incidence in countries belonging to the middle SDI group. This fact might suggest that countries with middle levels of SDI were undergoing rapid social and economic transitions[24]. In many LMICs, burdens due to infection-related cancers, such as cervical, gastric and liver cancer, remained top ranking, instead of breast cancer[1, 2]. Mammographic screening programs were generally implemented in high-income countries, especially for women aged 50 to 69 years[25-27]. Our subgroup analysis based on age conformed transient rises in incidence of women at this age group and subsequent falls in those elder than 70 years in high SDI countries.

The mortality rates from breast cancer did not differ significantly from the low to high SDI regions. Inequalities in deaths caused by breast cancer were possibly offset by better outcomes in more developed countries because of early detections and advanced treatments, and small scale of incidence but limited access to health cares in most LMICs[28, 29]. Therefore, mortality rates could not well represent the exact trends and current status of death burdens caused by cancer.

Cancer survival was another important indicator for death burden of malignancies. According to data from 59 countries in CONCORD-2 study[30], five-year survival for patients diagnosed with breast cancer during 2005-09 in the North America, Australia, Israel, Brazil, and most Northern and Western European countries had reached up to 85% or higher, while it remained 60% or lower in many LMICs, such as India, Mongolia, Algeria and South Africa. However, comprehensive survival data were scarce in most countries, especially in those with limited resources. It remained an important issue to conclude the extent of socioeconomic development associated inequalities in the survivorship of breast cancer and to compare the current survival status in each country across the world. Here in our study, we analyzed the trends of inequalities in breast cancer MI ratios, which evaluated the departure of mortality in relation to incidence from expectation and was suggested as an approximation for cancer survival[31-33]. Our results indicated widening disparities in the MI ratios of breast cancer among countries with different levels of development.

HDI was a metric composed by life expectancy at birth, mean and expected years of schooling and gross national income per capita[34]. It was used by a few researches to investigate how macro-socioeconomic determinants correlated with national disease burdens[2, 28, 35]. Nevertheless, it could be confusing when a measure of overall health (life expectancy at birth) was one important component of the index used to evaluate how socioeconomic development influences health. In the GBD 2015 study, SDI was first developed to identify where countries or geographic areas sit on the spectrum of societal development[8]. As reproductive patterns were proved to be risk factors for breast cancer[22], SDI, a yardstick constructed based on measures of income, education, and fertility rate, might be more appropriate to weigh the influence of socioeconomic status on the global patterns and trends in health inequality resulting from breast cancer.

To our knowledge, this study was a first overview about the global patterns and trends in breast cancer incidence and mortality in relation to levels of SDI. Limitations should also be considered when the results of our investigation were interpreted. Firstly, this study was subject to the limitations of the GBD 2016 study, such as data sources and statistical assumptions, which were detailed in the GBD 2016 reports[3, 4]. Estimates for most LMICs with poor-quality law data could be biased, especially for MI ratios calculated based on incidence and mortality data. Better primary data from national wide observational studies or cancer registries are needed for these countries in the future. Secondly, joinpoint analysis is sensitive to parameter settings. The pattern groupings of trends in incidence and mortality may change if parameters are set differently or more data are involved in the analysis. Thirdly, district data within each country, information on disease stage or histopathological characteristics were unavailable in GBD 2016 database. In the United States, for example, nationwide distributions and trends in breast cancer burdens differed by ethnicity, state, disease stage and intrinsic subtype[36, 37]. More studies are needed to further understand disparities due to these biases worldwide.

Conclusions

The socioeconomic development associated health inequality in breast cancer incidence has been declining since 1990. Countries undergoing an economic and lifestyle transition were experiencing a growing prevalence of breast cancer. Nonetheless, the incidence burden still concentrated in countries with higher SDIs by 2016. These findings highlighted that public health clinicians and cancer control specialists should pay more attention to the primary prevention of breast cancer especially in those high-incidence countries. Breast cancer mortality, in less developed countries, deviated from expectation seriously in relation to their low incidence. This situation even deteriorated with ever-increasing between-country inequalities for rate ratios from 1990 until 2016. Planners should try to carry out more sensitive and cost-effective detection and treatment interventions, particularly in low and low-middle SDI settings with limited healthcare resources, so as to combat premature deaths caused by breast cancer.

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Competing interests

The authors declared no conflict of interest.

Data sharing statement

The data used in this study is collected from the Global Health Data Exchange database.

Authors' contributions

Kaimin Hu designed the study, extracted and analyzed the data and prepared the figures. Peili Ding and Yinan Wu wrote the first draft of the manuscript. Tao Pan and Wei Tian revised the paper critically. Suzhan Zhang was the principle investigator and designed the study. All authors commented on manuscript drafts, approved the final version and declared no conflict of interest.

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Figure legend:

Figure 1. Distribution of breast cancer incidence and mortality counts and proportions by age at the global level and SDI quintiles in 2016.

Figure 2. Patterns for breast cancer, in terms of age-standardized and age-specific (A) incidence rates, (B) mortality rates and (C) MI ratios by SDI group in 2016. Black squares represent the medians of all rates from the countries included in each SDI level. Lines denote the interquartile ranges. $^{*}P < 0.05$, $^{***}P < 0.001$.

Figure 3. Relationship between the incidence rates, mortality rates, MI ratios and SDI levels by age. The best-fitted line according to linear regression analysis was showed.

Figure 4. Trends in (A) the Gini coefficients and (B) concentration indexes computed from health metrics of breast cancer, in terms of age-standardized and age-specific incidence rates, mortality rates and MI ratios, across countries worldwide during 1990 and 2016.

Table

Table 1. Breast cancer age-standardized incidence rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	815.4	41.0	39.8-43.1	1681.9	45.6	43.6-48.2	1990-1995	1.5*	1995-2000	0.2*	2000-2016	0.1*	0.4*
High SDI	463.0	83.6	82.0-85.1	719.4	88.9	86.5-93.0	1990-1995	1.3*	1995-2000	0.2*	2000-2016	-0.1*	0.2*
High-middle SDI	153.1	37.1	36.0-38.6	329.0	46.5	42.9-50.5	1990-1995	3.2*	1995-2016	0.4*			0.9*
Middle SDI	116.0	19.3	18.1-22.1	408.8	33.2	30.4-36.0	1990-2000	2.6*	2000-2009	2.0*	2009-2016	1.5*	2.1*
Low-middle SDI	69.7	17.7	14.9-21.9	187.0	23.1	21.1-27.8	1990-1999	1.3*	1999-2010	0.4*	2010-2016	1.8*	1*
Low SDI	15.6	16.3	13.6-20.9	37.0	18.8	17.1-20.8	1990-1995	0.9*	1995-2010	0.3*	2010-2016	0.8*	0.5*

95% UI, 95% uncertainty interval; ASR, age-standardized rate; APC, annual percent change; AAPC, average annual percent change. *P < 0.05.

Table 2. Breast cancer age-standardized mortality rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	336.9	17.2	16.4-18.8	535.3	14.6	13.8-15.6	1990-1994	0.8*	1994-2002	-0.6*	2002-2016	-1.1*	-0.7*
High SDI	141.1	24.2	23.8-24.7	162.1	17.6	16.9-18.3	1990-1995	-0.6*	1995-2010	-1.6*	2010-2016	-1*	-1.3*
High-middle SDI	65.5	15.9	15.2-17.0	97.9	13.7	12.2-15.7	1990-1994	2.9*	1994-2004	-0.4*	2004-2016	-1.9*	-0.6*
Middle SDI	65.5	11.6	10.7-13.7	138.5	11.8	10.8-12.7	1990-2002	0.8*	2002-2016	-0.5*			0.1*
Low-middle SDI	50.7	13.6	11.4-17.3	104.5	13.8	12.1-17.2	1990-1999	0.7*	1999-2012	-0.6*	2012-2016	0.7*	0
Low SDI	13.9	15.7	13.0-20.2	31.9	17.6	15.7-19.9	1990-1996	0.9*	1995-2009	0	2009-2016	0.8*	0.5*

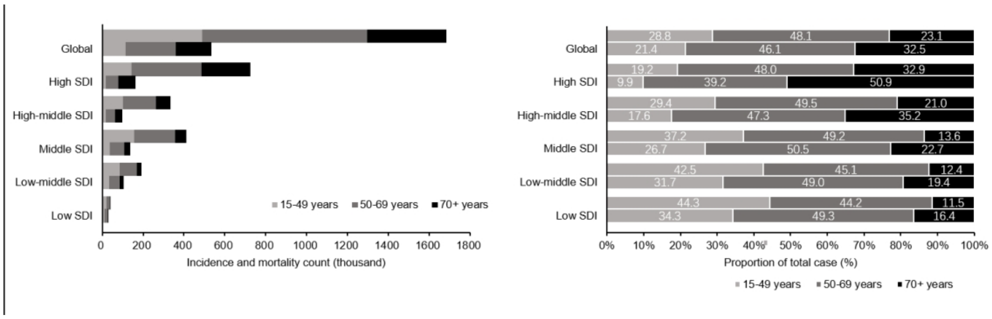

Figure 1

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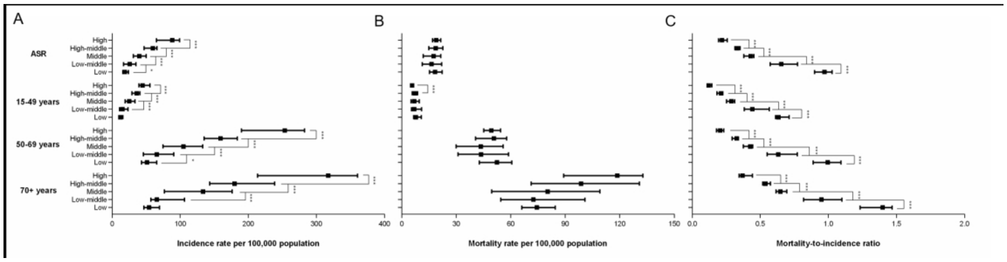

Figure 2

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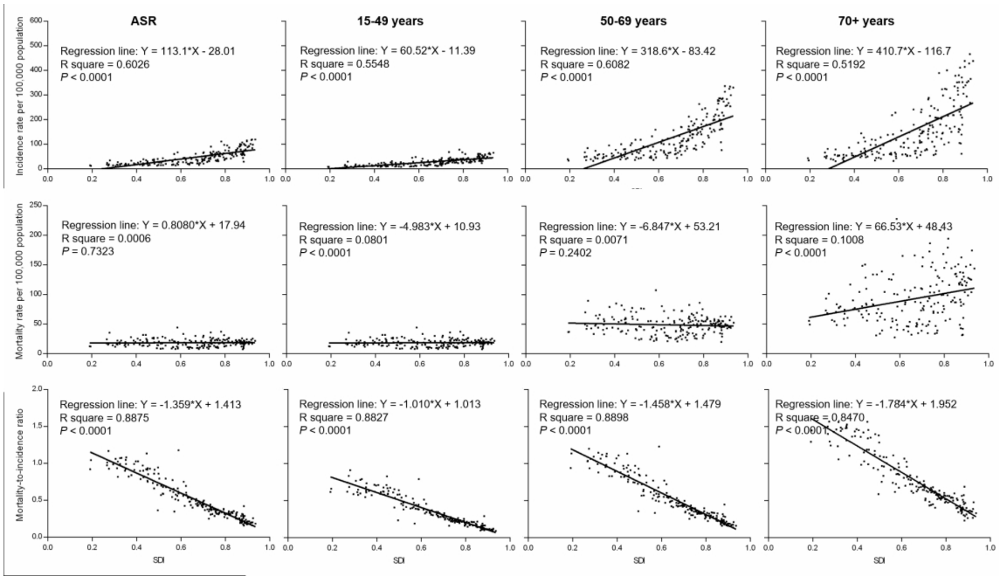

Figure 3

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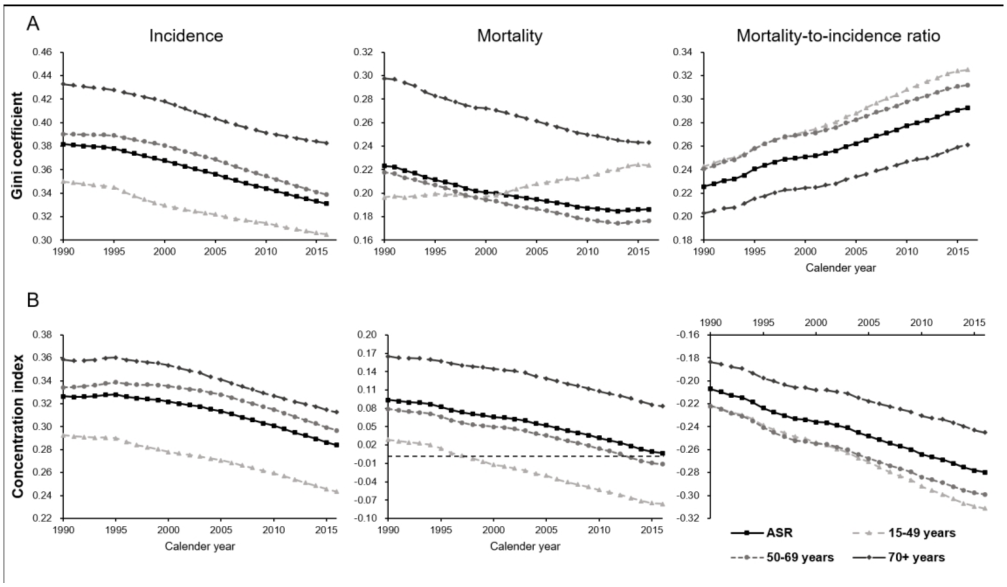


Figure 4

283x163mm (150 x 150 DPI)

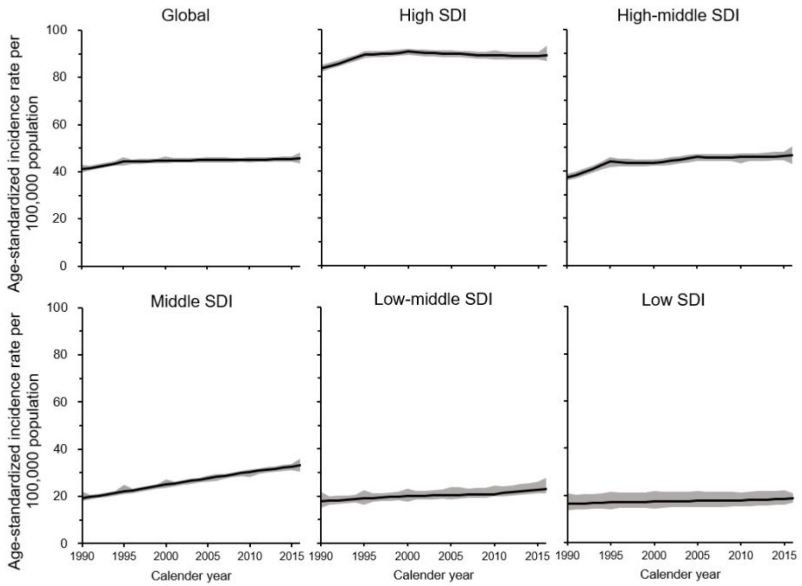
Supplementary figures and tables

Supplementary table 1. Breast cancer age-specific incidence rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

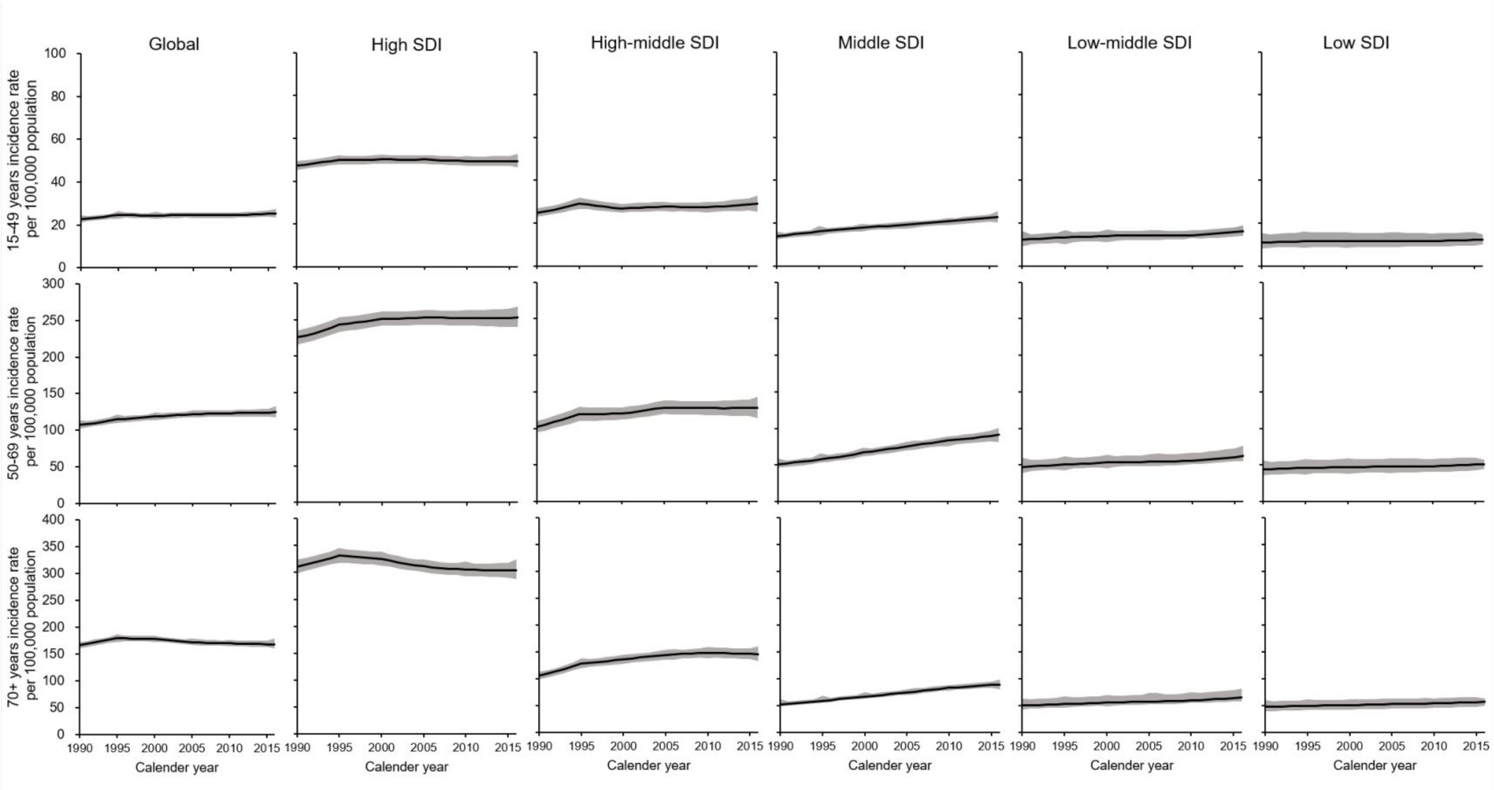
		1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Age	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	248.2	22.7	21.0-24.6	484.0	25.4	23.6-27.5	1990-1995	1.6*	1995-2011	0	2011-2016	0.7*	0.4*
	50-69 years	372.8	107.0	102.4-113.5	809.6	124.4	117.4-132.8	1990-1995	1.4*	1995-2005	0.6*	2005-2016	0.2*	0.6*
	70+ years	194.4	165.8	159.8-172.8	388.3	167.8	159.8-178.5	1990-1995	1.7*	1995-2008	-0.4*	2008-2016	-0.2*	0.1*
High SDI	15-49 years	111.6	47.3	45.3-49.4	137.8	49.4	46.6-52.6	1990-1995	1.0*	1995-2000	0.2	2000-2016	-0.1*	0.2*
	50-69 years	208.8	225.6	216.1-235.4	345.1	252.7	239.8-268.1	1990-1995	1.5*	1995-2000	0.8*	2000-2016	0*	0.5*
	70+ years	142.7	310.7	297.6-324.2	236.5	303.7	287.7-324.7	1990-1995	1.4*	1995-2008	-0.6*	2008-2016	-0.1*	-0.1*
High-middle SDI	15-49 years	48.8	24.8	23.0-26.9	96.9	29.0	25.3-33.0	1990-1995	3.3*	1995-2000	-1.5*	2000-2016	0.4*	0.6*
	50-69 years	76.1	101.6	94.5-110.0	163.0	128.1	113.7-143.2	1990-1994	3.5*	1994-2006	0.8*	2006-2016	0	0.9*
	70+ years	28.2	106.1	99.1-114.0	69.2	146.0	133.2-161.1	1990-1995	4.0*	1995-2007	1.2*	2007-2016	-0.1*	1.3*
Middle SDI	15-49 years	51.0	14.0	12.2-16.2	152.2	22.9	20.4-25.6	1990-1995	2.9*	1995-1999	2.2*	1999-2016	1.6*	1.9*
	50-69 years	50.5	50.8	46.2-59.0	201.0	91.0	81.0-100.8	1990-2004	2.7*	2004-2010	2.0*	2010-2016	1.5*	2.3*
	70+ years	14.4	52.8	48.5-62.3	55.6	89.8	80.8-98.7	1990-2000	2.4*	2000-2010	2.2*	2010-2016	1.2*	2.1*
Low-middle SDI	15-49 years	30.6	12.4	9.2-16.2	79.5	16.0	14.2-19.1	1990-2000	1.3*	2000-2010	0.2*	2010-2016	1.8*	1.0*
	50-69 years	31.4	47.1	38.9-59.8	84.4	61.9	54.7-76.1	1990-1999	1.3*	1999-2010	0.4*	2010-2016	1.9*	1.0*
	70+ years	7.6	50.6	42.9-63.7	23.1	65.2	57.8-82.6	1990-2000	1.0*	2000-2010	0.7*	2010-2016	1.4*	1.0*
Low SDI	15-49 years	7.0	10.9	8.1-15.5	16.4	12.2	10.2-14.6	1990-1995	1.1*	1995-2010	0.1*	2010-2016	0.8*	0.4*
	50-69 years	7.0	43.9	35.5-56.2	16.4	50.7	44.2-57.4	1990-1998	0.8*	1998-2010	0.3*	2010-2016	0.8*	0.5*
	70+ years	1.6	48.5	39.8-60.8	4.3	57.3	50.5-63.5	1990-2010	0.6*	2010-2016	0.8*			0.6*

Supplementary table 2. Breast cancer age-specific mortality rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

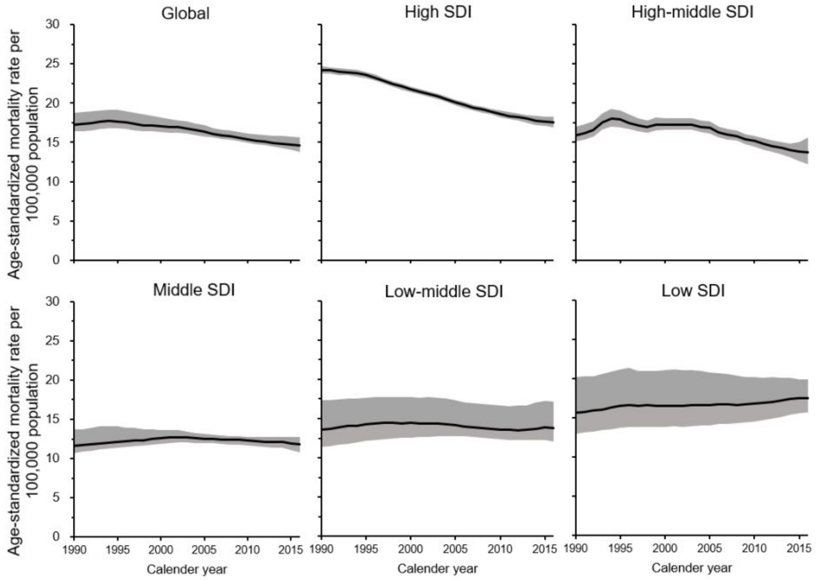
	Age	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
		Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	80.7	7.4	6.6-8.4	114.3	6.0	5.6-6.6	1990-1995	0.8*	1995-2012	-1.4*	2012-2016	-0.3*	-0.8*
	50-69 years	156.5	44.9	42.2-49.4	246.9	38.0	35.6-41.4	1990-1994	0.5*	1994-2003	-0.5*	2003-2016	-1.1*	-0.7*
	70+ years	99.6	85.6	81.8-92.2	174.1	74.5	69.9-80.5	1990-1994	0.9*	1994-2002	-0.5*	2002-2016	-1.0*	-0.5*
High SDI	15-49 years	20.9	8.9	8.6-9.1	16.0	5.7	5.4-6.0	1990-1994	-1.1*	1994-2012	-2.1*	2012-2016	-0.4	-1.7*
	50-69 years	59.8	64.2	62.2-66.3	63.5	46.2	43.9-48.5	1990-1995	-0.8*	1995-2012	-1.5*	2012-2016	-0.7*	-1.3*
	70+ years	60.4	128.9	123.9-134.0	82.6	99.5	93.2-106.4	1990-1995	0	1995-2009	-1.3*	2009-2016	-1.0*	-1.0*
High-middle SDI	15-49 years	14.5	7.5	6.9-8.2	17.2	5.2	4.5-5.9	1990-1994	2.7*	1994-2016	-2.2*			-1.5*
	50-69 years	33.0	43.9	40.7-48.0	46.2	36.5	31.4-43.2	1990-1994	2.7*	1994-2004	-0.4*	2004-2016	-2.1*	-0.7*
	70+ years	17.9	67.9	63.2-74.0	34.4	71.1	62.6-82.0	1990-1994	3.5*	1994-2003	0.9*	2003-2016	-1.2*	0.2*
Middle SDI	15-49 years	22.5	6.3	5.6-7.3	37.0	5.6	5.0-6.2	1990-2002	0.3*	2002-2008	-1.8*	2008-2016	-0.7*	-0.5*
	50-69 years	30.9	31.1	28.2-37.1	70.0	31.8	28.8-34.7	1990-2002	0.8*	2002-2012	-0.2*	2012-2016	-0.9*	0.1*
	70+ years	12.1	45.8	41.6-57.5	31.5	51.7	46.8-56.7	1990-2002	1.1*	2002-2011	0.2*	2011-2016	-0.7*	0.5*
Low-middle SDI	15-49 years	17.7	7.3	5.5-9.7	33.1	6.7	5.8-8.2	1990-1999	0.5*	1999-2012	-1.2*	2012-2016	0.6	-0.4*
	50-69 years	25.8	38.9	31.4-50.6	51.2	37.9	32.7-48.1	1990-1999	0.7*	1999-2012	-0.8*	2012-2016	0.5	-0.1*
	70+ years	7.2	47.8	37.8-66.7	20.2	57.5	47.8-74.6	1990-2001	0.9*	2001-2011	0.3*	2011-2016	1.0*	0.7*
Low SDI	15-49 years	5.0	7.9	5.8-11.4	10.9	8.3	6.7-10.3	1990-1995	1.2*	1995-2010	-0.3*	2010-2016	0.7*	0.2*
	50-69 years	7.0	44.4	35.7-58.2	15.7	49.1	42.1-56.5	1990-1996	1.0*	1996-2009	0	2009-2016	0.7*	0.4*
	70+ years	1.9	59.9	48.7-76.3	5.2	72.6	62.3-82.3	1990-1995	1.0*	1995-2009	0.5*	2009-2016	1.1*	0.8*



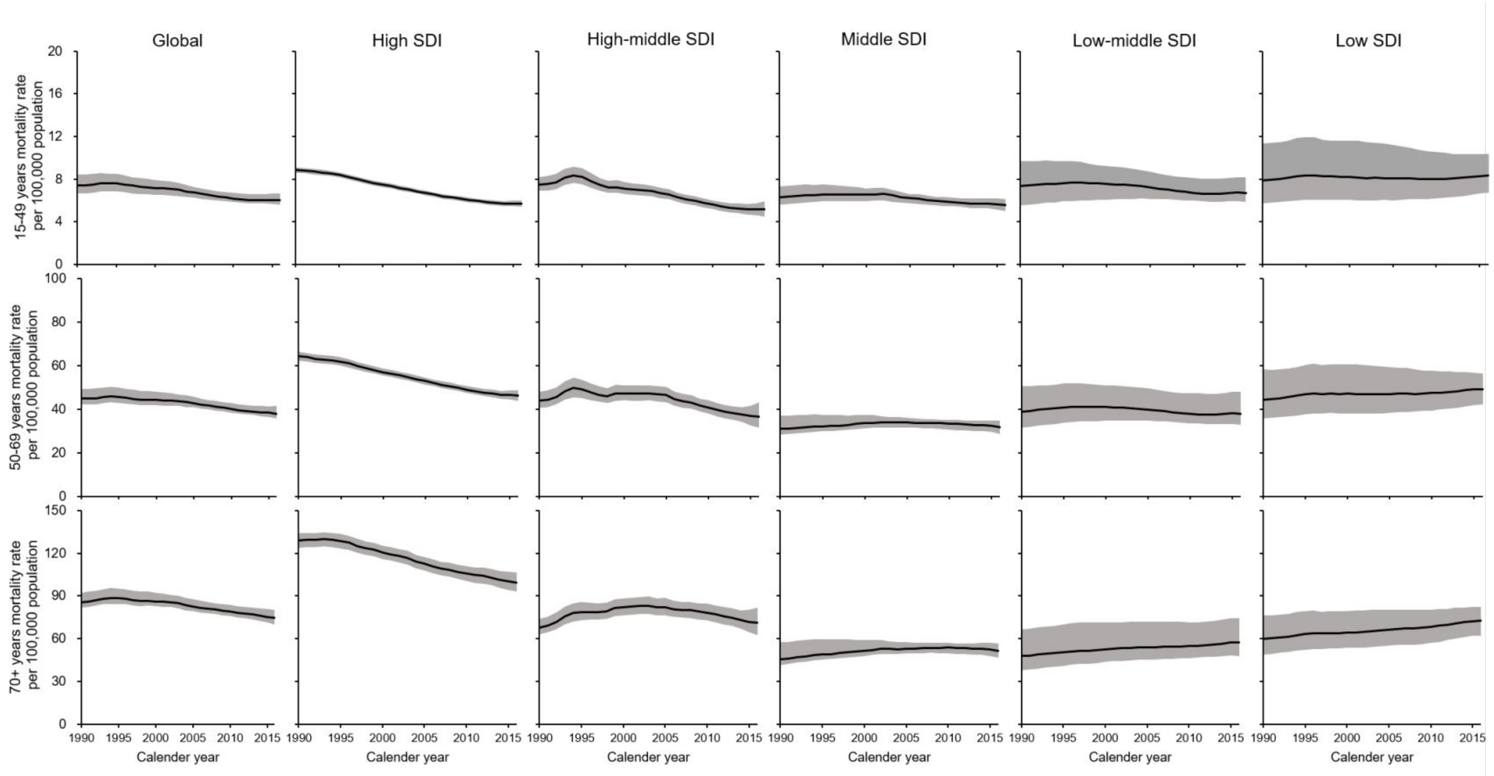
Supplementary figure 1A. Trends in breast cancer age-standardized incidence rate (ASIR) according to SDI settings, 1990-2016. The black lines represent the estimated ASIRs, and areas shaded in gray denote 95% uncertainty intervals.



Supplementary figure 1B. Trends in incidence rate for groups of 15-49, 50-69 and 70+ years old according to SDI settings, 1990-2016. The black lines represent the estimated age-specific rates adjusted within each group by the new world population age-standard, and areas shaded in gray denote 95% uncertainty intervals.



Supplementary figure 2A. Trends in breast cancer age-standardized mortality rate (ASMR) according to SDI settings, 1990-2016. The black lines represent the estimated ASMRs, and areas shaded in gray denote 95% uncertainty intervals.



Supplementary figure 2B. Trends in mortality rate for groups of 15-49, 50-69 and 70+ years old according to SDI settings, 1990-2016. The black lines represent the estimated age-specific rates adjusted within each group by the new world population age-standard, and areas shaded in gray denote 95% uncertainty intervals.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#4
Objectives	3	State specific objectives, including any prespecified hypotheses	#4
Methods			
Study design	4	Present key elements of study design early in the paper	#5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	#5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#5-6
Bias	9	Describe any efforts to address potential sources of bias	#5-6
Study size	10	Explain how the study size was arrived at	#5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#6-7
		(*b*) Describe any methods used to examine subgroups and interactions	#6-7
		(*c*) Explain how missing data were addressed	#6-7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	#6-7
		(*e*) Describe any sensitivity analyses	#6-7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#7-9
		(b) Give reasons for non-participation at each stage	#7-9
		(c) Consider use of a flow diagram	#7-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#7-9
		(b) Indicate number of participants with missing data for each variable of interest	#7-9
Outcome data	15*	Report numbers of outcome events or summary measures	#7-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#7-9
		(*b*) Report category boundaries when continuous variables were categorized	#7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	#9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	#11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	#9-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#12-13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Global Patterns and Trends in Breast Cancer Incidence and Mortality According to Socio-demographic Indices: An Observational Study Based on the Global Burden of Diseases

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Primary Subject Heading:	Epidemiology
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Keywords:	breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini coefficient, concentration index

Title page:

Global Patterns and Trends in Breast Cancer Incidence and Mortality According to Socio-demographic Indices: An Observational Study Based on the Global Burden of Diseases

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Word count: 3065

Abstract:

Objectives: Disparities exist in the global burden of breast cancer. We aimed to investigate the recent patterns and trends in the incidence and mortality rate of breast cancer; we also assessed health inequalities related to breast cancer according to socioeconomic development factors.

Design: An observational study based on the Global Burden of Diseases.

Methods: Estimates of breast cancer incidence and mortality between 1990 and 2016 were obtained from the Global Health Data Exchange database. Data in 2016 were then described using the age-standardized and age-specific incidence, mortality and mortality-to-incidence (MI) ratio, according to the socio-demographic index (SDI) levels. Trends were assessed by measuring the annual percent change using the joinpoint regression. Inequalities with respect to between-country health systems were measured using the Gini coefficients and concentration indices.

Results: Countries with higher SDI levels had a worse disease incidence burden in 2016, while the health inequality in breast cancer incidence decreased since 1990. The mortality rate showed opposite trends between high and low SDI countries, with the concentration indices declining and even turning negative in the 15-49 and 50-69 age groups, suggesting an increase in the mortality burden in undeveloped regions. Conversely, inequality related to the MI ratio increased. In 2016, the MI ratios showed distinct gradients from high to low SDI regions in all age groups.

Conclusions: Patterns and trends in breast cancer incidence and mortality closely correlated with SDI levels. Our findings highlighted that the two pressing needs in the next decades are the primary prevention of breast cancer in high SDI countries with high incidence and the

development of cost-effective diagnosis and treatment interventions in low SDI countries with poor MI ratios.

Keywords: breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini coefficient, concentration index

Article summary

Strengths and limitations of this study：

- This study was the first overview of the current global patterns and long-term period trends in breast cancer burden, stratified according to the levels of socio-demographic development.
- Gini coefficient and concentration index were used to evaluate the extent, trend and concentration of health inequality caused by breast cancer.
- The study is limited by the use of secondary estimated data from the Global Burden of Disease database, as the estimates for some countries with poor-quality raw data could be biased.

Introduction

Breast cancer is the most common cancer and the first leading cause of cancer death among women, with an estimated 2.4 million new cases and 523,000 deaths worldwide in 2015[1]. Where and in which socioeconomic status women live can significantly affect their odds of developing breast cancer and whether she will ultimately survive[1]. The incidence rate in high-income countries is higher than in low- and middle-income countries (LMICs)[1-3]. Because of better awareness of the risk factors, regular mammography screening and sufficient and effective medical services, the breast cancer mortality rates in many high-income countries significantly declined in the last decades, and the incidence rates kept stable or even decreased since the 2000. Breast cancer is not confined to high-income countries. The cancer-related mortality rates in LMICs do not correspond to their low incidence rates[3-5]. In many resource-poor settings or countries undergoing rapid transition, both the incidence and mortality rates of breast cancer increased, partially due to changes in the reproductive patterns and delayed diagnosis and treatments, independently from the increase in breast cancer awareness[6, 7].

Disparities do exist in the global burden of breast cancer, especially among counties with different development levels. Understanding the exact correlations between the disease burden and the socioeconomic status is critical for the world's health policymakers to formulate appropriate measures according to local conditions. The Socio-demographic Index (SDI) was first introduced in the Global Burden of Disease Study 2015 (GBD 2015) by the Institute for Health Metrics and Evaluation to quantitatively measure the development of a country or region[8]. Through combining the latest SDI data with breast cancer incidence and mortality data between 1990 and 2016, this study aimed to describe the current patterns and trends in breast cancer incidence and mortality according to the country-level wellbeing. This approach will enable a comprehensive investigation on the distributions and changes in the breast cancer-associated health inequalities, according to the spectrum of countries' development.

Material and Methods

Breast cancer was defined by the International Classification of Disease-Revision 10 with code C50. Incidence and mortality data between 1990 and 2016 from 195 individual countries, belonging to 5 predefined SDI groups were collected from the Global Health Data Exchange database[5]. The annual incidence and mortality rates, stratified in 5-year age bracket from age 15 to 95+, were extracted for each involved country. Detailed methods for the estimation of age-standardized incidence and mortality rate (ASIR and ASMR, respectively) per 100,000 population had been previously described in the GBD 2016 reports[3, 4]. Women aged between 50 and 69 years constituted the major population participating in regular screening programs. We further calculated the age-specific incidence and mortality rates per 100,000 population into three subgroups: 15-49, 50-69 and 70+ years of age, which were adjusted following the new world population age-standard[3]. Mortality-to-incidence (MI) ratio was calculated by dividing the breast cancer mortality rate for a given year, age-group, country, and SDI group by its corresponding incidence rate.

Patient and Public Involvement

Patients or public were not involved in the recruitment and conduct of this study.

Ethics approval

Ethical approval was not obtained because the data included in this study were publicly available.

Socio-demographic index (SDI)

SDI is a comparable metric of overall development calculated using an equal weighting of lag-distributed income per capita, average years of education in the population over 15 years, and total fertility rate[9]. SDI is expressed on a scale of 0 to 1. A greater value of SDI implies a higher level of development. SDI data from 1990 to 2016 for the 195 countries involved in the study were obtained from the Global Health Data Exchange database[5]. Countries were grouped into the following quintiles, based on their SDI values in 2016: high, high-middle, middle, low-middle and low SDI. Detailed methods describing the SDI computation as well as the choice of the quintile cutoffs were reported elsewhere[1, 3].

Gini coefficient and concentration index

The Gini coefficient and concentration index, used in the economics field, were adopted to measure breast cancer-associated health inequalities in our study[10, 11]. The Gini coefficient was calculated based on the Lorenz curve. It ranges between 0 and 1, with 0 representing perfect equality and 1 total inequality[11]. Annual ASIRs, ASMRs, age-specific incidence, age-specific mortality rates and MI ratios of breast cancer from 195 countries were used to calculate the Gini coefficients and to describe the health inequality trend between countries from 1990 to 2016. The concentration index, derived from the concentration curve, is commonly used to measure socioeconomic-related health inequality[12]. Concentration indices were computed by relating the abovementioned breast cancer metrics to the corresponding national SDIs. The value of the index varies between -1 and +1. A positive (negative) value of the concentration index indicated that the breast cancer disease burden was more concentrated in countries with high (low) levels of development, as measured by the SDI[12]. The absolute value is related to the degree of a "pro-developed" or "pro-underdeveloped" distribution in health limitations. A value of zero means an absence of inequality associated with the socioeconomic gradient, rather than an absolute absence of inequality.

Statistical analyses

For comparing data with a normal distribution but heterogeneity in variances, such as the incidence, mortality and MI ratio across 5 SDI-based country groups, we performed the one-way ANOVA, followed by pairwise comparisons using the Tamhane T2 test[13]. The liner regression model was used to test the correlation between the indicators for breast cancer burden and SDI values. The joinpoint piecewise linear regression analysis was performed to identify the time points where significant changes occurred as well as to identify temporal trends for the age-standardized and age-specific incidence and mortality rates between 1990 and 2016[14]. Default parameters were used, except the minimum number of data points between two joints and at either end of the data, which was set to 5. To avoid over-fitting at the truncating points, the maximum number of joinpoints was defined as 2. The best-fit point where the rate had significantly changed was assessed with a permutation test, and the *P* value for each permutation test was estimated using Monte Carlo methods[14]. Statistics on the annual percent change (APC) for each segment and the average annual percent change (AAPC) for the overall period were summarized using the optimal joinpoint model. All joinpoint trend analyses were performed using the joinpoint statistical software (Version 4.5.0.1) from the surveillance research program of the United States National Cancer Institute[15]. The Gini coefficient was computed using the AINEQUAL module[16], and the concentration index with the CONINDEX module[17] by the Stata 14.0 software (Stata Corp, Texas, USA). Other statistical analyses were performed with the SPSS 20.0 software (IBM Corp, Chicago, USA).

Results

Current profiles in breast cancer incidence and mortality rates according to SDIs

Figure 1 showed the year 2016 distribution of counts and proportions of new cases and deaths due to breast cancer in the 5 SDI groups. There were 719,000 new cases in high SDI countries, about 20 times higher than the 37,000 in low SDI countries. The number of deaths in these two groups were 162,000 and 32,000, respectively. About half of the new cases occurred in women aged between 50 and 69 years across all SDI groups. In countries belonging to the middle, low-middle, and low SDI group, more than one-third of the new cases appeared in the 15-49 age group, along with higher death proportion in this age group. By contrast, deaths in the age of 70 or older accounted for 50.9% of the total breast cancer-related deaths in high SDI countries.

The one-way ANOVA analysis suggested significant differences for both the age-standardized and the age-specific incidence rates and MI ratios ($P < 0.01$), but not for the mortality rates among countries belonging to different SDI groups. Pairwise comparisons indicated lower MI ratios in countries representing the highest level of development based on SDI, where the mortality rates were not proportional to their high incidence rates (Figure 2). The Incidence rates in all age groups were shown to have a positive relationship with SDI, while we observed a negative relationship between MI ratios and SDI (Figure 3). Moreover, the MI ratios exhibited well-fitting linear relationships in all age groups, whereas the incidence and mortality rates in the elder age groups were more scattered across countries with different SDIs.

Temporal trends in breast cancer incidence and mortality across SDI groups

According to the joinpoint trend analysis (Table 1), the ASIR in high and high-middle SDI groups reached a plateau after a quick increase in the early 1990s. The ASIR in the high SDI group even showed a declining trend of 0.1% per year since the year 2000. In contrast, significant increases were found in the middle, low-middle and low SDI groups through the whole period (Supplementary figure 1A). The ASIR AAPC for the middle SDI group was 2.1%, the highest increase among the SDI groups. The trend of incidence rates changes in the 15-49, 50-69, and 70+ age groups was comparable with the ASIR values across SDI groups (Supplementary table 1 and supplementary figure 1B).

Changes in ASMR were contradictory across SDI groups, as shown in table 2 and supplementary figure 2A. In the high SDI group, the ASMR continuously decreased from 24.2 in 1990 to 17.6 in 2016, with an AAPC of -1.3%. The ASMR in the high-middle SDI group began to decline in 1994, and we observed an accelerated decrease (APC: -1.9%) between 2004 and 2016. The ASMR in the middle SDI group also slightly diminished from 2002 to 2016, with an average decrease of 0.5% per year. Opposite trends were instead observed in the low-middle (2002-2016, APC: 0.7%) and low SDI groups (2009-2016, APC: 0.8%), especially in recent years. The change patterns in the 3 age groups were similar to the ASMR in each SDI group, but the degree of change differed (Supplementary table 2 and supplementary figure 2B). For example, our results showed, among the 70+ age group, a lower decrease in more developed regions and a higher increase in less developed regions in the mortality rate.

Global health inequality related to breast cancer

The Gini coefficients for the incidence of breast cancer decreased continuously from 1990 to 2016 (Figure 4A). The values calculated from the ASIRs and the incidence rate in the 15-49, 50-69 and 70+ age groups dropped to 0.33, 0.30, 0.34 and 0.38 by 2016, starting from 0.38, 0.35, 0.39 and 0.43 in 1990, respectively. Similarly, the Gini coefficients calculated with mortality rates showed markedly declining trends during the same period in all age groups, except the 15-49 group. On the contrary, the Gini coefficients calculated with the MI ratios distribution increased, reaching a value of 0.29 in 2016 from the 0.23 in 1990.

The concentration indices according to the breast cancer age-standardized and age-specific incidence and mortality rates were all above zero in 1990, suggesting that the inequalities associated with socioeconomic development were more concentrated in countries with a higher level of development, as measured by SDI. Moreover, the concentration indices for the 70+ group were higher than those for the other groups. Both the concentration indices of incidence and mortality rate decreased between 1990 and 2016, with the decrease rate accelerating since late 1990s, as shown in figure 4B. The mortality rate concentration indices in the age groups of 15-49 and 50-69 crossed the zero and became negative in 1998 and 2013, respectively. In contrast, the concentration indices based on age-standardized and age-specific MI ratios were already below zero in 1990, with values of -0.21, -0.22, -0.22 and -0.18. By 2016, the values had decreased to -0.28, -0.31, -0.30 and -0.25.

Discussion

The socioeconomic development-associated inequality in the global incidence of breast cancer has been decreasing since 1990. However, countries with higher levels of development according to the SDI had a worse incidence burden by 2016. Consistently with the opposite trends between countries with high and low SDI regarding the mortality rate, in recent years the mortality concentration index turned to be negative in the 15-49 and 50-69 age groups. This observation points towards a transition in the concentration of mortality burden from developed to undeveloped countries. Conversely, both the overall inequality and the inequality correlated with socioeconomic development calculated using the MI ratio increased from 1990 to 2016. In 2016, the MI ratio distribution showed a distinct gradient from high to low SDI countries among all age groups.

Thanks to the availability of epidemiological data from individual countries, the prevailing perception has been that inequalities existed in breast cancer incidence worldwide, especially between the high-income countries and LMICs[18-21]. However, quantitative evidence about the relationship between the global breast cancer burden and national socioeconomic development were still limited. According to the GLOBOCAN 2012 estimates, the breast cancer incidence burden was distributed with obvious disparities among countries with different levels of human development index (HDI)[2]. This is consistent with our results, which were based on the SDI and data from the GBD 2016 study. We observed that the overall inequality in breast cancer incidence had not yet been eliminated and is still concentrated in countries with high SDI levels. The higher prevalence of breast cancer is somewhat associated with the so-called western lifestyle (i.e., specific reproductive patterns and excessive body weight)[22, 23], making it a marker for the extent of development. Trend analyses in our study demonstrated a fast increase in the breast cancer incidence rate in countries belonging to the middle SDI group. This result might suggest that countries with middle levels of SDI were undergoing rapid social and economic transitions in the period considered in the study[24]. In many LMICs, the burden of infection-related cancers, such as cervical, gastric and liver cancer, remained higher than that of breast cancer[1, 2]. Mammographic screening programs were generally implemented in high-income countries, especially for women aged between 50 and 69 years[25-27]. Consistently, our subgroup analysis based on the age confirmed a transient rise in the incidence for women in this age group and a subsequent fall in the 70+ group in high SDI countries.

The mortality rates did not differ significantly from low to high SDI countries. Inequalities in breast cancer deaths were possibly offset by better clinical outcomes in more developed countries because of early diagnosis and the development of advanced treatments, while a small scale of incidence but a limited access to health care existed in most LMICs[28, 29]. Therefore, mortality rates could not well represent the exact trends and current status of cancer-related death burden. Cancer survival is another important indicator for evaluating the malignancies-related death burden. According to the data from 59 countries used in the CONCORD-2 study[30], the 5-year survival rate for patients diagnosed with breast cancer during the 2005-2009 period was 85% or higher in North America, Australia, Israel, Brazil, and most Northern and Western European countries, while it remained 60% or lower in many LMICs, such as India, Mongolia, Algeria and South Africa. However, the availability of comprehensive survival data was scarce in most countries, especially in those with limited resources. Thus, calculating the role of socioeconomic development-associated inequalities in the survival rate of breast cancer patients and comparing the current survival status in each country across the world remained critical issues. In the present study, we analyzed the trends of inequalities for breast cancer MI ratios, which is a marker that estimate the departure of mortality in relation to incidence from expectation and is suggested as an approximation for cancer survival[31-33]. Our results suggest a widening disparity according to the breast cancer MI ratios among countries with different levels of development.

HDI was a metric composed by life expectancy at birth, mean and expected years of schooling and gross national income per capita[34]. It was used to investigate how macro-socioeconomic determinants correlated with national disease burdens[2, 28, 35]. However, the use of this index is not ideal to evaluate how socioeconomic development influences health, because the measure of overall health (life expectancy at birth) is one important component of the index and can introduce a bias. In the GBD 2015 study, the SDI was first developed to identify where countries or geographic areas sit on the spectrum of social development[8]. As reproductive patterns were proved to be risk factors for breast cancer[22], the SDI, a yardstick based on income, education, and fertility rate measurements, might be more appropriate than HDI to weigh the influence of socioeconomic status on the global patterns and trends in health inequality of breast cancer.

To our knowledge, this study is the first overview of the global patterns and trends in breast cancer incidence and mortality in relation to SDI levels. However, the following limitations should be considered when interpreting the results of our investigation. First, this study is subject to the limitations of the GBD 2016 study, such as data sources and statistical assumptions, which are detailed in the GBD 2016 reports[3, 4]. Estimates for most LMICs could be biased due to poor-quality raw data, especially for MI ratios. Better primary data from nation-wide observational studies or cancer registries in these countries are needed for future studies. Second, the joinpoint analysis is particularly sensitive to the parameter settings. The pattern trends of incidence and mortality may change if parameters are set differently or more data are analyzed. Third, regional data within each country, information on disease stage and histopathological characteristics were unavailable in the GBD 2016 database. In the United States, for example, nation-wide distributions and trends in breast cancer burden can differ by ethnicity, state, disease stage, and intrinsic subtype[36, 37]. Thus, more studies are needed to further understand the disparities worldwide and eliminate the biases in the data.

Conclusions

The socioeconomic development-associated health inequality in breast cancer incidence has been declining since 1990. Countries undergoing an economic and lifestyle transition were experiencing a growing incidence of breast cancer. Nonetheless, in 2016 the incidence burden still concentrated in countries with a higher SDI. These findings highlighted that public health clinicians and cancer control specialists should pay more attention to the primary prevention of breast cancer, especially in high-incidence countries. In less developed countries, breast cancer mortality greatly deviated from the expectation based on their low incidence. Furthermore, this situation deteriorated in the considered period, with an ever-increasing rate ratio inequality between countries from 1990 to 2016. Public health planners should carry out more sensitive and cost-effective detection and treatment interventions, particularly in low and low-middle SDI settings with limited healthcare resources, to counteract the premature deaths caused by breast cancer.

Funding

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Competing interests

The authors declared no conflict of interest.

Data sharing statement

The data used in this study is collected from the Global Health Data Exchange database. Available from: http://www.healthdata.org/gbd-results-tool.

Authors' contributions

Kaimin Hu designed the study, extracted and analyzed the data and prepared the figures. Peili Ding and Yinan Wu wrote the first draft of the manuscript. Tao Pan and Wei Tian revised the paper critically. Suzhan Zhang was the principle investigator and designed the study. All authors commented on manuscript drafts and approved the final version.

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Figure legend:

Figure 1. Distribution of breast cancer incidence and mortality counts and proportions by age at the global level and SDI quintiles in 2016.

Figure 2. Patterns for breast cancer, in terms of age-standardized and age-specific (A) incidence rates, (B) mortality rates and (C) MI ratios by SDI group in 2016. Black squares represent the medians of all rates from the countries included in each SDI level. Lines denote the interquartile ranges. $^{*}P < 0.05$, $^{***}P < 0.001$.

Figure 3. Relationship between the incidence rates, mortality rates, MI ratios and SDI levels by age. The best-fitted line according to linear regression analysis was shown.

Figure 4. Trends in (A) the Gini coefficients and (B) concentration indexes computed from health metrics of breast cancer, in terms of age-standardized and age-specific incidence rates, mortality rates and MI ratios, across countries worldwide between 1990 and 2016.

Table

Table 1. Breast cancer age-standardized incidence rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	815.4	41.0	39.8-43.1	1681.9	45.6	43.6-48.2	1990-1995	1.5*	1995-2000	0.2*	2000-2016	0.1*	0.4*
High SDI	463.0	83.6	82.0-85.1	719.4	88.9	86.5-93.0	1990-1995	1.3*	1995-2000	0.2*	2000-2016	-0.1*	0.2*
High-middle SDI	153.1	37.1	36.0-38.6	329.0	46.5	42.9-50.5	1990-1995	3.2*	1995-2016	0.4*			0.9*
Middle SDI	116.0	19.3	18.1-22.1	408.8	33.2	30.4-36.0	1990-2000	2.6*	2000-2009	2.0*	2009-2016	1.5*	2.1*
Low-middle SDI	69.7	17.7	14.9-21.9	187.0	23.1	21.1-27.8	1990-1999	1.3*	1999-2010	0.4*	2010-2016	1.8*	1*
Low SDI	15.6	16.3	13.6-20.9	37.0	18.8	17.1-20.8	1990-1995	0.9*	1995-2010	0.3*	2010-2016	0.8*	0.5*

95% UI, 95% uncertainty interval; ASR, age-standardized rate; APC, annual percent change; AAPC, average annual percent change. *$P < 0.05$.

Table 2. Breast cancer age-standardized mortality rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	336.9	17.2	16.4-18.8	535.3	14.6	13.8-15.6	1990-1994	0.8*	1994-2002	-0.6*	2002-2016	-1.1*	-0.7*
High SDI	141.1	24.2	23.8-24.7	162.1	17.6	16.9-18.3	1990-1995	-0.6*	1995-2010	-1.6*	2010-2016	-1*	-1.3*
High-middle SDI	65.5	15.9	15.2-17.0	97.9	13.7	12.2-15.7	1990-1994	2.9*	1994-2004	-0.4*	2004-2016	-1.9*	-0.6*
Middle SDI	65.5	11.6	10.7-13.7	138.5	11.8	10.8-12.7	1990-2002	0.8*	2002-2016	-0.5*			0.1*
Low-middle SDI	50.7	13.6	11.4-17.3	104.5	13.8	12.1-17.2	1990-1999	0.7*	1999-2012	-0.6*	2012-2016	0.7*	0
Low SDI	13.9	15.7	13.0-20.2	31.9	17.6	15.7-19.9	1990-1996	0.9*	1995-2009	0	2009-2016	0.8*	0.5*

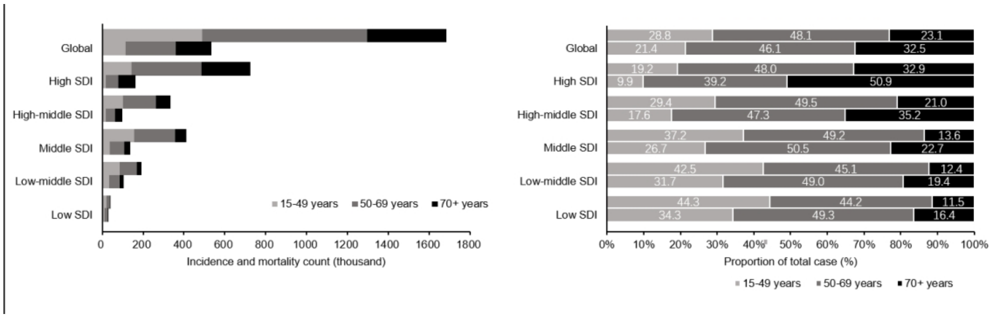

Figure 1

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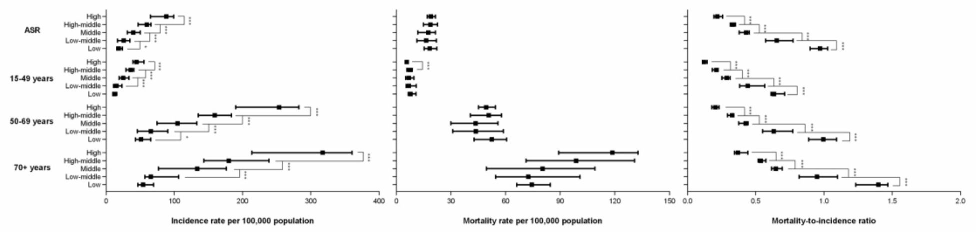

Figure 2

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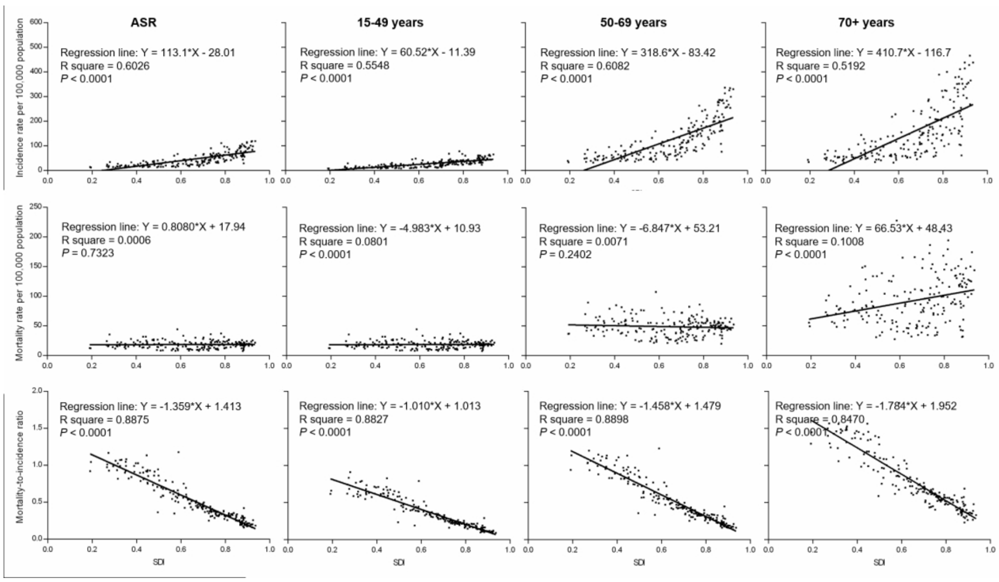

Figure 3

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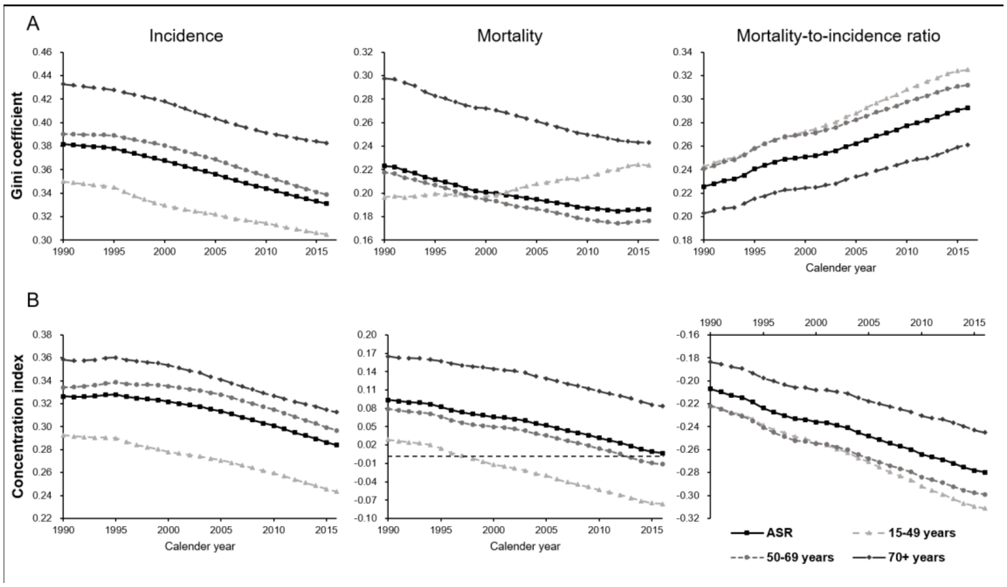

Figure 4

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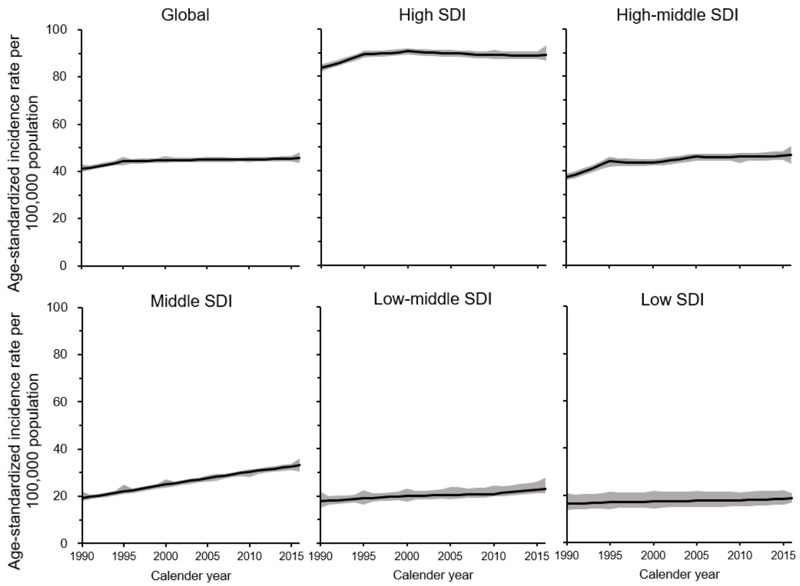
Supplementary figures and tables

Supplementary table 1. Breast cancer age-specific incidence rates in 1990, 2016 and the joinpoint trend analysis between 1990 and 2016 by SDI settings.

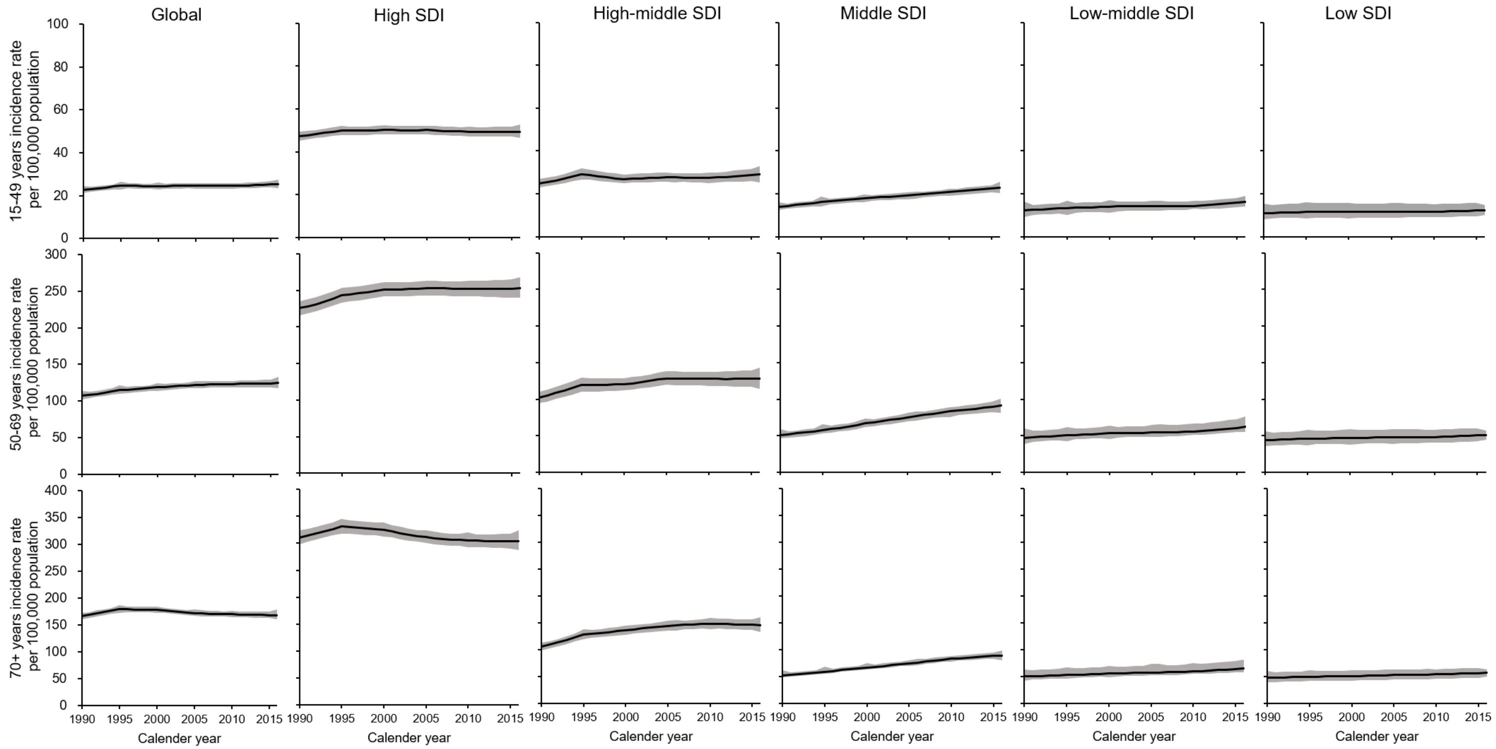
		1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Age	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	248.2	22.7	21.0-24.6	484.0	25.4	23.6-27.5	1990-1995	1.6*	1995-2011	0	2011-2016	0.7*	0.4*
	50-69 years	372.8	107.0	102.4-113.5	809.6	124.4	117.4-132.8	1990-1995	1.4*	1995-2005	0.6*	2005-2016	0.2*	0.6*
	70+ years	194.4	165.8	159.8-172.8	388.3	167.8	159.8-178.5	1990-1995	1.7*	1995-2008	-0.4*	2008-2016	-0.2*	0.1*
High SDI	15-49 years	111.6	47.3	45.3-49.4	137.8	49.4	46.6-52.6	1990-1995	1.0*	1995-2000	0.2	2000-2016	-0.1*	0.2*
	50-69 years	208.8	225.6	216.1-235.4	345.1	252.7	239.8-268.1	1990-1995	1.5*	1995-2000	0.8*	2000-2016	0*	0.5*
	70+ years	142.7	310.7	297.6-324.2	236.5	303.7	287.7-324.7	1990-1995	1.4*	1995-2008	-0.6*	2008-2016	-0.1*	-0.1*
High-middle SDI	15-49 years	48.8	24.8	23.0-26.9	96.9	29.0	25.3-33.0	1990-1995	3.3*	1995-2000	-1.5*	2000-2016	0.4*	0.6*
	50-69 years	76.1	101.6	94.5-110.0	163.0	128.1	113.7-143.2	1990-1994	3.5*	1994-2006	0.8*	2006-2016	0	0.9*
	70+ years	28.2	106.1	99.1-114.0	69.2	146.0	133.2-161.1	1990-1995	4.0*	1995-2007	1.2*	2007-2016	-0.1*	1.3*
Middle SDI	15-49 years	51.0	14.0	12.2-16.2	152.2	22.9	20.4-25.6	1990-1995	2.9*	1995-1999	2.2*	1999-2016	1.6*	1.9*
	50-69 years	50.5	50.8	46.2-59.0	201.0	91.0	81.0-100.8	1990-2004	2.7*	2004-2010	2.0*	2010-2016	1.5*	2.3*
	70+ years	14.4	52.8	48.5-62.3	55.6	89.8	80.8-98.7	1990-2000	2.4*	2000-2010	2.2*	2010-2016	1.2*	2.1*
Low-middle SDI	15-49 years	30.6	12.4	9.2-16.2	79.5	16.0	14.2-19.1	1990-2000	1.3*	2000-2010	0.2*	2010-2016	1.8*	1.0*
	50-69 years	31.4	47.1	38.9-59.8	84.4	61.9	54.7-76.1	1990-1999	1.3*	1999-2010	0.4*	2010-2016	1.9*	1.0*
	70+ years	7.6	50.6	42.9-63.7	23.1	65.2	57.8-82.6	1990-2000	1.0*	2000-2010	0.7*	2010-2016	1.4*	1.0*
Low SDI	15-49 years	7.0	10.9	8.1-15.5	16.4	12.2	10.2-14.6	1990-1995	1.1*	1995-2010	0.1*	2010-2016	0.8*	0.4*
	50-69 years	7.0	43.9	35.5-56.2	16.4	50.7	44.2-57.4	1990-1998	0.8*	1998-2010	0.3*	2010-2016	0.8*	0.5*
	70+ years	1.6	48.5	39.8-60.8	4.3	57.3	50.5-63.5	1990-2010	0.6*	2010-2016	0.8*			0.6*

Supplementary table 2. Breast cancer age-specific mortality rates in 1990, 2016 and the joinpoint trend analysis between 1990 and 2016 by SDI settings.

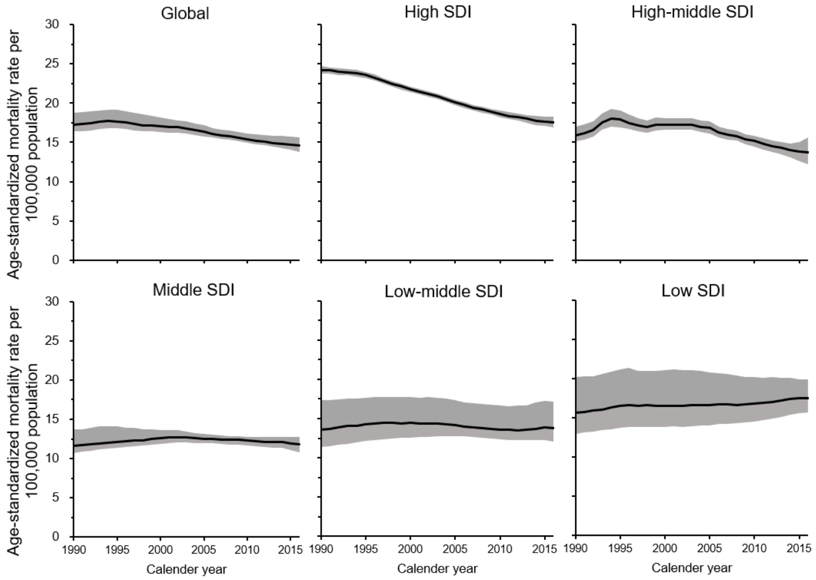
	Age	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
		Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	80.7	7.4	6.6-8.4	114.3	6.0	5.6-6.6	1990-1995	0.8*	1995-2012	-1.4*	2012-2016	-0.3*	-0.8*
	50-69 years	156.5	44.9	42.2-49.4	246.9	38.0	35.6-41.4	1990-1994	0.5*	1994-2003	-0.5*	2003-2016	-1.1*	-0.7*
	70+ years	99.6	85.6	81.8-92.2	174.1	74.5	69.9-80.5	1990-1994	0.9*	1994-2002	-0.5*	2002-2016	-1.0*	-0.5*
High SDI	15-49 years	20.9	8.9	8.6-9.1	16.0	5.7	5.4-6.0	1990-1994	-1.1*	1994-2012	-2.1*	2012-2016	-0.4	-1.7*
	50-69 years	59.8	64.2	62.2-66.3	63.5	46.2	43.9-48.5	1990-1995	-0.8*	1995-2012	-1.5*	2012-2016	-0.7*	-1.3*
	70+ years	60.4	128.9	123.9-134.0	82.6	99.5	93.2-106.4	1990-1995	0	1995-2009	-1.3*	2009-2016	-1.0*	-1.0*
High-middle SDI	15-49 years	14.5	7.5	6.9-8.2	17.2	5.2	4.5-5.9	1990-1994	2.7*	1994-2016	-2.2*			-1.5*
	50-69 years	33.0	43.9	40.7-48.0	46.2	36.5	31.4-43.2	1990-1994	2.7*	1994-2004	-0.4*	2004-2016	-2.1*	-0.7*
	70+ years	17.9	67.9	63.2-74.0	34.4	71.1	62.6-82.0	1990-1994	3.5*	1994-2003	0.9*	2003-2016	-1.2*	0.2*
Middle SDI	15-49 years	22.5	6.3	5.6-7.3	37.0	5.6	5.0-6.2	1990-2002	0.3*	2002-2008	-1.8*	2008-2016	-0.7*	-0.5*
	50-69 years	30.9	31.1	28.2-37.1	70.0	31.8	28.8-34.7	1990-2002	0.8*	2002-2012	-0.2*	2012-2016	-0.9*	0.1*
	70+ years	12.1	45.8	41.6-57.5	31.5	51.7	46.8-56.7	1990-2002	1.1*	2002-2011	0.2*	2011-2016	-0.7*	0.5*
Low-middle SDI	15-49 years	17.7	7.3	5.5-9.7	33.1	6.7	5.8-8.2	1990-1999	0.5*	1999-2012	-1.2*	2012-2016	0.6	-0.4*
	50-69 years	25.8	38.9	31.4-50.6	51.2	37.9	32.7-48.1	1990-1999	0.7*	1999-2012	-0.8*	2012-2016	0.5	-0.1*
	70+ years	7.2	47.8	37.8-66.7	20.2	57.5	47.8-74.6	1990-2001	0.9*	2001-2011	0.3*	2011-2016	1.0*	0.7*
Low SDI	15-49 years	5.0	7.9	5.8-11.4	10.9	8.3	6.7-10.3	1990-1995	1.2*	1995-2010	-0.3*	2010-2016	0.7*	0.2*
	50-69 years	7.0	44.4	35.7-58.2	15.7	49.1	42.1-56.5	1990-1996	1.0*	1996-2009	0	2009-2016	0.7*	0.4*
	70+ years	1.9	59.9	48.7-76.3	5.2	72.6	62.3-82.3	1990-1995	1.0*	1995-2009	0.5*	2009-2016	1.1*	0.8*



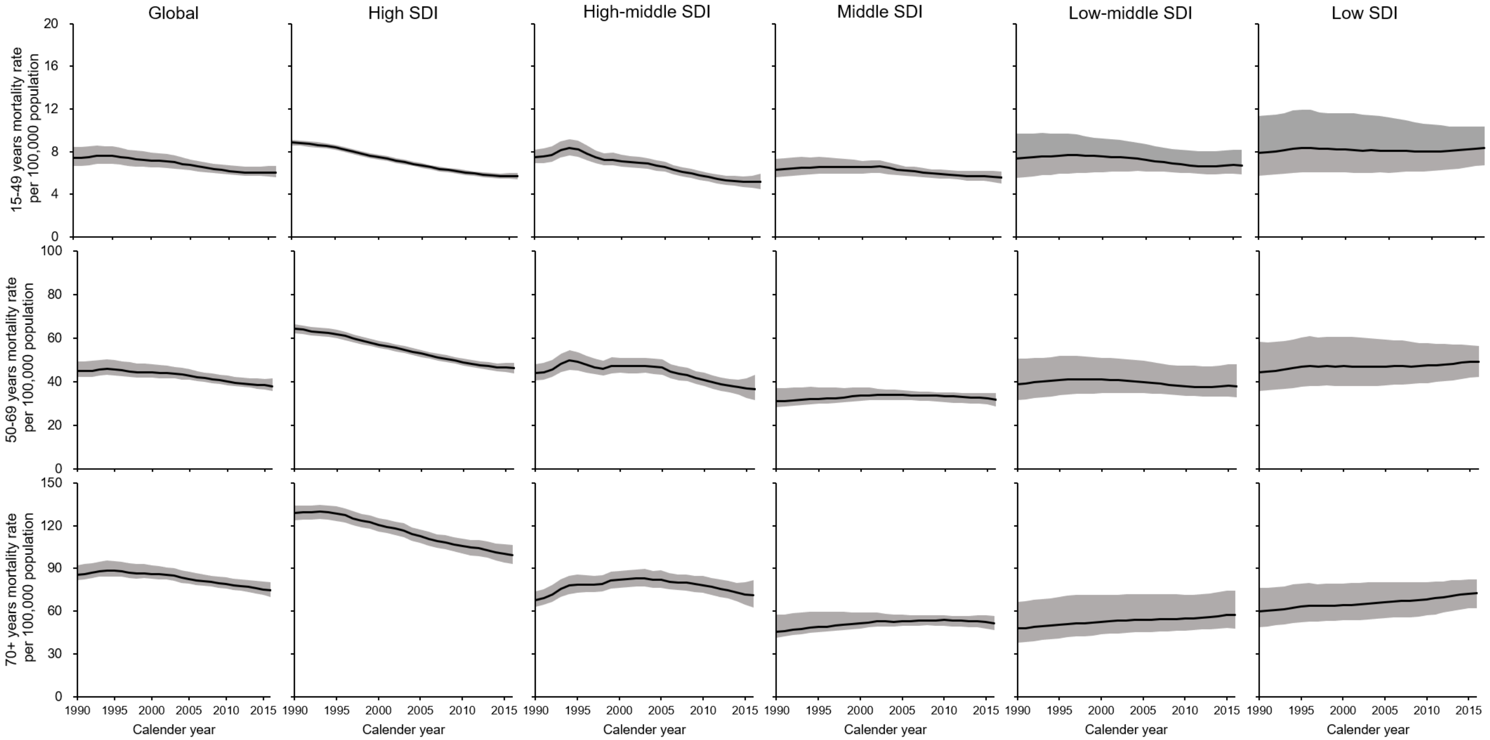
Supplementary figure 1A. Trends in breast cancer age-standardized incidence rate (ASIR) according to SDI settings, 1990-2016. The black lines represent the estimated ASIRs, and areas shaded in gray represent 95% uncertainty intervals.



Supplementary figure 1B. Trends in incidence rate for 15-49, 50-69 and 70+ age groups according to SDI settings, 1990-2016. The black lines represent the estimated age-specific rates adjusted within each group following the new world population age-standard, and areas shaded in gray represent the 95% uncertainty intervals.



Supplementary figure 2A. Trends in breast cancer age-standardized mortality rate (ASMR) according to SDI settings, 1990-2016. The black lines represent the estimated ASMRs, and areas shaded in gray represent 95% uncertainty intervals.



Supplementary figure 2B. Trends in mortality rate for 15-49, 50-69 and 70+ age groups according to SDI settings, 1990-2016. The black lines represent the estimated age-specific rates adjusted within each group following the new world population age-standard, and areas shaded in gray represent the 95% uncertainty intervals.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#4
Objectives	3	State specific objectives, including any prespecified hypotheses	#4
Methods			
Study design	4	Present key elements of study design early in the paper	#5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	#5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#5-6
Bias	9	Describe any efforts to address potential sources of bias	#5-6
Study size	10	Explain how the study size was arrived at	#5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#6-7
		(*b*) Describe any methods used to examine subgroups and interactions	#6-7
		(*c*) Explain how missing data were addressed	#6-7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	#6-7
		(*e*) Describe any sensitivity analyses	#6-7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#7-9
		(b) Give reasons for non-participation at each stage	#7-9
		(c) Consider use of a flow diagram	#7-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#7-9
		(b) Indicate number of participants with missing data for each variable of interest	#7-9
Outcome data	15*	Report numbers of outcome events or summary measures	#7-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#7-9
		(*b*) Report category boundaries when continuous variables were categorized	#7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	#9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	#11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	#9-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#12-13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Keywords:	breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini coefficient, concentration index

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Global Patterns and Trends in the Breast Cancer Incidence and Mortality According to Socio-demographic Indices: An Observational Study Based on the Global Burden of Diseases

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Abstract:

Objectives: Disparities in the global burden of breast cancer have been identified. We aimed to investigate recent patterns and trends in the breast cancer incidence and associated mortality. We also assessed breast cancer-related health inequalities according to socioeconomic development factors.

Design: An observational study based on the Global Burden of Diseases.

Methods: Estimates of breast cancer incidence and mortality during 1990–2016 were obtained from the Global Health Data Exchange database. Subsequently, data obtained in 2016 were described using the age-standardized and age-specific incidence, mortality and mortality-to-incidence (MI) ratios according to socio-demographic index (SDI) levels. Trends were assessed by measuring the annual percent change using the joinpoint regression. The Gini coefficients and concentration indices were used to identify between-country inequalities.

Results: Countries with higher SDI levels had worse disease incidence burdens in 2016, whereas inequalities in the breast cancer incidence had decreased since 1990. Opposite trends were observed in the mortality rates of high and low SDI countries. Moreover, the decreasing concentration indices, some of which became negative, among people aged 15–49 and 50–69 years suggested an increase in the mortality burdens in undeveloped regions. Conversely, inequality related to the MI ratio increased. In 2016, the MI ratios exhibited distinct gradients from high to low SDI regions across all age groups.

Conclusions: The patterns and trends in breast cancer incidence and mortality closely correlated

with the SDI levels. Our findings highlighted the primary prevention of breast cancer in high SDI countries with a high disease incidence and the development of cost-effective diagnostic and treatment interventions for low SDI countries with poor MI ratios as the two pressing needs in the next decades.

Keywords: breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini coefficient, concentration index

Article summary

Strengths and limitations of this study:

- This study provides the first overview of current global patterns and long-term trends in breast cancer burdens stratified according to socio-demographic development.
- The Gini coefficient and concentration index were used to evaluate the extent, trend, and concentration of health inequalities caused by breast cancer.
- The study was limited by the use of secondary estimated data from the Global Burden of Disease database, as the estimates for some countries with poor-quality raw data may have been biased.

Introduction

Breast cancer is the most common type of cancer worldwide and the leading cause of cancer-related deaths among women, with an estimated 2.4 million new cases and 523,000 deaths reported in 2015[1]. A woman's place of residence and socioeconomic status are significant determinants of the odds of developing breast cancer and the ultimate survival outcome[1]. The breast cancer incidence rate is higher in high-income countries than in low- and middle-income countries (LMICs)[1-3]. In many high-income countries, a better awareness of the risk factors, regular mammography screening, and sufficient and effective medical services have led to significant decrease in breast cancer mortality rates in recent decades and stable or even decreasing incidence rates since 2000. However, breast cancer is not restricted to high-income countries. The low cancer incidence rates in LMICs have not necessarily translated to lower cancer-related mortality rates[3-5]. Both the breast cancer incidence and related mortality have increased in many resource-poor settings or countries, partially due to changes in reproductive patterns and delays in diagnosis and treatment, which are independent of an increase in breast cancer awareness[6, 7].

Disparities in the global burden of breast cancer have been identified, especially among counties with different levels of development. Global health policy makers rely on understanding of the exact correlations between the disease burden and socioeconomic status to formulate appropriate measures according to local conditions. The Institute for Health Metrics and Evaluation first introduced the socio-demographic index (SDI) in the Global Burden of Disease Study 2015 (GBD 2015) as a quantitative measure of development in a country or region[8]. This study aimed to describe current patterns and trends in breast cancer incidence and mortality among countries according to national-level wellbeing by combining the latest SDI data with breast cancer incidence and mortality data collected between 1990 and 2016. This approach would enable a comprehensive investigation of the distribution of breast cancer-associated health inequalities and related changes according to the level of national development.

Materials and Methods

Breast cancer was defined using code C50 from the International Classification of Disease-Revision, 10th edition. Incidence and mortality data from 195 individual countries across 5 predefined SDI groups during 1990–2016 were collected from the Global Health Data Exchange database[5]. The annual incidence and mortality rates for subjects aged 15 to 95+ years were extracted for each involved country and stratified into 5-year age brackets. Detailed methods for estimating the age-standardized incidence and mortality rates (ASIR and ASMR, respectively) per 100,000 women in a population were described in the GBD 2016 reports[3, 4]. Women aged 50–69 years comprised the largest population participating in regular screening programs. We further calculated the age-specific incidence and mortality rates per 100,000 women into three age subgroups: 15–49, 50–69 and 70+ (including 70) years, and these rates were adjusted according to the new world population age-standard[3]. The mortality-to-incidence (MI) ratio was calculated by dividing the breast cancer mortality rate for a given year, age group, country, and SDI group by the corresponding incidence rate.

Patient and Public Involvement

Neither patients nor the public were involved in the recruitment and conduct of this study.

Ethics approval

Ethical approval was not obtained because the data included in this study were publicly available.

SDI

The SDI, a comparable metric of overall development, was calculated using the lag-distributed income per capita, average years of education in the population older than 15 years, and total fertility rate, with equal weighting of these variables[9]. The SDI is expressed using a scale of 0 to 1, with a greater value indicating a higher level of development. SDI data from the 195 countries involved in the study during 1990–2016 were obtained from the Global Health Data Exchange database[5]. Countries were classified into the following quintiles based on their SDI values in 2016: high, high-middle, middle, low-middle, and low SDI. Detailed methods describing the calculation of SDI and the selection of the quintile cutoffs have been previously reported[1, 3].

Gini coefficient and concentration index

We adopted the Gini coefficient and concentration index, which are used in the field of economics, to measure breast cancer-associated health inequalities in our study[10, 11]. The Gini coefficient is calculated based on the Lorenz curve. The coefficient ranges between 0 and 1, with 0 and 1 representing perfect equality and total inequality, respectively[11]. The annual ASIRs, ASMRs, age-specific incidence rates, age-specific mortality rates, and MI ratios of breast cancer from the 195 included countries were used to calculate the Gini coefficients and describe trends in health inequality between countries from 1990 to 2016. The concentration index, which is derived from the concentration curve, is a common measure of socioeconomic-related health inequality[12]. The concentration indices were calculated by correlating the abovementioned breast cancer metrics with the corresponding national SDIs. The concentration index values range between -1 and +1. A positive or negative concentration index value indicated that the breast cancer disease burden was more concentrated in countries with high or low levels of development, respectively, as measured by the SDI[12]. The absolute index value was related to the degree of a “pro-developed” or “pro-underdeveloped” distribution of health limitations. A value of zero indicated an absence of inequality associated with the socioeconomic gradient rather than an absolute absence of inequality.

Statistical analyses

We performed one-way ANOVA, followed by pairwise comparisons with the Tamhane T2 test to compare variables with normal distributions but heterogeneous variances, such as the incidence, mortality and MI ratio, across five SDI-based country groups[13]. A linear regression model was used to test the correlations between indicators of the breast cancer burden and the SDI values. A joinpoint piecewise linear regression analysis was performed to identify the time points corresponding to significant changes and identify temporal trends in the age-standardized and age-specific incidence and mortality rates between 1990 and 2016[14]. Default parameters were used for all analyses except for the minimum number of data points between two joints or at either end of the data; these two values were set to 5. The maximum number of joinpoints was set to 2 to avoid over-fitting at the truncating points. The best-fit point corresponding to a significant change in the rate was assessed using a permutation test, and the *P* value for each test was estimated using Monte Carlo methods[14]. Statistics relating to the annual percent change (APC) for each segment and average annual percent change (AAPC) for the overall period were summarized using the optimal joinpoint model. All joinpoint trend analyses were performed using joinpoint statistical software (Version 4.5.0.1; Surveillance Research Program of the United States National Cancer Institute, Bethesda, MD, USA)[15]. The Gini coefficient and concentration index values were computed using the AINEQUAL[16] and CONINDEX modules[17] of Stata 14.0 software (Stata Corp, College Station, TX, USA). Other statistical analyses were performed using SPSS 20.0 software (IBM Corp., Armonk, NY, USA).

Results

Current profiles in breast cancer incidence and mortality rates according to SDIs

Figure 1 presents the distribution of counts and proportions of new breast cancer cases and related deaths in the 5 SDI groups during the year 2016. Approximately 719,000 new cases were reported in high SDI countries, and this value was about 20 times higher than the 37,000 new cases reported in low SDI countries. Moreover, 162,000 and 32,000 deaths were reported in these groups, respectively. Approximately half of all new breast cancer cases occurred in women aged 50–69 years across all SDI groups. In middle, low-middle, and low SDI countries, more than a third of new breast cancer cases were identified in women aged 15–49 years, and this group also had a higher proportion of related deaths. In contrast, in high SDI countries, people age 70+ years accounted for 50.9% of all reported breast cancer-related deaths.

One-way ANOVA suggested significant differences in both the age-standardized and age-specific incidence rates and MI ratios ($P < 0.01$) but not in the mortality rates among countries belonging to different SDI groups. Pairwise comparisons showed the mortality rates were not proportional to the corresponding high incidence rates in countries with higher level of development indicated by SDI, and the lowest MI ratios were observed in high SDI countries (Figure 2). In all age groups, positive relationships existed between the incidence rates and SDI values, and negative relationships existed between the MI ratios and SDI values (Figure 3). Moreover, the MI ratios exhibited well-fitting linear relationships in all age groups, whereas the incidence and mortality rates in older age groups were more scattered among countries with different SDIs.

Temporal trends in breast cancer incidence and mortality across SDI groups

According to the joinpoint trend analysis (Table 1), the ASIRs in high and high-middle SDI groups plateaued after rapidly increasing in the early 1990s. In the high SDI group, the ASIR even exhibited a declining trend of 0.1% per year since 2000. In contrast, significant increases in the ASIRs were observed in the middle, low-middle and low SDI groups over the whole study period (Supplementary Figure 1A). The AAPC in ASIR was 2.1% for the middle SDI group, and this was the highest increase among the SDI groups. The trends in incidence rate changes among women aged 15–49, 50–69, and 70+ years were comparable with the ASIR values across the SDI groups (Supplementary Table 1 and Supplementary Figure 1B).

Changes in the ASMR varied across the SDI groups, as shown in Table 2 and Supplementary Figure 2A. In the high SDI group, the ASMR decreased continuously from 24.2 in 1990 to 17.6 in 2016, with an AAPC of -1.3%. In the high-middle SDI group, the ASMR began to decline in 1994, with an accelerated decrease (APC: -1.9%) between 2004 and 2016. In the middle SDI group, the ASMR also decreased slightly from 2002 to 2016, with an average decrease of 0.5% per year. Opposite trends were observed in the low-middle (2002–2016, APC: 0.7%) and low SDI groups (2009–2016, APC: 0.8%), especially in more recent years. Although the patterns of change in the three age groups were similar to the ASMR in each SDI group, the degrees of change differed among the groups (Supplementary Table 2 and Supplementary Figure 2B). For example, among subjects aged 70+ years, we observed lesser decreases and greater increases in the mortality rate in more and less developed regions, respectively.

Global health inequality related to breast cancer

The Gini coefficients for the incidence of breast cancer continuously decreased from 1990 to 2016 (Figure 4A). The values calculated from the ASIRs and incidence rates among women aged 15–49, 50–69, and 70+ years decreased to 0.33, 0.30, 0.34 and 0.38 by 2016, respectively, from starting values of 0.38, 0.35, 0.39, and 0.43 in 1990, respectively. Similarly, the Gini coefficients calculated using the mortality rates exhibited markedly declining trends over the same period in all age groups, except those aged 15–49 years. In contrast, the Gini coefficients calculated using the age-standardized MI ratio distributions increased, from 0.23 in 1990 to 0.29 in 2016.

In 1990, all the concentration indices based on the breast cancer age-standardized and age-specific incidence and mortality rates exceeded zero, suggesting that the inequalities associated with socioeconomic development were more concentrated in countries with higher levels of development (as indicated by SDI). Moreover, the concentration indices were higher among subjects aged 70+ years than in other groups. Both the concentration indices for the incidence and mortality rate decreased between 1990 and 2016, and the rate of decrease began to accelerate in the late 1990s (Figure 4B). The concentration indices for mortality rates in the age groups of 15–49 and 50–69 years decreased below zero and became negative in 1998 and 2013, respectively. In contrast, the concentration indices based on age-standardized MI ratios and age-specific rate ratios for age groups of 15–49, 50–69, and 70+ years were already below zero in 1990, with values of -0.21, -0.22, -0.22, and -0.18, respectively. By 2016, these values had decreased to -0.28, -0.31, -0.30, and -0.25, respectively.

Discussion

Socioeconomic development-associated inequalities in the global incidence of breast cancer have continued to decrease since 1990. However, countries with higher levels of development according to the SDI reported a worse burden of breast cancer incidence by 2016. Consistent with the opposite trends in mortality rates between countries with high and low SDI values, the mortality concentration indices among women aged 15–49 and 50–69 years have become negative in recent years. This phenomenon suggests a shift in the concentration of the mortality burden from developed to undeveloped countries. Conversely, both the overall inequality and inequality associated with socioeconomic development, which was calculated using the MI ratio, increased from 1990 to 2016. In 2016, the MI ratio distribution exhibited a distinct gradient from high to low SDI countries across all age groups.

The availability of epidemiological data from individual countries has led to a prevailing perception that inequalities exist in the global breast cancer incidence, especially between high-income countries and LMICs[18-21]. However, there remains a paucity of quantitative evidence regarding the relationship between the global breast cancer burden and national levels of socioeconomic development. According to the GLOBOCAN 2012 estimates, the breast cancer incidence burden was distributed among countries at different human development index (HDI) levels, with obvious disparities[2]. The results of that report are consistent with our results, which were based on the SDI and data from the GBD 2016 study. We observed that the overall inequality in the breast cancer incidence had not yet been eliminated and remained concentrated in countries with high SDI levels. This higher prevalence of breast cancer is somewhat associated with the so-called western lifestyle (i.e., specific reproductive patterns and excessive body weight)[22, 23], and thus can be used as a marker of the extent of development. Our trend analyses demonstrated rapid increases in the breast cancer incidence rates of countries classified in the middle SDI group. This result suggests that countries with SDI levels near the middle of the spectrum were undergoing rapid social and economic changes during the study period[24]. In many LMICs, the burdens of infection-related cancers, including cervical, gastric, and liver cancer, remained higher than those of breast cancer[1, 2]. Moreover, high-income countries have generally implemented mammographic screening programs, especially for women aged 50–69 years[25-27]. Consistently, our age-based subgroup analysis confirmed a transient increase in the incidence of breast cancer among women aged 50–69 years and a subsequent decrease among those aged 70+ years in countries with high SDI values.

The mortality rates did not differ significantly between low and high SDI countries. Inequalities in breast cancer deaths were possibly offset by better clinical outcomes in more developed countries due to early diagnosis and the development of advanced treatments; in contrast, the situation in most LMICs were characterized by a low incidence of breast cancer but limited access to health cares[28, 29]. Therefore, the mortality rates do not represent the exact trends and current statuses of the burdens of cancer-related death. Cancer survival is another important indicator used to evaluate the malignancy-related death burden. According to data from 59 countries in the CONCORD-2 study[30], the 5-year survival rates of patients diagnosed with breast cancer during 2005–2009 were ≥85% in North America, Australia, Israel, Brazil, and most Northern and Western European countries but ≤60% in many LMICs, such as India, Mongolia, Algeria and South Africa. However, little comprehensive survival data were available from most countries, especially those with limited resources. Accordingly, the determination of the effects of socioeconomic development-associated inequalities on the survival rates of breast cancer patients and comparisons of current survival statuses among various countries across the world remained critical issues. In this study, we analyzed the trends in inequality of the breast cancer MI ratio, a marker used to estimate the extent to which actual mortality differs from the expected mortality relative to disease incidence; the marker has been suggested as an approximation of cancer survival[31-33]. Our results suggest increasing disparities according to breast cancer MI ratios among countries with different levels of development.

The HDI, a metric comprising the life expectancy at birth, mean and expected years of education, and gross national income per capita[34], was used to investigate the correlations between macro-socioeconomic determinants and national disease burdens[2, 28, 35]. However, this index is not ideal for evaluating the effects of socioeconomic development on health because the measure relies on the overall health (i.e., life expectancy at birth), which could introduce bias. The SDI was initially developed in the GBD 2015 study, to determine the placement of countries or geographic areas on the spectrum of social development[8]. Given the role of reproductive patterns as risk factors for breast cancer[22], the SDI, a measure based on measures of income, education, and fertility rate, might be more appropriate than the HDI when assessing the degree of influence of the socioeconomic status on global patterns and trends in health inequality associated with breast cancer.

To our knowledge, this study provides the first overview of global patterns and trends in breast cancer incidence and mortality according to the SDI. However, our results should be interpreted in light of the following limitations. First, this study is subject to the limitations of the GBD 2016 study such as the data sources and statistical assumptions, as detailed in the related reports[3, 4]. For most LMICs, the estimates, particularly the MI ratios, might have been biased due to poor-quality raw data. Future studies will require better primary data from nation-wide observational studies or cancer registries. Second, the joinpoint analysis is particularly sensitive to parameter settings. Accordingly, trends in the patterns of incidence and mortality may change if the parameters are changed or more data are analyzed. Third, the GBD 2016 database did not provide regional data within each country or information about disease stages and histopathological characteristics. In the United States, for example, nation-wide distributions and trends in breast cancer burden can differ by ethnicity, state, disease stage and intrinsic subtype[36, 37]. Therefore, more studies are needed to understand the global disparities more fully and to eliminate biases in the data.

Conclusions

The patterns and trends in breast cancer incidence and mortality closely correlated with the SDI levels. The health inequality associated with the breast cancer incidence according to the SDI has been decreasing since 1990. Countries with middle-level SDI values, which may have been experiencing shifts in economic and lifestyle factors, exhibited increasing incidence rates of breast cancer. Nonetheless, the incidence burden in 2016 remained more concentrated in countries with higher SDI levels. These findings emphasize that public health clinicians and cancer control specialists should pay more attention to the primary prevention of breast cancer, especially in most developed countries with high incidence. In low-middle and low SDI countries, the actual breast cancer mortality rates differed greatly from the expected mortality rates based on the corresponding low incidence rates. Public health planners should implement more sensitive and cost-effective detection and treatment interventions to counteract the premature deaths caused by breast cancer, particularly in less developed countries with limited healthcare resources.

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Competing interests

The authors declared no conflict of interest.

Data sharing statement

The data used in this study is collected from the Global Health Data Exchange database. Available from: http://www.healthdata.org/gbd-results-tool.

Authors' contributions

Kaimin Hu designed the study, extracted and analyzed the data and prepared the figures. Peili Ding and Yinan Wu wrote the first draft of the manuscript. Tao Pan and Wei Tian revised the paper critically. Suzhan Zhang was the principle investigator and designed the study. All authors commented on manuscript drafts and approved the final version.

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Figure legend:

Figure 1. Distribution of breast cancer incidence and mortality counts and proportions by age at the global level and SDI quintiles in 2016.

Figure 2. Patterns for breast cancer, in terms of age-standardized and age-specific (A) incidence rates, (B) mortality rates and (C) MI ratios by SDI group in 2016. Black squares represent the medians of all rates from the countries included in each SDI level. Lines denote the interquartile ranges. $^{*}P < 0.05$, $^{***}P < 0.001$.

Figure 3. Relationship between the incidence rates, mortality rates, MI ratios and SDI levels by age. The best-fitted line according to linear regression analysis was shown.

Figure 4. Trends in (A) the Gini coefficients and (B) concentration indices calculated based on health metrics of breast cancer, in terms of age-standardized and age-specific incidence rates, mortality rates and MI ratios, across 195 countries worldwide between 1990 and 2016.

Table

Table 1. Breast cancer age-standardized incidence rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	815.4	41.0	39.8-43.1	1681.9	45.6	43.6-48.2	1990-1995	1.5*	1995-2000	0.2*	2000-2016	0.1*	0.4*
High SDI	463.0	83.6	82.0-85.1	719.4	88.9	86.5-93.0	1990-1995	1.3*	1995-2000	0.2*	2000-2016	-0.1*	0.2*
High-middle SDI	153.1	37.1	36.0-38.6	329.0	46.5	42.9-50.5	1990-1995	3.2*	1995-2016	0.4*			0.9*
Middle SDI	116.0	19.3	18.1-22.1	408.8	33.2	30.4-36.0	1990-2000	2.6*	2000-2009	2.0*	2009-2016	1.5*	2.1*
Low-middle SDI	69.7	17.7	14.9-21.9	187.0	23.1	21.1-27.8	1990-1999	1.3*	1999-2010	0.4*	2010-2016	1.8*	1*
Low SDI	15.6	16.3	13.6-20.9	37.0	18.8	17.1-20.8	1990-1995	0.9*	1995-2010	0.3*	2010-2016	0.8*	0.5*

95% UI, 95% uncertainty interval; ASR, age-standardized rate; APC, annual percent change; AAPC, average annual percent change. *$P < 0.05$.

Table 2. Breast cancer age-standardized mortality rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	336.9	17.2	16.4-18.8	535.3	14.6	13.8-15.6	1990-1994	0.8*	1994-2002	-0.6*	2002-2016	-1.1*	-0.7*
High SDI	141.1	24.2	23.8-24.7	162.1	17.6	16.9-18.3	1990-1995	-0.6*	1995-2010	-1.6*	2010-2016	-1*	-1.3*
High-middle SDI	65.5	15.9	15.2-17.0	97.9	13.7	12.2-15.7	1990-1994	2.9*	1994-2004	-0.4*	2004-2016	-1.9*	-0.6*
Middle SDI	65.5	11.6	10.7-13.7	138.5	11.8	10.8-12.7	1990-2002	0.8*	2002-2016	-0.5*			0.1*
Low-middle SDI	50.7	13.6	11.4-17.3	104.5	13.8	12.1-17.2	1990-1999	0.7*	1999-2012	-0.6*	2012-2016	0.7*	0
Low SDI	13.9	15.7	13.0-20.2	31.9	17.6	15.7-19.9	1990-1996	0.9*	1995-2009	0	2009-2016	0.8*	0.5*

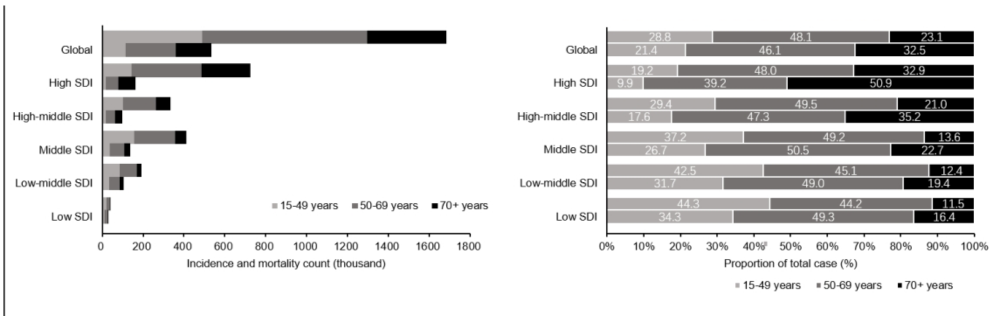

Figure 1

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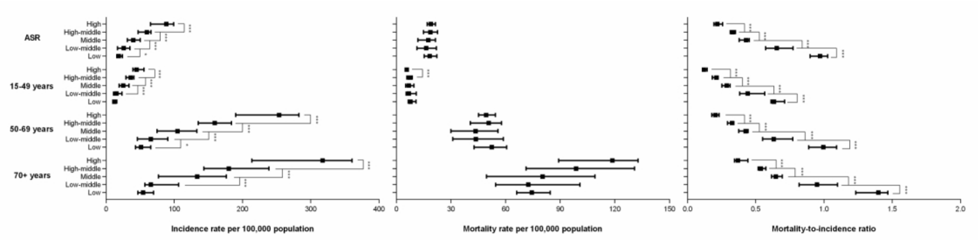

Figure 2

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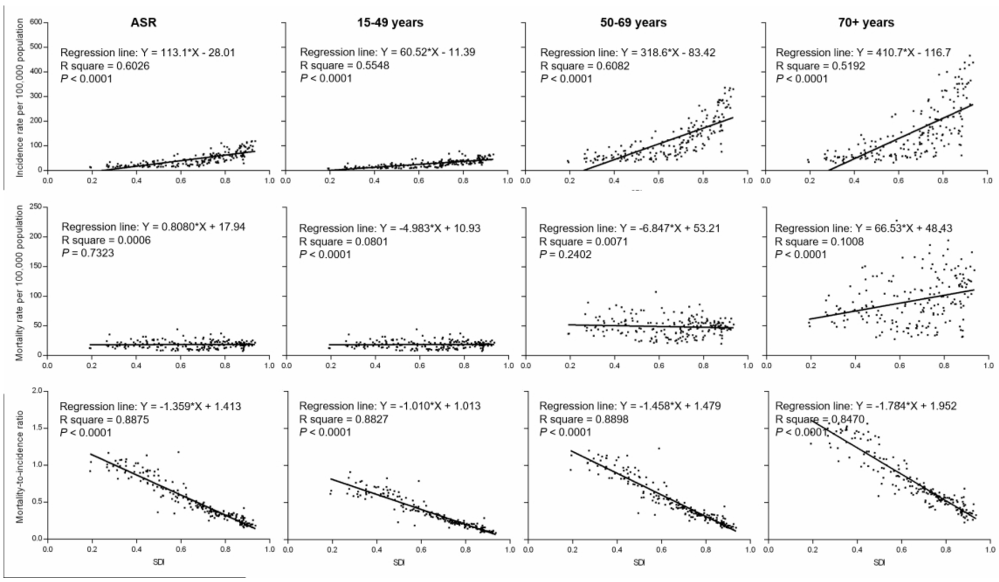

Figure 3

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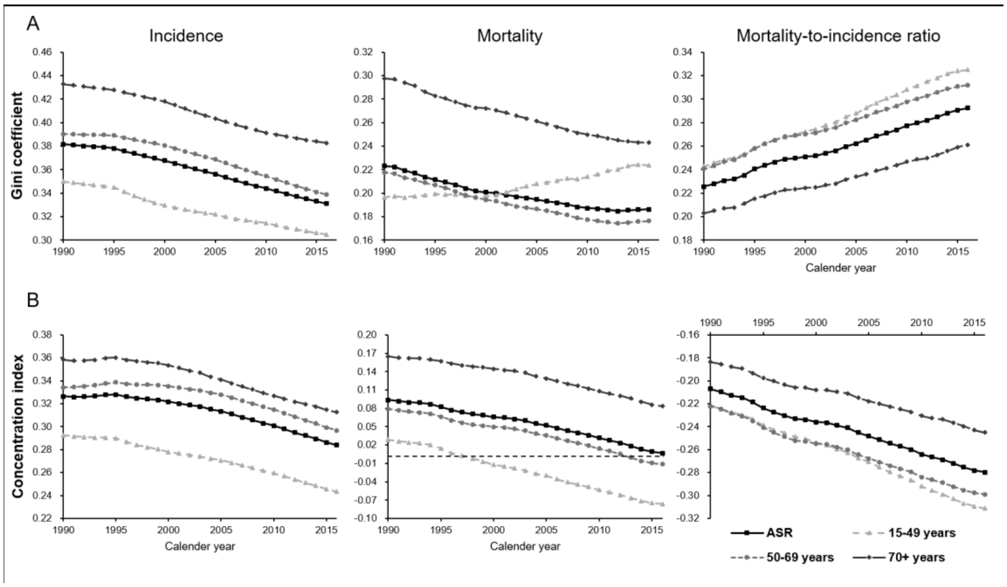

Figure 4

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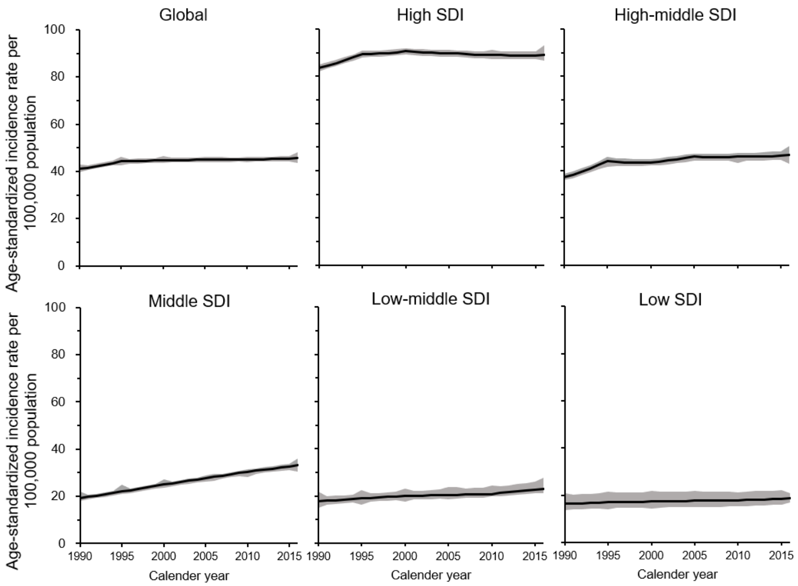
Supplementary figures and tables

Supplementary table 1. Breast cancer age-specific incidence rates in 1990, 2016 and the joinpoint trend analysis between 1990 and 2016 by SDI settings.

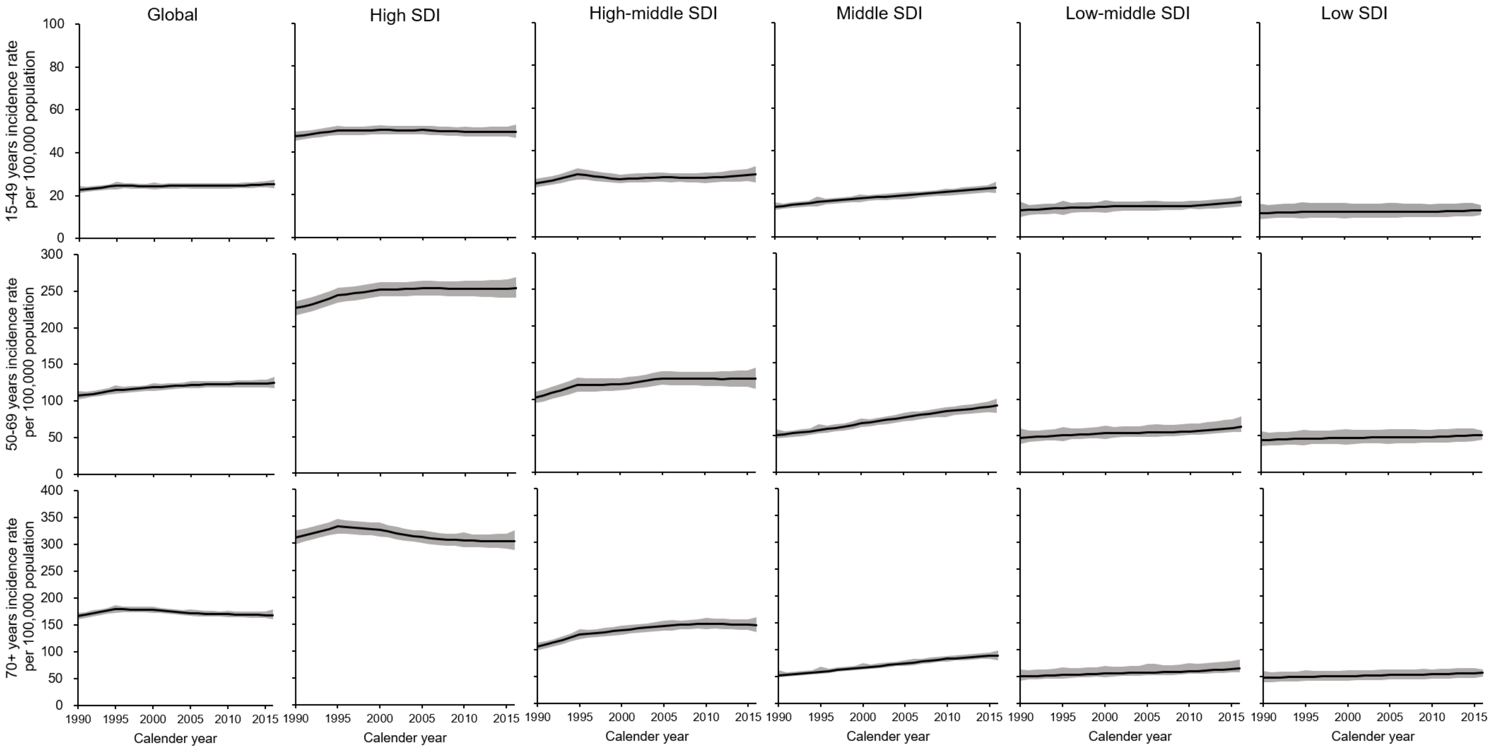
		1990			2016			Trend1		Trend2		Trend3		AAPC (%)
	Age	Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	248.2	22.7	21.0-24.6	484.0	25.4	23.6-27.5	1990-1995	1.6*	1995-2011	0	2011-2016	0.7*	0.4*
	50-69 years	372.8	107.0	102.4-113.5	809.6	124.4	117.4-132.8	1990-1995	1.4*	1995-2005	0.6*	2005-2016	0.2*	0.6*
	70+ years	194.4	165.8	159.8-172.8	388.3	167.8	159.8-178.5	1990-1995	1.7*	1995-2008	-0.4*	2008-2016	-0.2*	0.1*
High SDI	15-49 years	111.6	47.3	45.3-49.4	137.8	49.4	46.6-52.6	1990-1995	1.0*	1995-2000	0.2	2000-2016	-0.1*	0.2*
	50-69 years	208.8	225.6	216.1-235.4	345.1	252.7	239.8-268.1	1990-1995	1.5*	1995-2000	0.8*	2000-2016	0*	0.5*
	70+ years	142.7	310.7	297.6-324.2	236.5	303.7	287.7-324.7	1990-1995	1.4*	1995-2008	-0.6*	2008-2016	-0.1*	-0.1*
High-middle SDI	15-49 years	48.8	24.8	23.0-26.9	96.9	29.0	25.3-33.0	1990-1995	3.3*	1995-2000	-1.5*	2000-2016	0.4*	0.6*
	50-69 years	76.1	101.6	94.5-110.0	163.0	128.1	113.7-143.2	1990-1994	3.5*	1994-2006	0.8*	2006-2016	0	0.9*
	70+ years	28.2	106.1	99.1-114.0	69.2	146.0	133.2-161.1	1990-1995	4.0*	1995-2007	1.2*	2007-2016	-0.1*	1.3*
Middle SDI	15-49 years	51.0	14.0	12.2-16.2	152.2	22.9	20.4-25.6	1990-1995	2.9*	1995-1999	2.2*	1999-2016	1.6*	1.9*
	50-69 years	50.5	50.8	46.2-59.0	201.0	91.0	81.0-100.8	1990-2004	2.7*	2004-2010	2.0*	2010-2016	1.5*	2.3*
	70+ years	14.4	52.8	48.5-62.3	55.6	89.8	80.8-98.7	1990-2000	2.4*	2000-2010	2.2*	2010-2016	1.2*	2.1*
Low-middle SDI	15-49 years	30.6	12.4	9.2-16.2	79.5	16.0	14.2-19.1	1990-2000	1.3*	2000-2010	0.2*	2010-2016	1.8*	1.0*
	50-69 years	31.4	47.1	38.9-59.8	84.4	61.9	54.7-76.1	1990-1999	1.3*	1999-2010	0.4*	2010-2016	1.9*	1.0*
	70+ years	7.6	50.6	42.9-63.7	23.1	65.2	57.8-82.6	1990-2000	1.0*	2000-2010	0.7*	2010-2016	1.4*	1.0*
Low SDI	15-49 years	7.0	10.9	8.1-15.5	16.4	12.2	10.2-14.6	1990-1995	1.1*	1995-2010	0.1*	2010-2016	0.8*	0.4*
	50-69 years	7.0	43.9	35.5-56.2	16.4	50.7	44.2-57.4	1990-1998	0.8*	1998-2010	0.3*	2010-2016	0.8*	0.5*
	70+ years	1.6	48.5	39.8-60.8	4.3	57.3	50.5-63.5	1990-2010	0.6*	2010-2016	0.8*			0.6*

Supplementary table 2. Breast cancer age-specific mortality rates in 1990, 2016 and the joinpoint trend analysis between 1990 and 2016 by SDI settings.

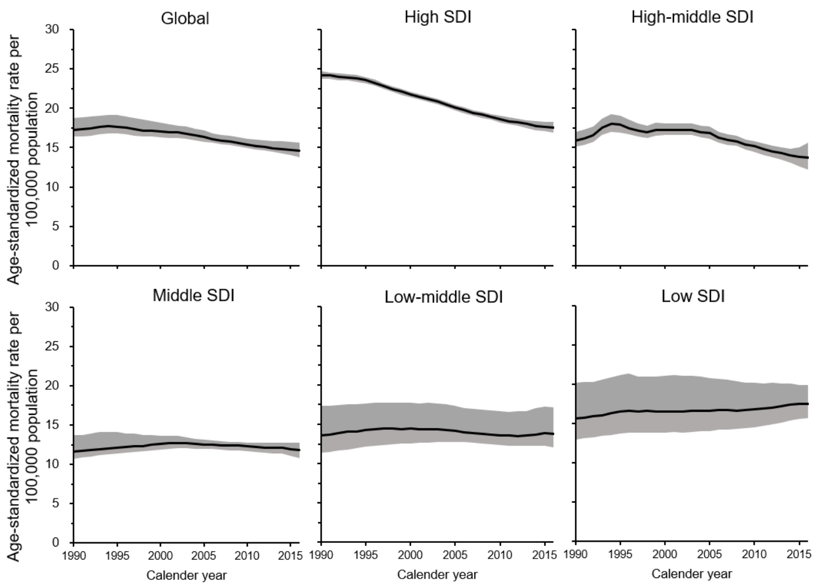
	Age	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
		Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	80.7	7.4	6.6-8.4	114.3	6.0	5.6-6.6	1990-1995	0.8*	1995-2012	-1.4*	2012-2016	-0.3*	-0.8*
	50-69 years	156.5	44.9	42.2-49.4	246.9	38.0	35.6-41.4	1990-1994	0.5*	1994-2003	-0.5*	2003-2016	-1.1*	-0.7*
	70+ years	99.6	85.6	81.8-92.2	174.1	74.5	69.9-80.5	1990-1994	0.9*	1994-2002	-0.5*	2002-2016	-1.0*	-0.5*
High SDI	15-49 years	20.9	8.9	8.6-9.1	16.0	5.7	5.4-6.0	1990-1994	-1.1*	1994-2012	-2.1*	2012-2016	-0.4	-1.7*
	50-69 years	59.8	64.2	62.2-66.3	63.5	46.2	43.9-48.5	1990-1995	-0.8*	1995-2012	-1.5*	2012-2016	-0.7*	-1.3*
	70+ years	60.4	128.9	123.9-134.0	82.6	99.5	93.2-106.4	1990-1995	0	1995-2009	-1.3*	2009-2016	-1.0*	-1.0*
High-middle SDI	15-49 years	14.5	7.5	6.9-8.2	17.2	5.2	4.5-5.9	1990-1994	2.7*	1994-2016	-2.2*			-1.5*
	50-69 years	33.0	43.9	40.7-48.0	46.2	36.5	31.4-43.2	1990-1994	2.7*	1994-2004	-0.4*	2004-2016	-2.1*	-0.7*
	70+ years	17.9	67.9	63.2-74.0	34.4	71.1	62.6-82.0	1990-1994	3.5*	1994-2003	0.9*	2003-2016	-1.2*	0.2*
Middle SDI	15-49 years	22.5	6.3	5.6-7.3	37.0	5.6	5.0-6.2	1990-2002	0.3*	2002-2008	-1.8*	2008-2016	-0.7*	-0.5*
	50-69 years	30.9	31.1	28.2-37.1	70.0	31.8	28.8-34.7	1990-2002	0.8*	2002-2012	-0.2*	2012-2016	-0.9*	0.1*
	70+ years	12.1	45.8	41.6-57.5	31.5	51.7	46.8-56.7	1990-2002	1.1*	2002-2011	0.2*	2011-2016	-0.7*	0.5*
Low-middle SDI	15-49 years	17.7	7.3	5.5-9.7	33.1	6.7	5.8-8.2	1990-1999	0.5*	1999-2012	-1.2*	2012-2016	0.6	-0.4*
	50-69 years	25.8	38.9	31.4-50.6	51.2	37.9	32.7-48.1	1990-1999	0.7*	1999-2012	-0.8*	2012-2016	0.5	-0.1*
	70+ years	7.2	47.8	37.8-66.7	20.2	57.5	47.8-74.6	1990-2001	0.9*	2001-2011	0.3*	2011-2016	1.0*	0.7*
Low SDI	15-49 years	5.0	7.9	5.8-11.4	10.9	8.3	6.7-10.3	1990-1995	1.2*	1995-2010	-0.3*	2010-2016	0.7*	0.2*
	50-69 years	7.0	44.4	35.7-58.2	15.7	49.1	42.1-56.5	1990-1996	1.0*	1996-2009	0	2009-2016	0.7*	0.4*
	70+ years	1.9	59.9	48.7-76.3	5.2	72.6	62.3-82.3	1990-1995	1.0*	1995-2009	0.5*	2009-2016	1.1*	0.8*



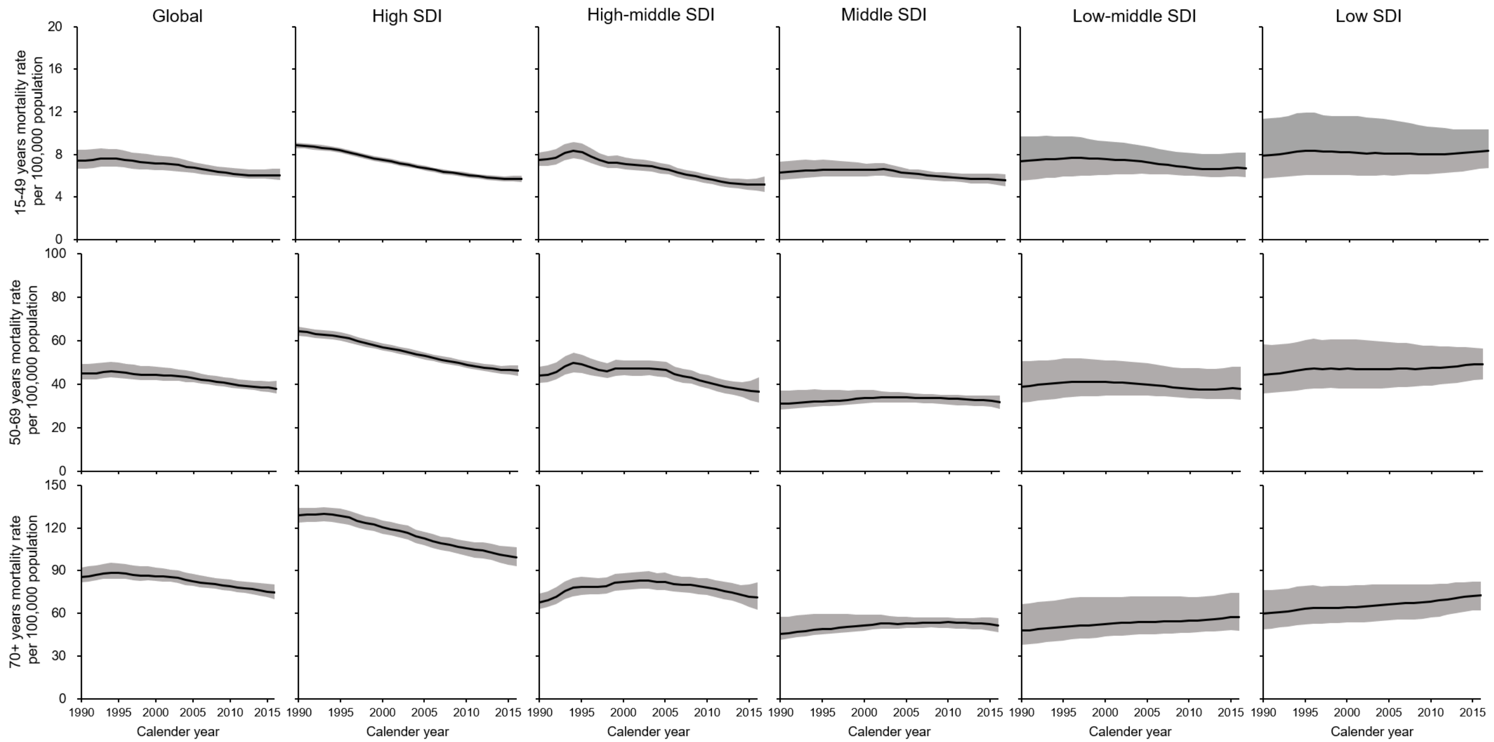
Supplementary figure 1A. Trends in breast cancer age-standardized incidence rate (ASIR) according to SDI settings, 1990-2016. The black lines represent the estimated ASIRs, and areas shaded in gray represent 95% uncertainty intervals.



Supplementary figure 1B. Trends in incidence rate for 15-49, 50-69 and 70+ age groups according to SDI settings, 1990-2016. The black lines represent the estimated age-specific rates adjusted within each group following the new world population age-standard, and areas shaded in gray represent the 95% uncertainty intervals.



Supplementary figure 2A. Trends in breast cancer age-standardized mortality rate (ASMR) according to SDI settings, 1990-2016. The black lines represent the estimated ASMRs, and areas shaded in gray represent 95% uncertainty intervals.



Supplementary figure 2B. Trends in mortality rate for 15-49, 50-69 and 70+ age groups according to SDI settings, 1990-2016. The black lines represent the estimated age-specific rates adjusted within each group following the new world population age-standard, and areas shaded in gray represent the 95% uncertainty intervals.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#4
Objectives	3	State specific objectives, including any prespecified hypotheses	#4
Methods			
Study design	4	Present key elements of study design early in the paper	#5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	#5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#5-6
Bias	9	Describe any efforts to address potential sources of bias	#5-6
Study size	10	Explain how the study size was arrived at	#5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#6-7
		(*b*) Describe any methods used to examine subgroups and interactions	#6-7
		(*c*) Explain how missing data were addressed	#6-7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	#6-7
		(*e*) Describe any sensitivity analyses	#6-7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#7-9
		(b) Give reasons for non-participation at each stage	#7-9
		(c) Consider use of a flow diagram	#7-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#7-9
		(b) Indicate number of participants with missing data for each variable of interest	#7-9
Outcome data	15*	Report numbers of outcome events or summary measures	#7-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#7-9
		(*b*) Report category boundaries when continuous variables were categorized	#7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	#9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	#11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	#9-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#12-13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.