

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028461
Article Type:	Research
Date Submitted by the Author:	11-Dec-2018
Complete List of Authors:	Hu, Kaimin Ding, Peili Wu, Yinan Tian, Wei Pan, Tao Zhang, Suzhan; Cancer Institute,
Keywords:	breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini coefficient, concentration index

SCHOLARONE™
Manuscripts

1
2
3
4
5 1 Title page:
6
7

8 2 Global Patterns and Trends in Breast Cancer Incidence and
9
10 3 Mortality according to Socio-demographic Index
11
12
13
14 4

15 5 Kaimin Hu ^{1,2,#}

16
17 6 Peili Ding ^{1,#}

18
19 7 Yinan Wu ¹

20
21 8 Wei Tian ^{1,2}

22
23 9 Tao Pan ^{1,2}

24
25 10 Suzhan Zhang ¹
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

12 ¹ Cancer Institute, the Second Affiliated Hospital of Zhejiang University, College of Medicine,
13 Hangzhou, Zhejiang, China.

14 ² Department of Surgical Oncology, the Second Affiliated Hospital of Zhejiang University,
15 College of Medicine, Hangzhou, Zhejiang, China.

16 # These authors contributed equally to this work.
17

18 Corresponding Author:

19 Suzhan Zhang

20 Cancer Institute

21 The Second Affiliated Hospital of Zhejiang University, College of Medicine

22 Jiefang Road 88, Hangzhou, 310009, China.

23 Telephone: +86-5718778-4501

24 Fax: +86-5718721-4404

25 Email: zrsj@zju.edu.cn
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

26 **Abstract:**

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

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

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

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

48
49
50 **Keywords:** breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini
51 coefficient, concentration index

1
2
3
4 52

5 6 7 53 Article summary

8 9 10 54 Strengths and limitations of this study :

11
12 55 To our knowledge, this study was a first overview about the global patterns and trends in breast
13
14 56 cancer incidence and mortality in relation to levels of SDI. Limitations should also be considered
15
16 57 when interpreting the results of our investigation. Firstly, this study was subject to the limitations
17
18 58 of the GBD 2016 study, such as data sources and statistical assumptions, which were detailed in
19
20 59 the GBD 2016 reports. Secondly, joinpoint analysis is sensitive to parameter settings. The pattern
21
22 60 groupings of trends in incidence and mortality may change if parameters are set differently or
23
24 61 more data are involved in the analysis. Thirdly, district data within each country, information on
25
26 62 disease stage or histopathological characteristics were unavailable in GBD 2016 database. In the
27
28 63 United States, for example, nationwide distributions and trends in breast cancer burdens differed
29
30 64 by ethnicity, state, disease stage and intrinsic subtype. More studies are needed to further
31
32 65 understand disparities due to these biases worldwide.
33
34
35
36
37
38
39

40 68 Introduction

41
42 69 Breast cancer is the most common cancer and the first leading cause of cancer death among
43
44 70 women, with an estimated 2.4 million new cases and 523 thousand deaths worldwide in 2015¹.
45
46 71 Where and in which socioeconomic status a woman lives can significantly affect her odds of
47
48 72 developing breast cancer and whether she will ultimately survive¹. Breast cancer is not confined
49
50 73 to high-income countries, however, it more often occurred in developed regions, where the
51
52 74 incidence rates were multifold higher compared with those in low- and middle-income countries
53
54 75 (LMICs)¹⁻³. The cancer-related mortality rates in those LMICs were not fit in their low incidence
55
56 76 rates³⁻⁵. Along with better awareness of risk factors, regular mammography screening and
57
58
59
60

1
2
3
4 77 sufficient and effective medical services, the mortality rates in many high-income countries
5
6 78 significantly declined in recent decades, and their incidence rates also stabled or even decreased
7
8 79 since around 2000. Rather, in many resource-poor settings or countries undergoing rapid
9
10 80 transition, both the incidence and mortality rates from breast cancer have been increasing,
11
12 81 partially attributed by changes in reproductive patterns, increases in awareness but backward
13
14 82 detections or treatments^{6,7}.

15
16
17 83 Disparities do exist in the global burden of breast cancer, especially among counties and regions
18
19 84 with different levels of development. Understanding the exact correlations between the disease
20
21 85 burden and socioeconomic status are critical for the world's health policymakers to formulate
22
23 86 appropriate measures adapted to local conditions. Socio-demographic Index (SDI) was first
24
25 87 introduced in the Global Burden of Disease Study 2015 (GBD 2015) by the Institute for Health
26
27 88 Metrics and Evaluation to quantificationally measure the development of a country or region⁸.
28
29 89 The aims of our study were to describe the current patterns and trends in breast cancer incidence
30
31 90 and mortality according to the country-level wellbeing, and to further explore distributions and
32
33 91 changes in the breast cancer associated health inequality according to the spectrum of
34
35 92 development, by combining the latest updated SDI data with breast cancer incidence and mortality
36
37 93 data during 1990 and 2016 available at the GBD 2016 database.

38
39
40 94

41
42 95

43 44 96 Material and Methods

45 46 47 97 Patient and Public Involvement

48
49 98 Breast cancer was defined by the International Classification of Disease - Revision 10 with code
50
51 99 C50. Incidence and mortality data from 195 individual countries and predefined five SDI groups
52
53 100 between 1990 and 2016 were collected from the Global Health Data Exchange database⁵. Annual
54
55 101 incidence and mortality rates by a 5-year age bracket from age 15 to 95+ years were obtained for
56
57 102 each involved country. Detailed methods pertaining to estimation of age-standardized incidence
58
59
60

1
2
3
4 103 and mortality rate (ASIR and ASMR) per 100,000 population had been previously described in
5
6 104 the GBD 2016 reports^{3, 4}. Because women aged 50-69 years were the major population
7
8 105 participating in regular screening programs, we further calculated age-specific incidence and
9
10 106 mortality rates per 100,000 population into three subgroups by age: 15-49, 50-69 and 70+ years,
11
12 107 which were adjusted within age groups according to the new world population age-standard³.
13
14 108 Mortality-to-incidence ratio (MIR) was calculated by dividing the breast cancer mortality rate for
15
16 109 a given year, age-group, country or SDI group by its corresponding incidence rate.
17
18
19
20

21 111 Socio-demographic index

22
23 112 SDI is a comparable metric of overall development achieved by using an equal weighting of lag-
24
25 113 distributed income per capita, average years of education in the population over 15 years, and
26
27 114 total fertility rate⁹. SDI values on a scale of 0 to 1. A greater value of SDI implies higher level of
28
29 115 development. SDI data for the involved 195 countries from 1990 to 2016 were obtained from the
30
31 116 Global Health Data Exchange database⁵. Countries were grouped into quintiles based on their SDI
32
33 117 values in 2016: high, high-middle, middle, low-middle and low SDI groups. Detailed methods
34
35 118 describing computation of the SDI as well as choosing of the quintile cutoffs were reported
36
37 119 elsewhere^{1, 3}.
38
39

40 120

42 121 Gini coefficient and concentration index

43
44 122 Gini coefficient and concentration index drawn from the field of economics were used to measure
45
46 123 breast cancer associated health inequality in our study^{10, 11}. Gini coefficient was calculated based
47
48 124 on the Lorenz curve, and it ranged from 0 to 1, 0 representing perfect equality and 1 total
49
50 125 inequality¹¹. Annual ASIRs, ASMRs, age-specific incidence and mortality rates and MIRs of
51
52 126 breast cancer for 195 countries were used to calculate the Gini coefficients, to find out the trends
53
54 127 in between-country health inequality during 1990 and 2016. Concentration index was derived
55
56 128 from the concentration curve and commonly used to measure socioeconomic-related health
57
58
59
60

1
2
3
4 129 inequality¹². Concentration indexes were computed by relating the above breast cancer metrics to
5
6 130 corresponding national SDIs. The value of this index varies between -1 and +1. Positive (negative)
7
8 131 values of the concentration index indicated the disease burden owing to the occurrence or death
9
10 132 of breast cancer were more concentrated in countries with high (low) levels of development
11
12 133 measured by SDI¹². The absolute value demonstrates the degree of a “pro-developed” or “pro-
13
14 134 underdeveloped” distribution in health limitations, and zero means an absence of inequality
15
16 135 associated to the socioeconomic gradient instead of absence of inequality.
17
18
19 136

20 21 137 Statistical analyses

22
23 138 For a normal distribution but heterogeneity in variances of incidence, mortality and MIR data,
24
25 139 one-way ANOVA was performed to determine the statistical significance of differences in
26
27 140 incidence rates, mortality rates and MIRs across SDI-based country groups, followed by pairwise
28
29 141 comparisons using Tamhane T2 test¹³. Linear regression model was used to test for the correlation
30
31 142 between breast cancer indicators and SDI values. Joinpoint piecewise linear regression analysis
32
33 143 was performed to identify time points when significant changes occurred as well as temporal
34
35 144 trends in age-standardized and age-specific incidence and mortality rates during 1990 and 2016¹⁴.
36
37 145 Default parameters were used, except for setting the minimum number of data points between
38
39 146 two joints and at either end of the data to 5. To avoid over-fitting at the truncating points,
40
41 147 maximum number of joinpoints was defined as 2. The best-fit point where the rate had changed
42
43 148 prominently was decided by means of a permutation test, and the *P* value for each permutation
44
45 149 test was estimated using Monte Carlo methods¹⁴. Statistics on annual percent change (APC) for
46
47 150 each segment and average annual percent change (AAPC) for the overall period were summarized
48
49 151 using the optimal joinpoint model. All joinpoint trend analyses were undertaken via the joinpoint
50
51 152 statistical software (Version 4.5.0.1) from the surveillance research program of the United States
52
53 153 National Cancer Institute¹⁵. The Gini coefficient was computed by the AINEQUAL module¹⁶,
54
55 154 and the concentration index by the CONIDEX module¹⁷ using Stata 14.0 software (Stata Corp,
56
57
58
59
60

1
2
3
4 155 Texas, USA). Other statistical analyses were performed with SPSS 20.0 (IBM Corp, Chicago,
5
6 156 USA).

7
8 157
9

10 158

11 12 13 159 Results

14 15 160 Current profiles in breast cancer incidence and mortality according to SDIs

16
17 161 Figure 1 showed distinct distributions of counts and proportions of new cases and deaths due to
18
19 162 breast cancer in five SDI groups in 2016. There were 719 thousand new cases in high SDI
20
21 163 countries, about 20 times of that of 37 thousand in low SDI groups. Death number in these two
22
23 164 groups were 162 and 32 thousand, respectively. About half of the new cases were occurred in
24
25 165 women aged 50-69 years across all SDI groups. In countries belonging to middle, low-middle or
26
27 166 low SDI group, more than one third new cases happened in young ages between 15 and 49 years,
28
29 167 along with more proportion of deaths in this age group. Deaths in age 70 years or elder, by contrast,
30
31 168 made up 50.9% of total breast cancer deaths in high SDI countries.

32
33
34 169 One-way ANOVA suggested significant differences in both age-standardized and age-specific
35
36 170 incidence rates and MIRs ($P < 0.01$), but not mortality rates among countries in different SDI
37
38 171 groups. Pairwise comparisons indicated lower MIRs in countries representing the higher level of
39
40 172 development based on SDI, where the mortality rates were not proportional to their high incidence
41
42 173 rates (Figure 2). The Incidence rates in all age groups were shown to have a positive dose-response
43
44 174 relationship with SDIs, otherwise than a negative dose-response relationship between MIRs and
45
46 175 SDIs (Figure 3). Besides, the rate ratios exhibited well-fitting linear relationships in all age groups,
47
48 176 whereas the incidence and mortality rates in elder age groups were more scattered across countries
49
50 177 with varied SDIs.

51
52
53 178

54 55 179 Temporal trends in breast cancer incidence and mortality across SDI groups

56
57 180 According to the joinpoint trend analyses (Table 1), the ASIRs in high and high-middle SDI
58
59
60

1
2
3
4 181 groups plateaued after a quick increase at early 1990s. The ASIRs in high SDI group even
5
6 182 displayed a declining trend by 0.1% per year since 2000. However, significant increases were
7
8 183 found in middle, low-middle and low SDI groups through the whole period from 1990 to 2016
9
10 184 (Supplementary figure 1A). The AAPC in ASIR for the middle SDI group was 2.1%, far ahead
11
12 185 of increases in other groups. Trends of incidence rates in 15-49, 50-69 and 70+ years age groups
13
14 186 were comparable with those of ASIRs across SDI groups (Supplementary table 1 and figure 1B).

15
16
17 187 Changes in ASMRs were contradictory among SDI groups as shown in table 2 and
18
19 188 supplementary figure 2A. In high SDI group, the ASMR continuously decreased from 24.2 in
20
21 189 1990 to 17.6 in 2016, with an AAPC of -1.3%. The ASMR in high-middle SDI group began to
22
23 190 decline in 1994, and an accelerated decrease (APC: -1.9%) was witnessed between 2004 and 2016.
24
25 191 The ASMR in middle SDI group also slightly diminished in 2002 to 2016 with an average
26
27 192 decrease of 0.5% per year. Opposite trends were displayed in the low-middle (2002-2016, APC:
28
29 193 0.7%) and low SDI groups (2009-2016, APC: 0.8%), especially in recent years. Patterns of change
30
31 194 in three age groups were similar with those of ASMR in each SDI group, however, the spectrum
32
33 195 of change differed (Supplementary table 2 and figure 2B). For example, our results showed a
34
35 196 much less decreasing in more developed regions and more increasing in less developed regions
36
37 197 in the mortality for 70+ years age group compared with other age groups, which was much less-
38
39 198 than-ideal.

40
41
42 199

43 44 200 Health inequality in worldwide breast cancer

45
46 201 The Gini coefficients for the incidence of breast cancer decreased continuously from 1990 to 2016
47
48 202 (Figure 4A), the values of which computed from ASIRs and incidence rates in 15-49, 50-69 and
49
50 203 70+ years age groups had dropped to 0.33, 0.30, 0.34 and 0.38 by 2016, compared with those of
51
52 204 0.38, 0.35, 0.39 and 0.43 in 1990, respectively. Similarly, the Gini coefficients calculated with
53
54 205 mortality rates in all age groups except the 15-49 years age group showed markedly declining
55
56 206 trends during the same period. Though the between-country inequalities due to both breast cancer
57
58
59
60

1
2
3
4 207 incidence and mortality decreased, the Gini coefficients according to the distribution of MIRs
5
6 208 conversely increased. For instance, the Gini coefficients derived from age-standardized MIRs
7
8 209 reached up to 0.29 in 2016 from a base of 0.23 in 1990.
9

10 210 The concentration indexes according to breast cancer age-standardized and age-specific
11
12 211 incidence and mortality rates were all above zero in 1990, suggesting that the inequalities
13
14 212 associated with socioeconomic development were more concentrated in countries with higher
15
16 213 level of development measured by SDI. Moreover, the concentration indexes for the 70+ years
17
18 214 age group were much greater than those in other age groups. As can be seen in Figure 4B, both
19
20 215 the concentration indexes of incidence and mortality rates decreased between 1990 and 2016, and
21
22 216 the rates of descent sped up since late 1990s. The concentration indexes computed with mortality
23
24 217 rates in 15-49 and 50-69 years age groups inclined to zero and became negative in 1998 and 2013,
25
26 218 respectively. In contrast, the concentration indexes based on age-standardized and age-specific
27
28 219 (15-49, 50-69 and 70+ years age group) MIRs were below zero, with values of -0.21, -0.22, -0.22
29
30 220 and -0.18 in 1990, and by 2016, the values of which had decreased to -0.28, -0.31, -0.30 and -
31
32 221 0.25, respectively.
33
34
35
36
37
38
39

40 224 Discussion

41
42 225 The socioeconomic development associated inequality in global incidence of breast cancer has
43
44 226 been decreasing since 1990. Still, countries with higher levels of development on the basis of
45
46 227 SDIs were shown to have worse incidence burdens by 2016. In keeping with the opposite trends
47
48 228 for mortality rates between countries with high and low SDIs, the concentration indexes by
49
50 229 mortality fell and even turned to be negative in 15-49 and 50-69 years age groups in recent years,
51
52 230 pointing towards a transition in the concentration of mortality burdens from the developed to
53
54 231 undeveloped regions. Conversely, both the overall inequality and the part correlated with
55
56 232 socioeconomic development in MIR - a health measure derived from the rate ratio of mortality
57
58
59
60

1
2
3
4 233 and incidence - increased from 1990 to 2016. In 2016, MIRs showed distinct gradients from the
5
6 234 high to low SDI regions in all age groups.

7
8 235 With epidemiological data reported for specific countries, it has been a prevailing perception
9
10 236 that inequalities existed in breast cancer incidence worldwide, especially between the high-
11
12 237 income countries and LMICs¹⁸⁻²¹. However, evidence about the quantitative relationship between
13
14 238 the breast cancer burdens and national socioeconomic development was still limited. On the basis
15
16 239 of GLOBOCAN 2012 estimates, incidence burden due to breast cancer distributed with obvious
17
18 240 disparities among countries in different levels of human development index (HDI)², which was
19
20 241 in accordance with our results in the light of data from the GBD 2016 study and SDI-a newly
21
22 242 developed indicator for socioeconomic status of a given country. The overall inequality in breast
23
24 243 cancer incidence had not yet been eliminated and was still more concentrated in countries with
25
26 244 higher levels of SDI. The prevalence of breast cancer is somewhat associated with a so-called
27
28 245 western lifestyle (ie, specific reproductive patterns and excess body weight)^{22, 23}, making it a
29
30 246 marker for the extent of development. Trend analyses in our study demonstrated a quick
31
32 247 increasing in breast cancer incidence in countries belonging to the middle SDI group. This fact
33
34 248 might suggest that countries with middle levels of SDI were undergoing rapid social and
35
36 249 economic transitions²⁴. In many LMICs, burden of infection-related cancers, such as cervical,
37
38 250 gastric and liver cancer, remained top ranking, instead of breast cancer^{1, 2}. Mammographic
39
40 251 screening programs were generally implemented in high-income countries, for women aged 50-
41
42 252 69 years²⁵⁻²⁷. Our subgroup analysis based on age conformed transient rises in incidence of women
43
44 253 at this age group and subsequent falls in those elder than 70 years in high SDI countries.

45
46 254 The mortality rates from breast cancer did not differ significantly from the low to high SDI
47
48 255 regions. Inequalities in breast cancer caused deaths were possibly offset by better outcomes in
49
50 256 more developed countries with early detections and advanced treatments, and small scale of
51
52 257 incidence but limited access to health cares in most LMICs^{28, 29}. Therefore, mortality rates could
53
54 258 not well represent the exact trends and current status of cancer caused death burdens. Cancer
55
56 259 survival was another important indicator for death burden of malignancies. According to data
57
58
59
60

1
2
3
4 260 from 59 countries in CONCORD-2 study³⁰, five-year survival for patients diagnosed with breast
5
6 261 cancer during 2005-09 in the North America, Australia, Israel, Brazil, and most Northern and
7
8 262 Western European countries had reached up to 85% or higher, while it remained 60% or lower in
9
10 263 many LMICs, such as India, Mongolia, Algeria and South Africa. However, comprehensive
11
12 264 survival data were scarce in most countries, especially in those with limited resources. It remained
13
14 265 an important issue to conclude the extent of socioeconomic development associated inequalities
15
16 266 in the survivorship of breast cancer and to compare the current survival status in each country
17
18 267 across the world. Here in our study, we analyzed the trends of inequalities in breast cancer MIRs,
19
20 268 which evaluated the departure of mortality in relation to incidence from expectation and was
21
22 269 suggested as an approximation for cancer survival³¹⁻³³. Our results indicated widening disparities
23
24 270 in the MIRs of breast cancer among countries with different levels of development.
25
26

27 271 HDI was a metric composed by life expectancy at birth, mean and expected years of schooling
28
29 272 and gross national income per capita³⁴, and was used by a few researches to investigate how
30
31 273 macro-socioeconomic determinants correlated with national disease burdens^{2, 28, 35}. Nevertheless,
32
33 274 it could be confusing when a measure of overall health (life expectancy at birth) was one important
34
35 275 component of the index used to evaluate how socioeconomic development influences health. In
36
37 276 the GBD 2015 study, SDI was first developed to identify where countries or geographic areas sit
38
39 277 on the spectrum of societal development⁸. As reproductive patterns were proved to be risk factors
40
41 278 for breast cancer²², SDI, a yardstick constructed based on measures of income, education, and
42
43 279 fertility rate, might be more appropriate to weigh the influence of socioeconomic status on the
44
45 280 global patterns and trends in health inequality due to breast cancer.
46
47

48 281 To our knowledge, this study was a first overview about the global patterns and trends in breast
49
50 282 cancer incidence and mortality in relation to levels of SDI. Limitations should also be considered
51
52 283 when interpreting the results of our investigation. Firstly, this study was subject to the limitations
53
54 284 of the GBD 2016 study, such as data sources and statistical assumptions, which were detailed in
55
56 285 the GBD 2016 reports^{3, 4}. Secondly, joinpoint analysis is sensitive to parameter settings. The
57
58 286 pattern groupings of trends in incidence and mortality may change if parameters are set differently
59
60

1
2
3
4 287 or more data are involved in the analysis. Thirdly, district data within each country, information
5
6 288 on disease stage or histopathological characteristics were unavailable in GBD 2016 database. In
7
8 289 the United States, for example, nationwide distributions and trends in breast cancer burdens
9
10 290 differed by ethnicity, state, disease stage and intrinsic subtype^{36, 37}. More studies are needed to
11
12 291 further understand disparities due to these biases worldwide.
13
14
15 292

17 293 Conclusions

19 294 The socioeconomic development associated health inequality in breast cancer incidence has been
20
21 295 declining since 1990. Countries undergoing an economic and lifestyle transition were
22
23 296 experiencing growing prevalence of breast cancer. Nonetheless, the incidence burden was still
24
25 297 more concentrated in countries with higher SDIs by 2016. These findings highlighted that public
26
27 298 health clinicians and cancer control specialists should pay more attention to primary prevent of
28
29 299 breast cancer especially in these high-incidence countries. Breast cancer mortality, in less
30
31 300 developed countries, deviated from expectation seriously in relation to their low incidence. This
32
33 301 situation even deteriorated with ever-increasing between-country inequalities for rate ratios from
34
35 302 1990 until 2016. Planners should try to carry out more sensitive and cost-effective detection and
36
37 303 treatment interventions, particularly in low and low-middle SDI settings with limited healthcare
38
39 304 resources, to combat premature deaths due to breast cancer.
40
41
42
43 305
44
45 306

47 307 Funding

49 308 This study was funded by National Natural Science Foundation of China (Grant Number
50
51 309 81502598 and 81602716).
52
53
54 310
55
56 311

58 312 Competing interests

1
2
3
4 313 The authors declare that they have no conflict of interest.
5
6 314
7
8 315
9

10 316 **Data sharing statement**
11
12

13 317 No additional data available.
14
15 318
16
17 319

18
19
20 320 **Authors' contributions**
21

22 321 Kaimin Hu designed the study, acquired and analyzed the data and prepared the figures. Peili
23
24 322 Ding and Yinan Wu interpreted the results and wrote the first draft of the manuscript. Tao Pan
25
26 323 and Wei Tian interpreted the results and supported the research funding. Suzhan Zhang was the
27
28 324 principle investigator and designed the study. All authors commented on manuscript drafts,
29
30 325 approved the final version and declared no conflict of interest.
31
32
33 326
34
35 327

36
37 328 **References**
38
39

- 40 329 1. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, et al. Global, Regional, and
41
42 330 National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and
43
44 331 Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for
45
46 332 the Global Burden of Disease Study. *JAMA Oncol.* 2017;3(4):524-548.
47
48
49
50
51 333 2. Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand
52
53
54 334 challenge in global health. *Lancet.* 2017;389(10071):847-860.
55
56
57 335 3. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence,
58
59
60

- 1
2
3
4 336 and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a
5
6
7 337 systematic analysis for the Global Burden of Disease Study 2016. *Lancet*.
8
9
10 338 2017;390(10100):1211-1259.
- 11
12
13 339 4. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264
14
15
16 340 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study
17
18
19 341 2016. *Lancet*. 2017;390(10100):1151-1210.
- 20
21
22 342 5. Global Health Data Exchange. GBD Results Tool. Available from:
23
24
25 343 <http://www.healthdata.org/gbd-results-tool>. Accessed Sep 26, 2017.
- 26
27
28 344 6. Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive
29
30
31 345 epidemiology of female breast cancer: an international comparison of screening, incidence,
32
33
34 346 survival and mortality. *Cancer Epidemiol*. 2012;36(3):237-248.
- 35
36
37 347 7. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global Cancer in Women: Burden and
38
39
40 348 Trends. *Cancer Epidemiol Biomarkers Prev*. 2017;26(4):444-457.
- 41
42
43 349 8. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause
44
45
46 350 mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic
47
48
49 351 analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459-1544.
- 50
51
52 352 9. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD
53
54
55 353 2016) Socio-demographic Index (SDI) 1970–2016. Seattle, United States: Institute for Health
56
57 354 Metrics and Evaluation (IHME), 2017.
- 58
59
60

- 1
2
3
4 355 10. Bleichrodt H, van Doorslaer E. A welfare economics foundation for health inequality
5
6
7 356 measurement. *J Health Econ.* 2006;25(5):945-957.
8
9
10 357 11. Pan American Health Organization. Measuring health inequalities: Gini coefficient and
11
12
13 358 concentration index. *Epidemiol Bull.* 2001;22(1):2.
14
15
16 359 12. Costa-Font J, Hernandez-Quevedo C. Measuring inequalities in health: What do we know?
17
18
19 360 What do we need to know? *Health Policy.* 2012;106(2):195-206.
20
21
22 361 13. Shingala MC, Rajyaguru A. Comparison of Post Hoc Tests for Unequal Variance.
23
24
25 362 *International Journal of New Technologies in Science and Engineering.* 2015;2:22-33.
26
27
28 363 14. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with
29
30
31 364 applications to cancer rates. *Stat Med.* 2000;19(3):335-351.
32
33
34 365 15. National Cancer Insititute. Surveillance Epidemiology and end results (SEER) program.
35
36 366 methods & tools: joinpoint trend analysis. Available from:
37
38
39 367 <https://surveillance.cancer.gov/joinpoint>. Accessed Oct 10, 2017.
40
41
42 368 16. Kerm PV. INEQUAL7: Stata module to compute measures of inequality. *Statistical Software*
43
44
45 369 *Components S416401, Boston College Department of Economics.* 2001.
46
47
48 370 17. O'Donnell O, O'Neill S, Van Ourti T, Walsh B. conindex: Estimation of concentration indices.
49
50
51 371 *Stata J.* 2016;16(1):112-138.
52
53
54 372 18. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin.*
55
56
57 373 2014;64(1):52-62.
58
59
60

- 1
2
3
4 374 19. Lundqvist A, Andersson E, Ahlberg I, Nilbert M, Gerdtham U. Socioeconomic inequalities in
5
6
7 375 breast cancer incidence and mortality in Europe-a systematic review and meta-analysis. *Eur*
8
9
10 376 *J Public Health*. 2016;26(5):804-813.
11
12
13 377 20. Li T, Mello-Thoms C, Brennan PC. Descriptive epidemiology of breast cancer in China:
14
15
16 378 incidence, mortality, survival and prevalence. *Breast Cancer Res Treat*. 2016;159(3):395-406.
17
18
19 379 21. Lukong KE, Ogunbolude Y, Kamdem JP. Breast cancer in Africa: prevalence, treatment
20
21
22 380 options, herbal medicines, and socioeconomic determinants. *Breast Cancer Res Treat*.
23
24
25 381 2017;166(2):351-365.
26
27
28 382 22. Porter P. "Westernizing" women's risks? Breast cancer in lower-income countries. *N Engl J*
29
30
31 383 *Med*. 2008;358(3):213-216.
32
33
34 384 23. Lahmann PH, Schulz M, Hoffmann K, et al. Long-term weight change and breast cancer risk:
35
36
37 385 the European prospective investigation into cancer and nutrition (EPIC). *Br J Cancer*.
38
39
40 386 2005;93(5):582-589.
41
42
43 387 24. Bray F. Transitions in human development and the global cancer burden. In: Steward BW,
44
45
46 388 Wild CP, eds. World Cancer Report 2014. *Lyon: International Agency for Research on Cancer*,
47
48
49 389 2014.
50
51
52 390 25. Gotzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. *Cochrane*
53
54
55 391 *Database Syst Rev*. 2013(6):CD001877.
56
57
58 392 26. Narod SA. Reflections on screening mammography and the early detection of breast cancer:
59
60

- 1
2
3
4 393 A Countercurrents Series. *Curr Oncol*. 2014;21(5):210-214.
5
6
7 394 27. Loberg M, Lousdal ML, Bretthauer M, Kalager M. Benefits and harms of mammography
8
9
10 395 screening. *Breast Cancer Res*. 2015;17:63.
11
12
13 396 28. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the
14
15
16 397 Human Development Index (2008-2030): a population-based study. *Lancet Oncol*.
17
18
19 398 2012;13(8):790-801.
20
21
22 399 29. Coughlin SS, Ekwueme DU. Breast cancer as a global health concern. *Cancer Epidemiol*.
23
24
25 400 2009;33(5):315-318.
26
27
28 401 30. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009:
29
30
31 402 analysis of individual data for 25,676,887 patients from 279 population-based registries in 67
32
33
34 403 countries (CONCORD-2). *Lancet*. 2015;385(9972):977-1010.
35
36
37 404 31. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and
38
39
40 405 prevalence across five continents: defining priorities to reduce cancer disparities in different
41
42
43 406 geographic regions of the world. *J Clin Oncol*. 2006;24(14):2137-2150.
44
45
46 407 32. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods
47
48
49 408 Part II. Completeness. *Eur J Cancer*. 2009;45(5):756-764.
50
51
52 409 33. Asadzadeh Vostakolaei F, Karim-Kos HE, Janssen-Heijnen ML, Visser O, Verbeek AL,
53
54
55 410 Kiemeny LA. The validity of the mortality to incidence ratio as a proxy for site-specific cancer
56
57
58 411 survival. *Eur J Public Health*. 2011;21(5):573-577.
59
60

- 1
2
3
4 412 34. Programme UND. Human development report. Available from:
5
6
7 413 <http://hdr.undp.org/en/content/human-development-index-hdi>. Accessed Nov 16, 2017.
8
9
10 414 35. Fidler MM, Soerjomataram I, Bray F. A global view on cancer incidence and national levels
11
12
13 415 of the human development index. *Int J Cancer*. 2016;139(11):2436-2446.
14
15
16 416 36. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer
17
18
19 417 statistics, 2015: Convergence of incidence rates between black and white women. *CA Cancer*
20
21
22 418 *J Clin*. 2016;66(1):31-42.
23
24
25 419 37. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017,
26
27
28 420 racial disparity in mortality by state. *CA Cancer J Clin*. 2017;67(6):439-448.
29

30 421
31
32 422
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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*

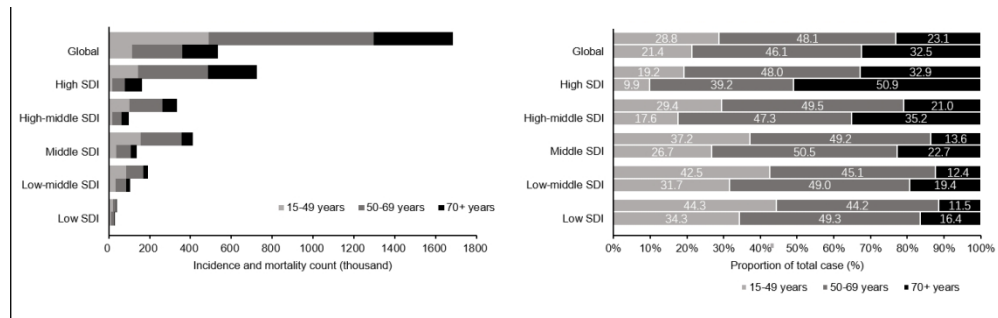


Figure 1

256x79mm (150 x 150 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

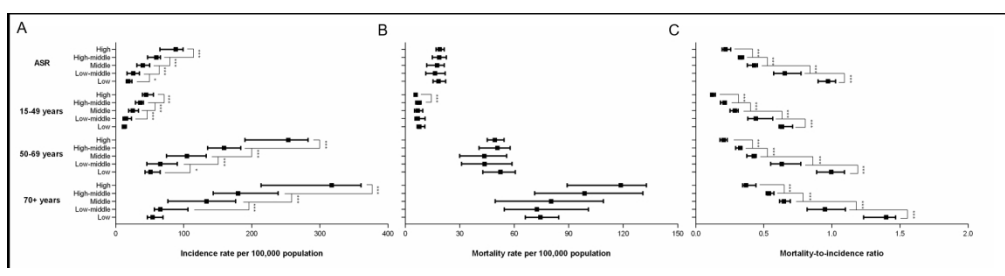


Figure 2

362x92mm (150 x 150 DPI)

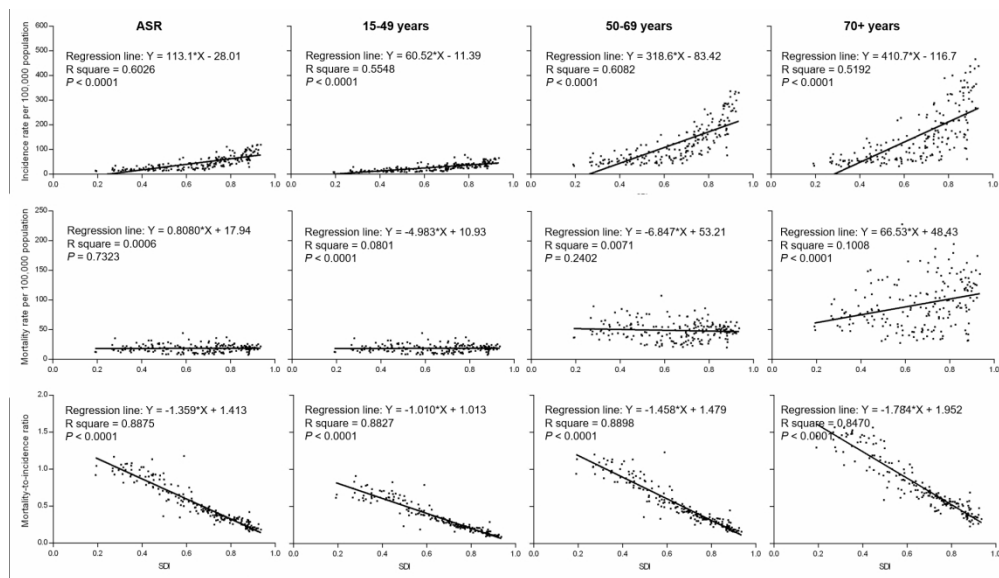


Figure 3

343x196mm (150 x 150 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

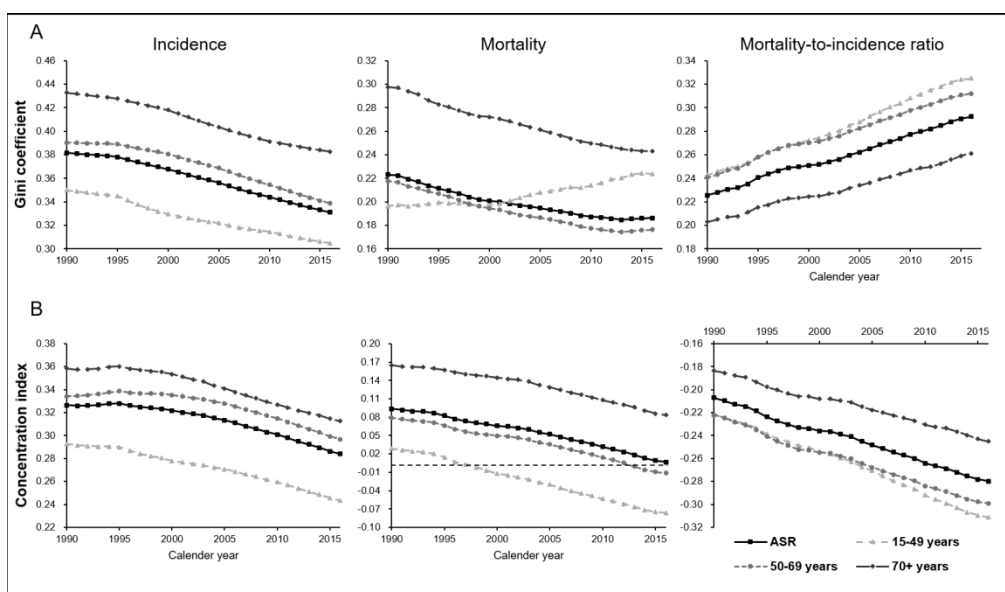


Figure 4

283x163mm (150 x 150 DPI)

Supplementary figures and tables

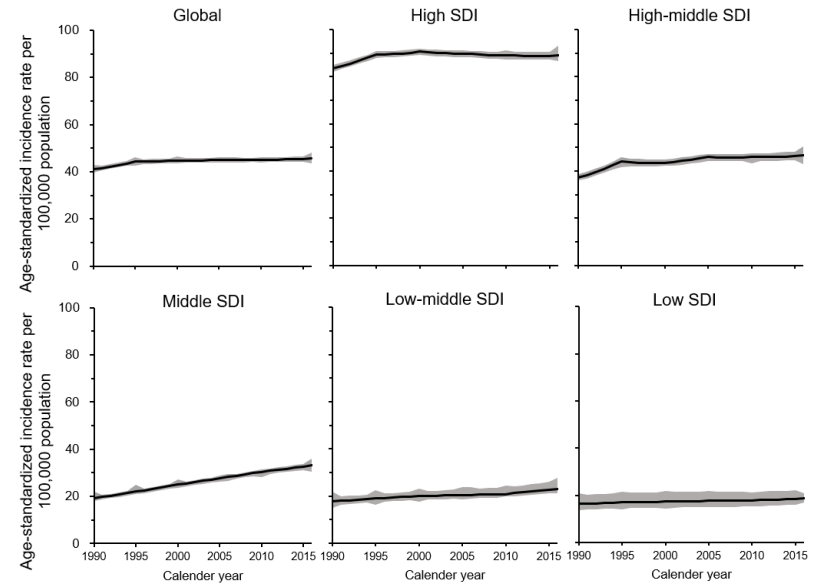
Supplementary table 1. Breast cancer age-specific incidence rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

	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	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*

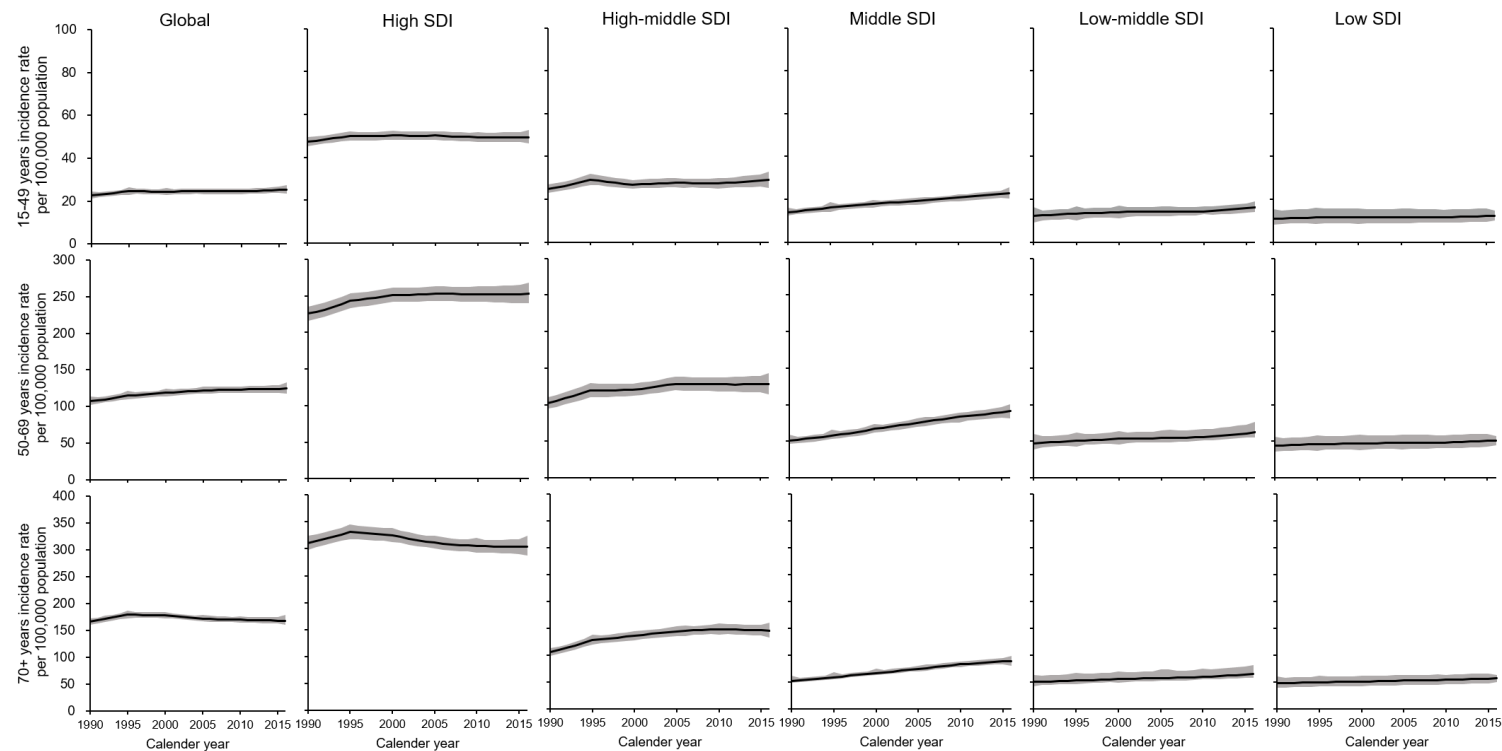
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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

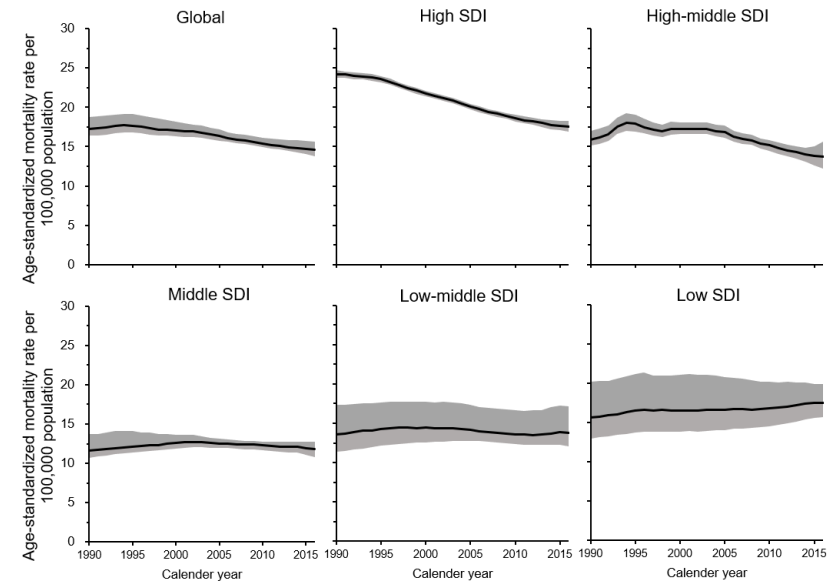
	Age	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
		Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	80.7	7.4	6.6-8.4	114.3	6.0	5.6-6.6	1990-1995	0.8*	1995-2012	-1.4*	2012-2016	-0.3*	-0.8*
	50-69 years	156.5	44.9	42.2-49.4	246.9	38.0	35.6-41.4	1990-1994	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*



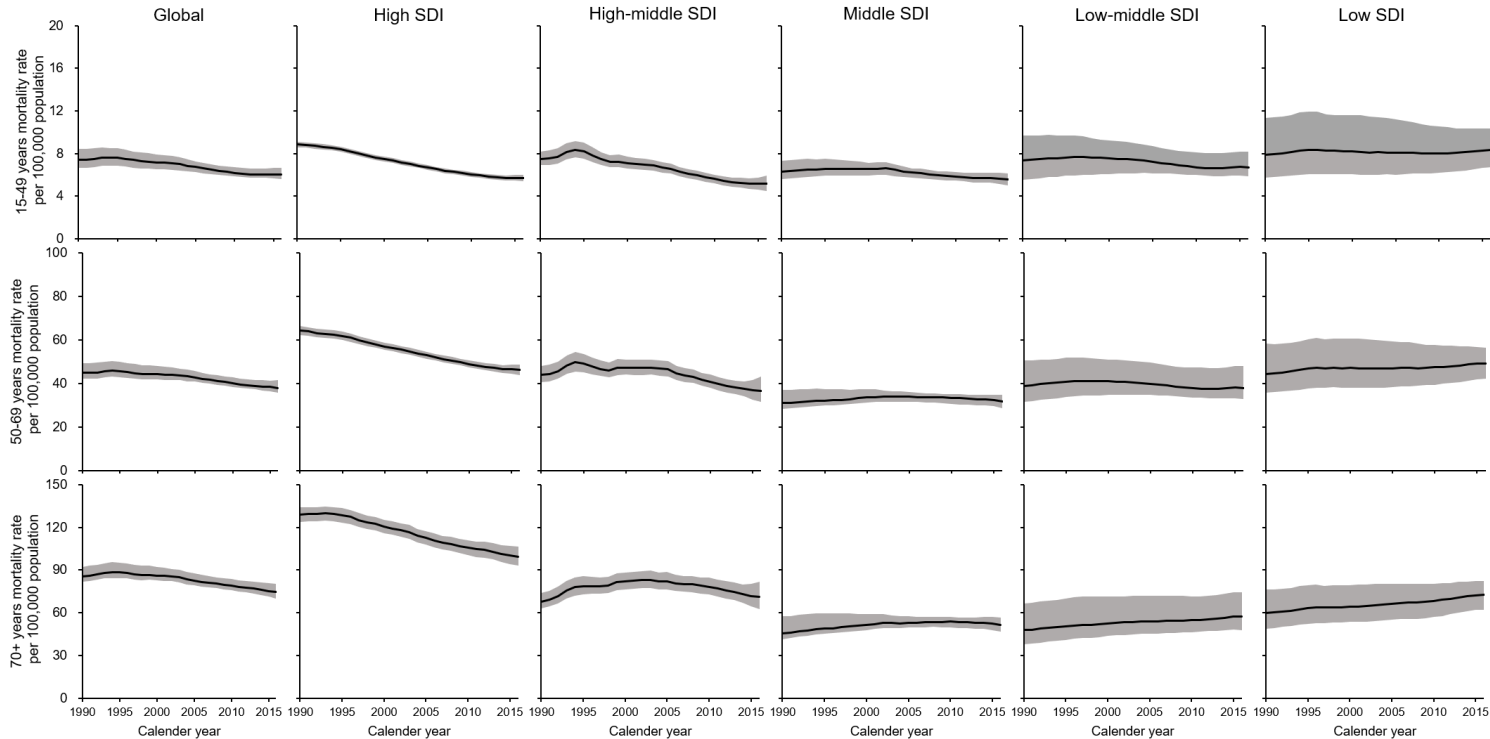
Supplementary figure 1A. Trends in breast cancer age-standardized incidence rate (ASIR) according to SDI settings, 1990-2016. The black lines represent the estimated ASIRs, and areas shaded in gray denote 95% uncertainty intervals.



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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028461.R1
Article Type:	Original research
Date Submitted by the Author:	01-Jul-2019
Complete List of Authors:	Hu, Kaimin; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Ding, Peili; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Wu, Yinan; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Tian, Wei; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Pan, Tao; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Zhang, Suzhan; Cancer Institute, the 2nd affiliated hospital of Zhejiang university
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Oncology, Global health
Keywords:	breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini coefficient, concentration index

SCHOLARONE™
Manuscripts

1
2
3
4
5 1 Title page:
6
7

8 2 Global Patterns and Trends in Breast Cancer Incidence and
9
10 3 Mortality according to Socio-demographic Index: An
11
12 4 Observational Study Based on the Global Burden of Diseases
13
14
15
16
17
18

19 6 Kaimin Hu ^{1,2,#}

20 7 Peili Ding ^{1,#}

21 8 Yinan Wu ¹

22 9 Wei Tian ^{1,2}

23 10 Tao Pan ^{1,2}

24 11 Suzhan Zhang ¹

25
26
27
28
29
30
31
32
33 13 ¹ Cancer Institute, the Second Affiliated Hospital of Zhejiang University, College of Medicine,
34 Hangzhou, Zhejiang, China.

35
36
37 15 ² Department of Breast Surgery, the Second Affiliated Hospital of Zhejiang University, College
38 of Medicine, Hangzhou, Zhejiang, China.

39
40
41 17 # These authors contributed equally to this work.
42
43
44
45

46 19 Corresponding Author:

47
48 20 Suzhan Zhang

49
50 21 Cancer Institute

51
52 22 The Second Affiliated Hospital of Zhejiang University, College of Medicine

53
54 23 Jiefang Road 88, Hangzhou, 310009, China.

55
56 24 Telephone: +86-5718778-4501

57
58
59 25 Fax: +86-5718721-4404
60

1
2
3
4 26 Email: zrsj@zju.edu.cn
5
6
7 27

8 28 **Abstract:**
9

10
11 29 Objectives: Disparities existed in the global burden of breast cancer. We aimed to figure out the
12
13 30 recent patterns and trends in incidence and mortality from breast cancer, and to assess health
14
15 31 inequalities related to breast cancer according to socioeconomic development.
16

17 32 Methods: Estimates of breast cancer incidence and mortality data from 1990 to 2016 were
18
19 33 obtained from the Global Health Data Exchange database. Patterns in 2016 were described with
20
21 34 age-standardized and age-specific incidence, mortality and mortality-to-incidence (MI) ratio
22
23 35 according to socio-demographic index (SDI) levels. Trends were assessed via the annual percent
24
25 36 change using joinpoint regression. The between-country health inequalities were measured with
26
27 37 the Gini coefficients and concentration indexes.
28

29
30 38 Results: Countries with higher levels of SDI were shown to have worse incidence burdens in 2016,
31
32 39 though the health inequality in breast cancer incidence, in terms of Gini coefficients and
33
34 40 concentration indexes, decreased since 1990. In keeping with the opposite trends in mortality rates
35
36 41 between high and low SDI countries, the concentration indexes for mortality also declined and
37
38 42 even turned negative in the age of 15-49 and 50-69 groups, pointing towards increasing
39
40 43 concentration in mortality burdens of undeveloped regions. Conversely, both the overall
41
42 44 inequality and the part related to socioeconomic development in MI ratio increased. In 2016, MI
43
44 45 ratios showed distinct gradients from high to low SDI regions for all age groups.
45

46
47 46 Conclusions: Patterns and trends in breast cancer incidence and mortality closely correlated with
48
49 47 SDI levels. Our findings highlighted that the two pressing needs in the following decades are 1)
50
51 48 the primary prevention of breast cancer in high SDI countries with high incidence and 2) the
52
53 49 development of cost-effective detection and treatment interventions in low SDI countries with
54
55 50 poor MI ratios.
56

57 51
58
59
60

1
2
3
4 52

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

55

56

57 Article summary

58 Strengths and limitations of this study :

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

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

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

66

67

68 Introduction

69 Breast cancer is the most common cancer and the first leading cause of cancer death among
70 women, with an estimated 2.4 million new cases and 523 thousand deaths worldwide in 2015¹.

71 Where and in which socioeconomic status a woman lives can significantly affect her odds of
72 developing breast cancer and whether she will ultimately survive¹. Breast cancer is not confined
73 to high-income countries. However, it often occurred in developed regions, where the incidence
74 rates were multifold higher compared with those in low- and middle-income countries (LMICs)¹⁻³.

75 The cancer-related mortality rates in those LMICs were not fit in their low incidence rates³⁻⁵.

76 Along with better awareness of risk factors, regular mammography screening and sufficient and

1
2
3
4 77 effective medical services, the mortality rates in many high-income countries significantly
5
6 78 declined in recent decades, and their incidence rates also kept stable or even decreased since
7
8 79 around 2000. In many resource-poor settings or countries undergoing rapid transition, both the
9
10 80 incidence and mortality rates from breast cancer have been increasing, partially attributed by
11
12 81 changes in reproductive patterns and delayed detections or treatments regardless of the increase
13
14
15 82 in awareness^{6,7}.

16
17 83 Disparities do exist in the global burden of breast cancer, especially among counties and regions
18
19 84 with different levels of development. Understanding the exact correlations between the disease
20
21 85 burden and socioeconomic status is critical for the world's health policymakers to formulate
22
23 86 appropriate measures according to local conditions. Socio-demographic Index (SDI) was first
24
25 87 introduced in the Global Burden of Disease Study 2015 (GBD 2015) by the Institute for Health
26
27 88 Metrics and Evaluation to quantitatively measure the development of a country or region⁸.
28
29 89 Through combining the latest updated SDI data with breast cancer incidence and mortality data
30
31 90 during 1990 and 2016 available at the GBD 2016 database, this study aimed to describe the current
32
33 91 patterns and trends in breast cancer incidence and mortality according to the country-level
34
35 92 wellbeing, thus further exploring distributions and changes in the breast cancer associated health
36
37 93 inequality according to the spectrum of development.

40 94

41 95

44 96 Material and Methods

46
47 97 Breast cancer was defined by the International Classification of Disease - Revision 10 with code
48
49 98 C50. Incidence and mortality data from 195 individual countries and predefined five SDI groups
50
51 99 between 1990 and 2016 were collected from the Global Health Data Exchange database⁵. Annual
52
53 100 incidence and mortality rates by a 5-year age bracket from age 15 to 95+ were extracted for each
54
55 101 involved country. Detailed methods pertaining to estimation of age-standardized incidence and
56
57 102 mortality rate (ASIR and ASMR) per 100,000 population had been previously described in the
58
59
60

1
2
3
4 103 GBD 2016 reports^{3, 4}. Women aged between 50 to 69 constituted the major population
5
6 104 participating in regular screening programs. We further calculated age-specific incidence and
7
8 105 mortality rates per 100,000 population into three subgroups by age: 15-49, 50-69 and 70+, which
9
10 106 were adjusted within age groups in terms of the new world population age-standard³. Mortality-
11
12 107 to-incidence (MI) ratio was calculated by dividing the breast cancer mortality rate for a given
13
14 108 year, age-group, country or SDI group by its corresponding incidence rate.
15
16
17 109

19 110 Patient and Public Involvement

21 111 Patients or public were not involved in the recruitment and conduct of this study.
22
23 112

25 113 Ethics approval

27 114 Ethical approval was not obtained because the data included in this study were publicly available.
28
29 115

32 116 Socio-demographic index

34 117 SDI is a comparable metric of overall development achieved by using an equal weighting of lag-
35
36 118 distributed income per capita, average years of education in the population over 15 years, and
37
38 119 total fertility rate⁹. SDI values on a scale of 0 to 1. A greater value of SDI implies higher level of
39
40 120 development. SDI data for the involved 195 countries from 1990 to 2016 were obtained from the
41
42 121 Global Health Data Exchange database⁵. Countries were grouped into quintiles based on their SDI
43
44 122 values in 2016: high, high-middle, middle, low-middle and low SDI groups. Detailed methods
45
46 123 describing computation of the SDI as well as the choice of the quintile cutoffs were reported
47
48 124 elsewhere^{1, 3}.
49

51 125

53 126 Gini coefficient and concentration index

55 127 Gini coefficient and concentration index drawn from the field of economics were used to measure
56
57 128 breast cancer associated health inequality in our study^{10, 11}. Gini coefficient was calculated based
58
59
60

1
2
3
4 129 on the Lorenz curve, and it ranged from 0 to 1, 0 representing perfect equality and 1 total
5
6 130 inequality¹¹. Annual ASIRs, ASMRs, age-specific incidence and mortality rates and MI ratios of
7
8 131 breast cancer for 195 countries were used to calculate the Gini coefficients and to find out the
9
10 132 trends in between-country health inequality during 1990 and 2016. Concentration index was
11
12 133 derived from the concentration curve and commonly used to measure socioeconomic-related
13
14 134 health inequality¹². Concentration indexes were computed by relating the above breast cancer
15
16 135 metrics to corresponding national SDIs. The value of this index varies between -1 and +1. Positive
17
18 136 (negative) value of the concentration index indicated the disease burden owing to the occurrence
19
20 137 or death of breast cancer was more concentrated in countries with high (low) levels of
21
22 138 development measured by SDI¹². The absolute value demonstrates the degree of a “pro-developed”
23
24 139 or “pro-underdeveloped” distribution in health limitations. Zero means an absence of inequality
25
26 140 associated to the socioeconomic gradient instead of the absence of inequality.
27
28
29
30

31 141

32 142 Statistical analyses

33
34 143 For a normal distribution but heterogeneity in variances of incidence, mortality and MI ratio data,
35
36 144 one-way ANOVA was performed to determine the statistical significance of differences in
37
38 145 incidence rates, mortality rates and MI ratios across SDI-based country groups, followed by
39
40 146 pairwise comparisons using Tamhane T2 test¹³. Linear regression model was used to test for the
41
42 147 correlation between breast cancer indicators and SDI values. Joinpoint piecewise linear regression
43
44 148 analysis was performed to identify time points when significant changes occurred as well as
45
46 149 temporal trends in age-standardized and age-specific incidence and mortality rates during 1990
47
48 150 and 2016¹⁴. Default parameters were used, except for setting the minimum number of data points
49
50 151 between two joints and at either end of the data to 5. To avoid over-fitting at the truncating points,
51
52 152 maximum number of joinpoints was defined as 2. The best-fit point where the rate had changed
53
54 153 prominently was decided by means of a permutation test, and the *P* value for each permutation
55
56 154 test was estimated using Monte Carlo methods¹⁴. Statistics on annual percent change (APC) for
57
58
59
60

1
2
3
4 155 each segment and average annual percent change (AAPC) for the overall period were summarized
5
6 156 using the optimal joinpoint model. All joinpoint trend analyses were undertaken via the joinpoint
7
8 157 statistical software (Version 4.5.0.1) from the surveillance research program of the United States
9
10 158 National Cancer Institute¹⁵. The Gini coefficient was computed by the AINEQUAL module¹⁶,
11
12 159 and the concentration index by the CONINDEX module¹⁷ using Stata 14.0 software (Stata Corp,
13
14 160 Texas, USA). Other statistical analyses were performed with SPSS 20.0 (IBM Corp, Chicago,
15
16 161 USA).

17
18
19 162

20 21 163 Results

22 23 164 Current profiles in breast cancer incidence and mortality according to SDIs

24
25 165 Figure 1 showed distinct distributions of counts and proportions of new cases and deaths due to
26
27 166 breast cancer in five SDI groups in 2016. There were 719 thousand new cases in high SDI
28
29 167 countries, about 20 times of that of 37 thousand in low SDI groups. Death number in these two
30
31 168 groups were 162 and 32 thousand, respectively. About half of the new cases occurred in women
32
33 169 aged 50 to 69 across all SDI groups. In countries belonging to middle, low-middle or low SDI
34
35 170 group, more than one third new cases happened in young ages between 15 and 49, along with
36
37 171 more proportion of deaths in this age group. Deaths in the age of 70 or elder, by contrast, made
38
39 172 up 50.9% of total breast cancer deaths in high SDI countries.

40
41 173 One-way ANOVA suggested significant differences in both age-standardized and age-specific
42
43 174 incidence rates and MI ratios ($P < 0.01$), but did not imply discrepancies of mortality rates among
44
45 175 countries in different SDI groups. Pairwise comparisons indicated lower MI ratios in countries
46
47 176 representing the higher level of development based on SDI, where the mortality rates were not
48
49 177 proportional to their high incidence rates (Figure 2). The Incidence rates in all age groups were
50
51 178 shown to have a positive dose-response relationship with SDIs, otherwise than a negative dose-
52
53 179 response relationship between MI ratios and SDIs (Figure 3). Besides, the rate ratios exhibited
54
55 180 well-fitting linear relationships in all age groups, whereas the incidence and mortality rates in
56
57
58
59
60

1
2
3
4 181 elder age groups were more scattered across countries with varied SDIs.
5
6

7 182

8 183 Temporal trends in breast cancer incidence and mortality across SDI groups
9

10 184 According to the joinpoint trend analyses (Table 1), the ASIRs in high and high-middle SDI
11
12 185 groups plateaued after a quick increase at early 1990s. The ASIRs in the high SDI group even
13
14 186 displayed a declining trend by 0.1% per year since 2000. However, significant increases were
15
16 187 found in middle, low-middle and low SDI groups through the whole period from 1990 to 2016
17
18 188 (Supplementary figure 1A). The AAPC in ASIR for the middle SDI group was 2.1%, far ahead
19
20 189 of increases in other groups. Trends of incidence rates in groups of 15-49, 50-69 and 70+ years
21
22 190 old were comparable with those of ASIRs across SDI groups (Supplementary table 1 and figure
23
24 191 1B).
25
26

27 192 Changes in ASMRs were contradictory across SDI groups as shown in table 2 and
28
29 193 supplementary figure 2A. In the high SDI group, the ASMR continuously decreased from 24.2 in
30
31 194 1990 to 17.6 in 2016, with an AAPC of -1.3%. The ASMR in high-middle SDI group began to
32
33 195 decline in 1994, and an accelerated decrease (APC: -1.9%) was witnessed between 2004 and 2016.
34
35 196 The ASMR in the middle SDI group also slightly diminished from 2002 to 2016 with an average
36
37 197 decrease of 0.5% per year. Opposite trends were displayed in the low-middle (2002-2016, APC:
38
39 198 0.7%) and low SDI groups (2009-2016, APC: 0.8%), especially in recent years. Patterns of change
40
41 199 in three age groups were similar with those of ASMR in each SDI group, but the spectrum of
42
43 200 change differed (Supplementary table 2 and figure 2B). For example, our results showed a much
44
45 201 less decrease in more developed regions and more increase in less developed regions in the
46
47 202 mortality among the group aged 70+, which was much less-than-ideal.
48
49

50 203

51 204 Global health inequality related to breast cancer
52

53 205 The Gini coefficients for the incidence of breast cancer decreased continuously from 1990 to 2016
54
55 206 (Figure 4A), the values of which computed from ASIRs and incidence rates in the age groups of
56
57
58
59
60

1
2
3
4 207 15-49, 50-69 and 70+ had dropped to 0.33, 0.30, 0.34 and 0.38 by 2016, compared with those of
5
6 208 0.38, 0.35, 0.39 and 0.43 in 1990, respectively. Similarly, the Gini coefficients calculated with
7
8 209 mortality rates in all age groups except the 15-49 group showed markedly declining trends during
9
10 210 the same period. On the contrary, the Gini coefficients, according to the distribution of MI ratios,
11
12 211 increased, which reached up to 0.29 in 2016 from a base of 0.23 in 1990.

13
14 212 The concentration indexes according to breast cancer age-standardized and age-specific
15
16 213 incidence and mortality rates were all above zero in 1990, suggesting that the inequalities
17
18 214 associated with socioeconomic development concentrated in countries with a higher level of
19
20 215 development measured by SDI. Moreover, the concentration indexes for the 70+ group were
21
22 216 much greater than those in others. As can be seen in Figure 4B, both the concentration indexes of
23
24 217 incidence and mortality rates decreased between 1990 and 2016, and the rates of descent sped up
25
26 218 since late 1990s. The concentration indexes computed with mortality rates in the age groups of
27
28 219 15-49 and 50-69 inclined to zero and became negative in 1998 and 2013, respectively. In contrast,
29
30 220 the concentration indexes based on age-standardized and age-specific MI ratios were below zero,
31
32 221 with values of -0.21, -0.22, -0.22 and -0.18 in 1990, and by 2016, the values of which had
33
34 222 decreased to -0.28, -0.31, -0.30 and -0.25, respectively.
35
36 223
37
38 224

39 40 41 42 225 Discussion

43
44 226 The socioeconomic development associated inequality in global incidence of breast cancer has
45
46 227 been decreasing since 1990. Still, countries with higher levels of development on the basis of
47
48 228 SDIs were shown to have worse incidence burdens by 2016. In keeping with the opposite trends
49
50 229 for mortality rates between countries with high and low SDIs, the concentration indexes of
51
52 230 mortality fell and even turned to be negative in the age groups of 15-49 and 50-69 in recent years,
53
54 231 pointing towards a transition in the concentration of mortality burdens from the developed to
55
56 232 undeveloped regions. Conversely, both the overall inequality and the part correlated with
57
58
59
60

1
2
3
4 233 socioeconomic development in MI ratio - a health measure derived from the rate ratio of mortality
5
6 234 and incidence - increased from 1990 to 2016. In 2016, MI ratios showed distinct gradients from
7
8 235 the high to low SDI regions among all age groups.
9

10 236 With epidemiological data reported for specific countries, it has been a prevailing perception
11
12 237 that inequalities existed in breast cancer incidence worldwide, especially between the high-
13
14 238 income countries and LMICs¹⁸⁻²¹. However, evidence about the quantitative relationship between
15
16 239 the breast cancer burdens and national socioeconomic development was still limited. On the basis
17
18 240 of GLOBOCAN 2012 estimates, incidence burden due to breast cancer distributed with obvious
19
20 241 disparities among countries in different levels of human development index (HDI)², which was
21
22 242 in accordance with our results in the light of data from the GBD 2016 study and SDI-a newly
23
24 243 developed indicator for socioeconomic status of a given country. The overall inequality in breast
25
26 244 cancer incidence had not yet been eliminated and still concentrated in countries with higher levels
27
28 245 of SDI. The prevalence of breast cancer is somewhat associated with a so-called western lifestyle
29
30 246 (ie, specific reproductive patterns and excess body weight)^{22, 23}, making it a marker for the extent
31
32 247 of development. Trend analyses in our study demonstrated a quick increasing in breast cancer
33
34 248 incidence in countries belonging to the middle SDI group. This fact might suggest that countries
35
36 249 with middle levels of SDI were undergoing rapid social and economic transitions²⁴. In many
37
38 250 LMICs, burdens due to infection-related cancers, such as cervical, gastric and liver cancer,
39
40 251 remained top ranking, instead of breast cancer^{1, 2}. Mammographic screening programs were
41
42 252 generally implemented in high-income countries, especially for women aged 50 to 69 years²⁵⁻²⁷.
43
44 253 Our subgroup analysis based on age conformed transient rises in incidence of women at this age
45
46 254 group and subsequent falls in those elder than 70 years in high SDI countries.
47
48
49

50 255 The mortality rates from breast cancer did not differ significantly from the low to high SDI
51
52 256 regions. Inequalities in deaths caused by breast cancer were possibly offset by better outcomes in
53
54 257 more developed countries because of early detections and advanced treatments, and small scale
55
56 258 of incidence but limited access to health cares in most LMICs^{28, 29}. Therefore, mortality rates
57
58 259 could not well represent the exact trends and current status of death burdens caused by cancer.
59
60

1
2
3
4 260 Cancer survival was another important indicator for death burden of malignancies. According to
5
6 261 data from 59 countries in CONCORD-2 study³⁰, five-year survival for patients diagnosed with
7
8 262 breast cancer during 2005-09 in the North America, Australia, Israel, Brazil, and most Northern
9
10 263 and Western European countries had reached up to 85% or higher, while it remained 60% or lower
11
12 264 in many LMICs, such as India, Mongolia, Algeria and South Africa. However, comprehensive
13
14 265 survival data were scarce in most countries, especially in those with limited resources. It remained
15
16 266 an important issue to conclude the extent of socioeconomic development associated inequalities
17
18 267 in the survivorship of breast cancer and to compare the current survival status in each country
19
20 268 across the world. Here in our study, we analyzed the trends of inequalities in breast cancer MI
21
22 269 ratios, which evaluated the departure of mortality in relation to incidence from expectation and
23
24 270 was suggested as an approximation for cancer survival³¹⁻³³. Our results indicated widening
25
26 271 disparities in the MI ratios of breast cancer among countries with different levels of development.

27 272 HDI was a metric composed by life expectancy at birth, mean and expected years of schooling
28
29 273 and gross national income per capita³⁴. It was used by a few researches to investigate how macro-
30
31 274 socioeconomic determinants correlated with national disease burdens^{2, 28, 35}. Nevertheless, it could
32
33 275 be confusing when a measure of overall health (life expectancy at birth) was one important
34
35 276 component of the index used to evaluate how socioeconomic development influences health. In
36
37 277 the GBD 2015 study, SDI was first developed to identify where countries or geographic areas sit
38
39 278 on the spectrum of societal development⁸. As reproductive patterns were proved to be risk factors
40
41 279 for breast cancer²², SDI, a yardstick constructed based on measures of income, education, and
42
43 280 fertility rate, might be more appropriate to weigh the influence of socioeconomic status on the
44
45 281 global patterns and trends in health inequality resulting from breast cancer.

46
47 282 To our knowledge, this study was a first overview about the global patterns and trends in breast
48
49 283 cancer incidence and mortality in relation to levels of SDI. Limitations should also be considered
50
51 284 when the results of our investigation were interpreted. Firstly, this study was subject to the
52
53 285 limitations of the GBD 2016 study, such as data sources and statistical assumptions, which were
54
55 286 detailed in the GBD 2016 reports^{3, 4}. Estimates for most LMICs with poor-quality law data could
56
57
58
59
60

1
2
3
4 287 be biased, especially for MI ratios calculated based on incidence and mortality data. Better
5
6 288 primary data from national wide observational studies or cancer registries are needed for these
7
8 289 countries in the future. Secondly, joinpoint analysis is sensitive to parameter settings. The pattern
9
10 290 groupings of trends in incidence and mortality may change if parameters are set differently or
11
12 291 more data are involved in the analysis. Thirdly, district data within each country, information on
13
14 292 disease stage or histopathological characteristics were unavailable in GBD 2016 database. In the
15
16 293 United States, for example, nationwide distributions and trends in breast cancer burdens differed
17
18 294 by ethnicity, state, disease stage and intrinsic subtype^{36, 37}. More studies are needed to further
19
20 295 understand disparities due to these biases worldwide.
21
22
23
24

296

297 Conclusions

298 The socioeconomic development associated health inequality in breast cancer incidence has been
299 declining since 1990. Countries undergoing an economic and lifestyle transition were
300 experiencing a growing prevalence of breast cancer. Nonetheless, the incidence burden still
301 concentrated in countries with higher SDIs by 2016. These findings highlighted that public health
302 clinicians and cancer control specialists should pay more attention to the primary prevention of
303 breast cancer especially in those high-incidence countries. Breast cancer mortality, in less
304 developed countries, deviated from expectation seriously in relation to their low incidence. This
305 situation even deteriorated with ever-increasing between-country inequalities for rate ratios from
306 1990 until 2016. Planners should try to carry out more sensitive and cost-effective detection and
307 treatment interventions, particularly in low and low-middle SDI settings with limited healthcare
308 resources, so as to combat premature deaths caused by breast cancer.

309

310

311 Funding

312 This work was supported by the National Natural Science Foundation of China (Grant Number,

313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360

1
2
3
4 313 81602716 and 81802628).

5
6 314

7
8 315

9
10 316 **Competing interests**

11
12
13 317 The authors declared no conflict of interest.

14
15 318

16
17 319

18
19
20 320 **Data sharing statement**

21
22 321 The data used in this study is collected from the Global Health Data Exchange database.

23
24 322

25
26 323

27
28
29 324 **Authors' contributions**

30
31 325 Kaimin Hu designed the study, extracted and analyzed the data and prepared the figures. Peili

32
33 326 Ding and Yinan Wu wrote the first draft of the manuscript. Tao Pan and Wei Tian revised the

34
35 327 paper critically. Suzhan Zhang was the principle investigator and designed the study. All authors

36
37 328 commented on manuscript drafts, approved the final version and declared no conflict of interest.

38
39 329

40
41 330

42
43
44 331 **References**

45
46
47 332 1. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, et al. Global, Regional, and

48
49 333 National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and

50
51 334 Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for

52
53
54
55 335 the Global Burden of Disease Study. *JAMA Oncol.* 2017;3(4):524-548.

56
57
58 336 2. Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand

- 1
2
3
4 337 challenge in global health. *Lancet*. 2017;389(10071):847-860.
5
6
7 338 3. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence,
8
9
10 339 and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a
11
12 340 systematic analysis for the Global Burden of Disease Study 2016. *Lancet*.
13
14 341 2017;390(10100):1211-1259.
15
16 342 4. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264
17
18 343 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study
19
20 344 2016. *Lancet*. 2017;390(10100):1151-1210.
21
22 345 5. Global Health Data Exchange. GBD Results Tool. Available from:
23
24 346 <http://www.healthdata.org/gbd-results-tool>. Accessed Sep 26, 2017.
25
26 347 6. Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive
27
28 348 epidemiology of female breast cancer: an international comparison of screening, incidence,
29
30 349 survival and mortality. *Cancer Epidemiol*. 2012;36(3):237-248.
31
32 350 7. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global Cancer in Women: Burden and
33
34 351 Trends. *Cancer Epidemiol Biomarkers Prev*. 2017;26(4):444-457.
35
36 352 8. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause
37
38 353 mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic
39
40 354 analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459-1544.
41
42 355 9. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 356 2016) Socio-demographic Index (SDI) 1970–2016. Seattle, United States: Institute for Health
5
6
7 357 Metrics and Evaluation (IHME), 2017.
8
9
10 358 10. Bleichrodt H, van Doorslaer E. A welfare economics foundation for health inequality
11
12
13 359 measurement. *J Health Econ.* 2006;25(5):945-957.
14
15
16 360 11. Pan American Health Organization. Measuring health inequalities: Gini coefficient and
17
18
19 361 concentration index. *Epidemiol Bull.* 2001;22(1):2.
20
21
22 362 12. Costa-Font J, Hernandez-Quevedo C. Measuring inequalities in health: What do we know?
23
24
25 363 What do we need to know? *Health Policy.* 2012;106(2):195-206.
26
27
28 364 13. Shingala MC, Rajyaguru A. Comparison of Post Hoc Tests for Unequal Variance.
29
30
31 365 *International Journal of New Technologies in Science and Engineering.* 2015;2:22-33.
32
33
34 366 14. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with
35
36
37 367 applications to cancer rates. *Stat Med.* 2000;19(3):335-351.
38
39
40 368 15. National Cancer Institute. Surveillance Epidemiology and end results (SEER) program.
41
42 369 methods & tools: joinpoint trend analysis. Available from:
43
44
45 370 <https://surveillance.cancer.gov/joinpoint>. Accessed Oct 10, 2017.
46
47
48 371 16. Kerm PV. INEQUAL7: Stata module to compute measures of inequality. *Statistical Software*
49
50
51 372 *Components S416401, Boston College Department of Economics.* 2001.
52
53
54 373 17. O'Donnell O, O'Neill S, Van Ourti T, Walsh B. conindex: Estimation of concentration indices.
55
56
57 374 *Stata J.* 2016;16(1):112-138.
58
59
60

- 1
2
3
4 375 18. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin.*
5
6
7 376 2014;64(1):52-62.
8
9
10 377 19. Lundqvist A, Andersson E, Ahlberg I, Nilbert M, Gerdtham U. Socioeconomic inequalities in
11
12
13 378 breast cancer incidence and mortality in Europe—a systematic review and meta-analysis. *Eur*
14
15
16 379 *J Public Health.* 2016;26(5):804-813.
17
18
19 380 20. Li T, Mello-Thoms C, Brennan PC. Descriptive epidemiology of breast cancer in China:
20
21
22 381 incidence, mortality, survival and prevalence. *Breast Cancer Res Treat.* 2016;159(3):395-406.
23
24
25 382 21. Lukong KE, Ogunbolude Y, Kamdem JP. Breast cancer in Africa: prevalence, treatment
26
27
28 383 options, herbal medicines, and socioeconomic determinants. *Breast Cancer Res Treat.*
29
30
31 384 2017;166(2):351-365.
32
33
34 385 22. Porter P. "Westernizing" women's risks? Breast cancer in lower-income countries. *N Engl J*
35
36
37 386 *Med.* 2008;358(3):213-216.
38
39
40 387 23. Lahmann PH, Schulz M, Hoffmann K, et al. Long-term weight change and breast cancer risk:
41
42
43 388 the European prospective investigation into cancer and nutrition (EPIC). *Br J Cancer.*
44
45
46 389 2005;93(5):582-589.
47
48
49 390 24. Bray F. Transitions in human development and the global cancer burden. In: Steward BW,
50
51
52 391 Wild CP, eds. World Cancer Report 2014. *Lyon: International Agency for Research on Cancer,*
53
54
55 392 2014.
56
57 393 25. Gotzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. *Cochrane*
58
59
60

- 1
2
3
4 394 *Database Syst Rev.* 2013(6):CD001877.
- 5
6
7 395 26. Narod SA. Reflections on screening mammography and the early detection of breast cancer:
8
9
10 396 A Countercurrents Series. *Curr Oncol.* 2014;21(5):210-214.
- 11
12
13 397 27. Loberg M, Lousdal ML, Bretthauer M, Kalager M. Benefits and harms of mammography
14
15
16 398 screening. *Breast Cancer Res.* 2015;17:63.
- 17
18
19 399 28. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the
20
21
22 400 Human Development Index (2008-2030): a population-based study. *Lancet Oncol.*
23
24
25 401 2012;13(8):790-801.
- 26
27
28 402 29. Coughlin SS, Ekwueme DU. Breast cancer as a global health concern. *Cancer Epidemiol.*
29
30
31 403 2009;33(5):315-318.
- 32
33
34 404 30. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009:
35
36
37 405 analysis of individual data for 25,676,887 patients from 279 population-based registries in 67
38
39
40 406 countries (CONCORD-2). *Lancet.* 2015;385(9972):977-1010.
- 41
42
43 407 31. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and
44
45
46 408 prevalence across five continents: defining priorities to reduce cancer disparities in different
47
48
49 409 geographic regions of the world. *J Clin Oncol.* 2006;24(14):2137-2150.
- 50
51
52 410 32. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods
53
54
55 411 Part II. Completeness. *Eur J Cancer.* 2009;45(5):756-764.
- 56
57
58 412 33. Asadzadeh Vostakolaei F, Karim-Kos HE, Janssen-Heijnen ML, Visser O, Verbeek AL,
59
60

- 1
2
3
4 413 Kiemeny LA. The validity of the mortality to incidence ratio as a proxy for site-specific cancer
5
6
7 414 survival. *Eur J Public Health*. 2011;21(5):573-577.
8
9
10 415 34. Programme UND. Human development report. Available from:
11
12
13 416 <http://hdr.undp.org/en/content/human-development-index-hdi>. Accessed Nov 16, 2017.
14
15
16 417 35. Fidler MM, Soerjomataram I, Bray F. A global view on cancer incidence and national levels
17
18
19 418 of the human development index. *Int J Cancer*. 2016;139(11):2436-2446.
20
21
22 419 36. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer
23
24
25 420 statistics, 2015: Convergence of incidence rates between black and white women. *CA Cancer*
26
27
28 421 *J Clin*. 2016;66(1):31-42.
29
30
31 422 37. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017,
32
33
34 423 racial disparity in mortality by state. *CA Cancer J Clin*. 2017;67(6):439-448.
35
36
37
38
39 425

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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*

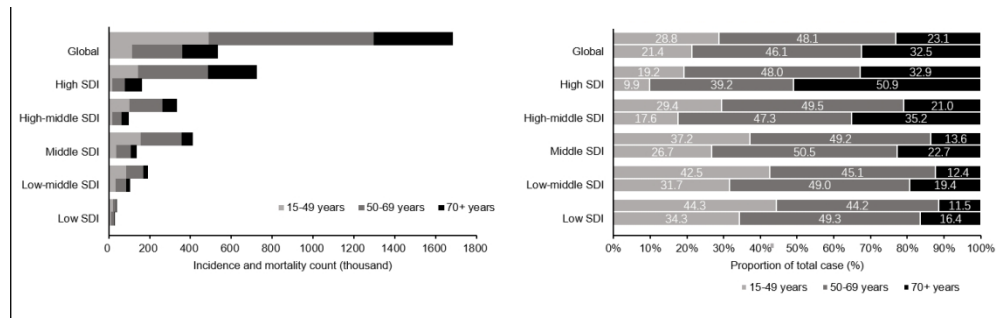


Figure 1

256x79mm (150 x 150 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

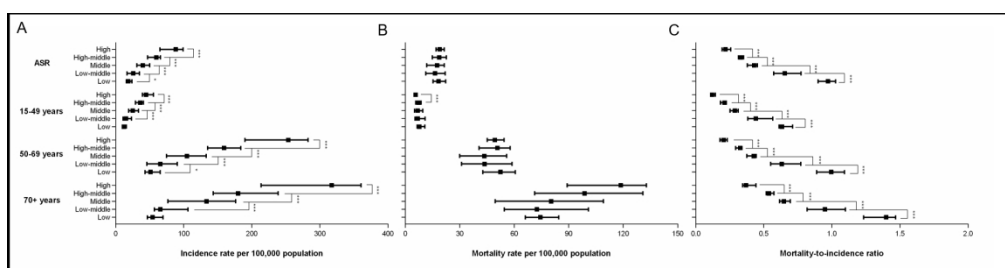


Figure 2

362x92mm (150 x 150 DPI)

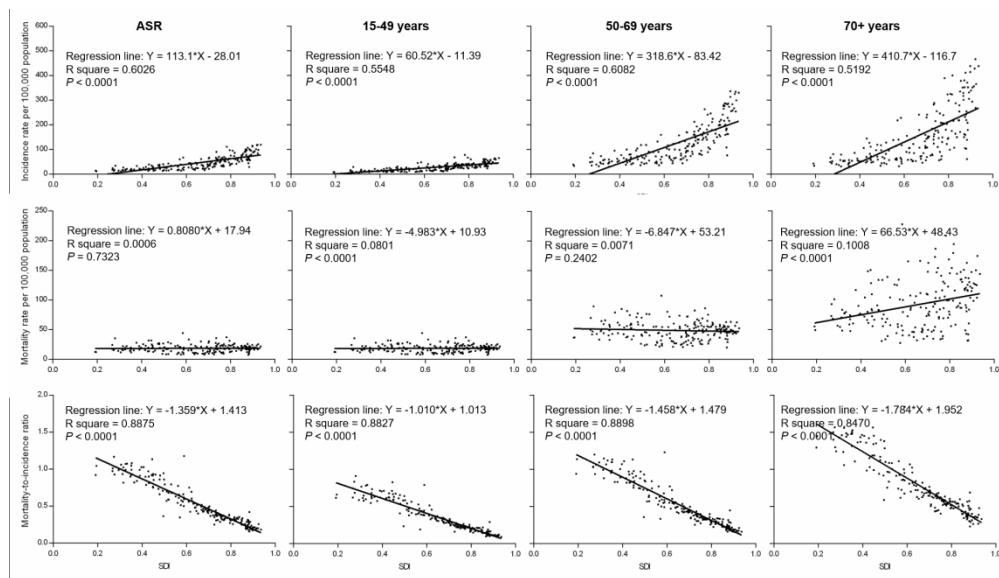


Figure 3

343x196mm (150 x 150 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

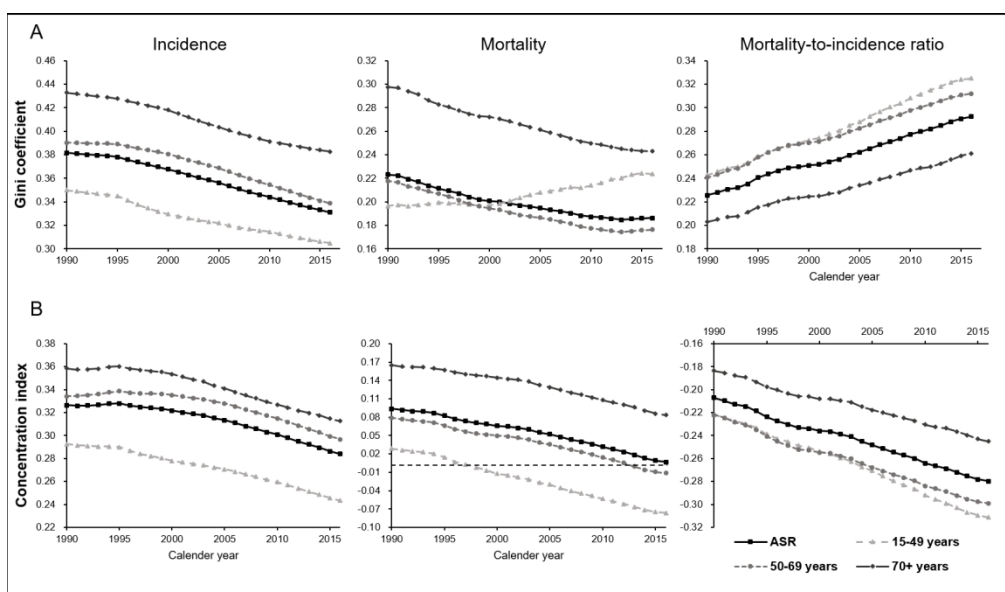


Figure 4

283x163mm (150 x 150 DPI)

Supplementary figures and tables

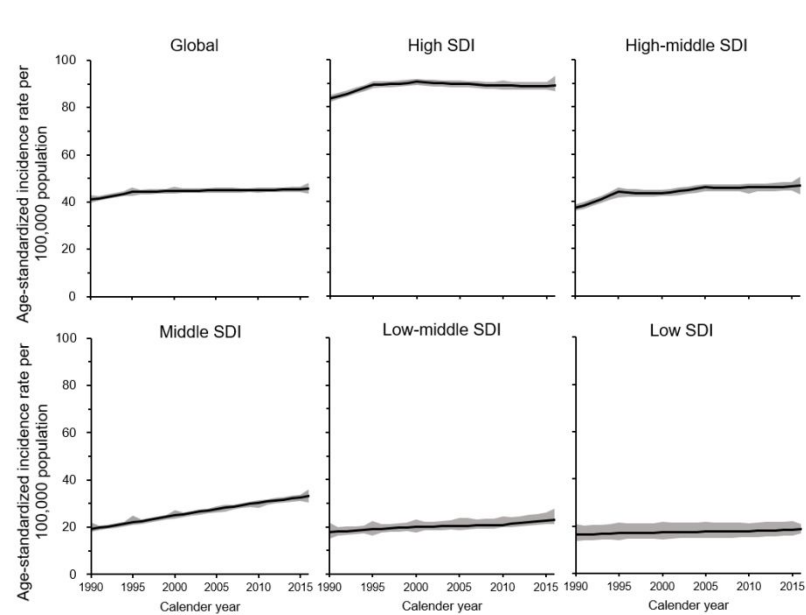
Supplementary table 1. Breast cancer age-specific incidence rates in 1990, 2016 and joinpoint trend analysis between 1990 and 2016 by SDI settings.

	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	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*

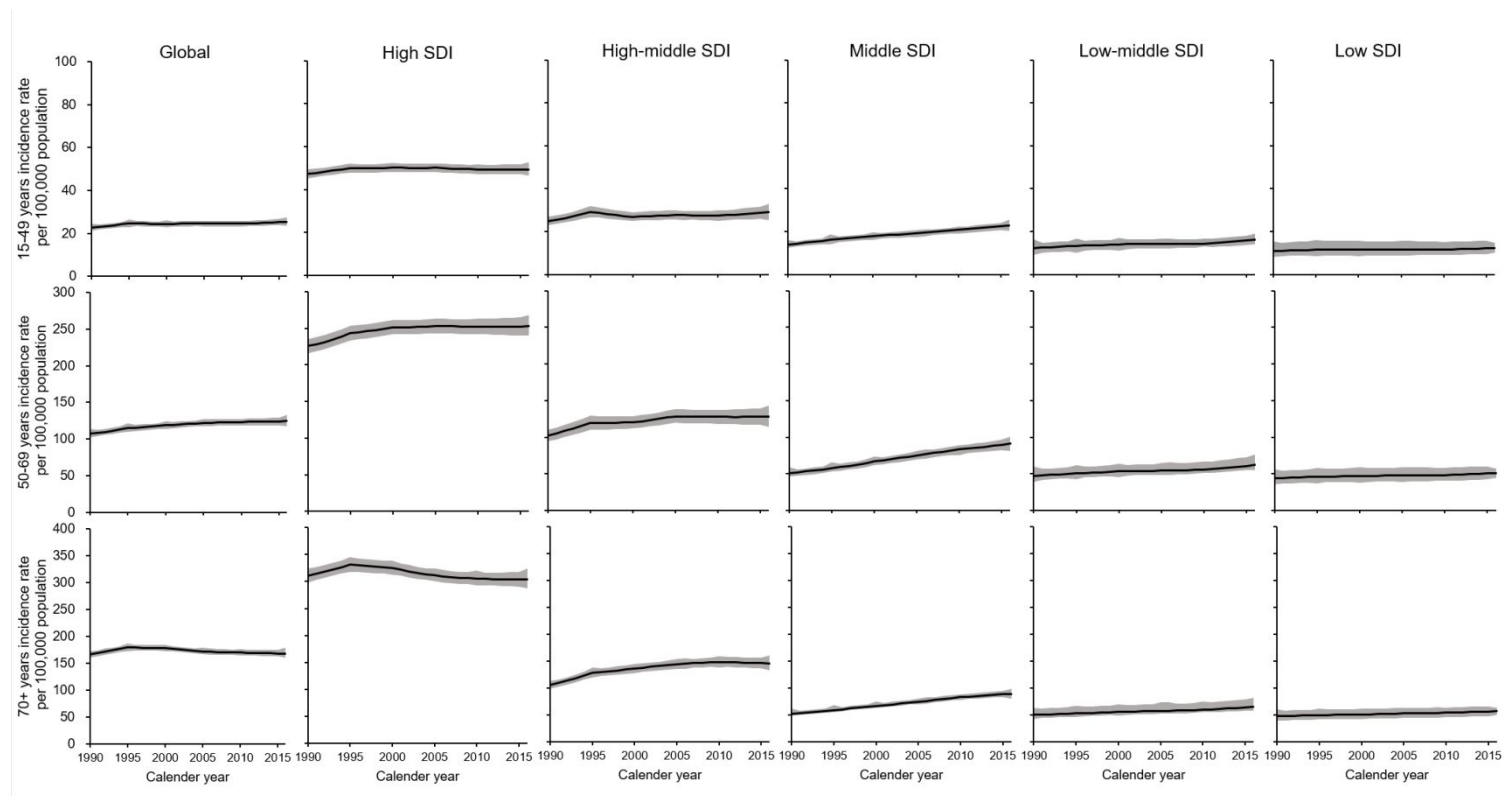
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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

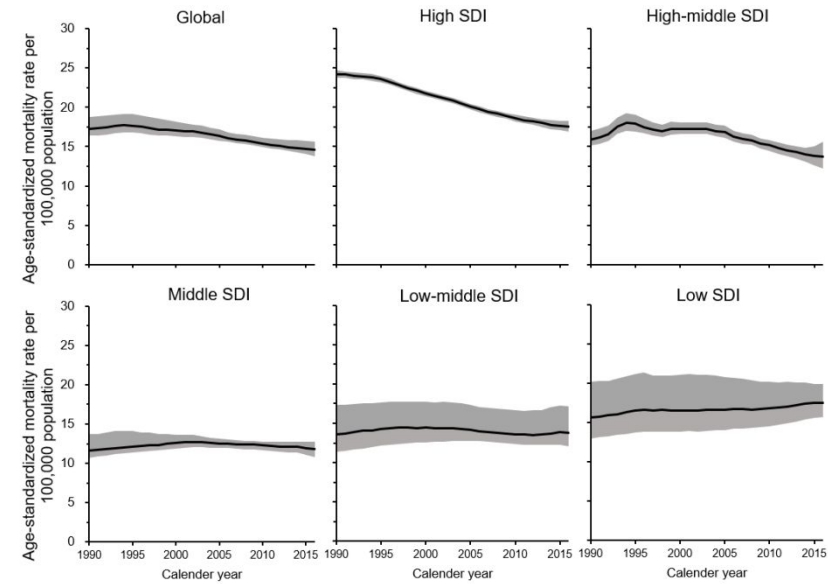
	Age	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
		Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	80.7	7.4	6.6-8.4	114.3	6.0	5.6-6.6	1990-1995	0.8*	1995-2012	-1.4*	2012-2016	-0.3*	-0.8*
	50-69 years	156.5	44.9	42.2-49.4	246.9	38.0	35.6-41.4	1990-1994	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*



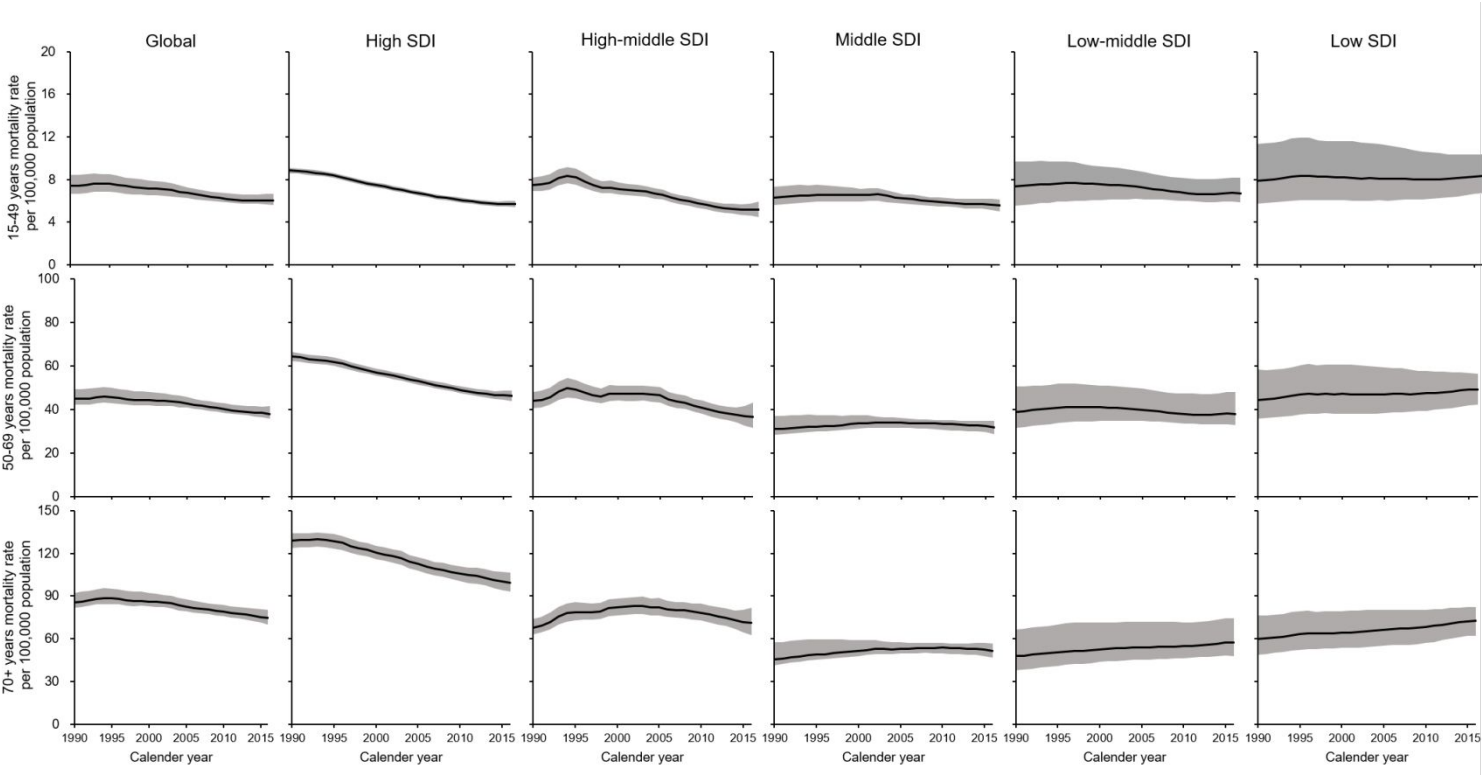
Supplementary figure 1A. Trends in breast cancer age-standardized incidence rate (ASIR) according to SDI settings, 1990-2016. The black lines represent the estimated ASIRs, and areas shaded in gray denote 95% uncertainty intervals.



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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028461.R2
Article Type:	Original research
Date Submitted by the Author:	30-Jul-2019
Complete List of Authors:	Hu, Kaimin; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Ding, Peili; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Wu, Yinan; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Tian, Wei; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Pan, Tao; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Zhang, Suzhan; Cancer Institute, the 2nd affiliated hospital of Zhejiang university
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Oncology, Global health
Keywords:	breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini coefficient, concentration index

SCHOLARONE™
Manuscripts

1
2
3
4
5 1 Title page:
6
7

8 2 Global Patterns and Trends in Breast Cancer Incidence and
9
10 3 Mortality According to Socio-demographic Indices: An
11
12 4 Observational Study Based on the Global Burden of Diseases
13
14
15
16
17 5

18 6 Kaimin Hu ^{1,2,#}

19 7 Peili Ding ^{1,#}

20 8 Yinan Wu ¹

21 9 Wei Tian ^{1,2}

22 10 Tao Pan ^{1,2}

23 11 Suzhan Zhang ¹

24 12
25 13 ¹ Cancer Institute, the Second Affiliated Hospital of Zhejiang University, College of Medicine,
26 14 Hangzhou, Zhejiang, China.

27 15 ² Department of Breast Surgery, the Second Affiliated Hospital of Zhejiang University, College
28 16 of Medicine, Hangzhou, Zhejiang, China.

29 17 # These authors contributed equally to this work.
30 18

31 19 Corresponding Author:

32 20 Suzhan Zhang

33 21 Cancer Institute

34 22 The Second Affiliated Hospital of Zhejiang University, College of Medicine

35 23 Jiefang Road 88, Hangzhou, 310009, China.

36 24 Telephone: +86-5718778-4501

37 25 Fax: +86-5718721-4404
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 26 Email: zrsj@zju.edu.cn
5
6
7 27
8
9 28
10
11 29 Word count: 3065
12
13 30
14
15 31
16
17 32 **Abstract:**
18
19
20 33 Objectives: Disparities exist in the global burden of breast cancer. We aimed to investigate the
21
22 34 recent patterns and trends in the incidence and mortality rate of breast cancer; we also assessed
23
24 35 health inequalities related to breast cancer according to socioeconomic development factors.
25
26 36 Design: An observational study based on the Global Burden of Diseases.
27
28 37 Methods: Estimates of breast cancer incidence and mortality between 1990 and 2016 were
29
30 38 obtained from the Global Health Data Exchange database. Data in 2016 were then described using
31
32 39 the age-standardized and age-specific incidence, mortality and mortality-to-incidence (MI) ratio,
33
34 40 according to the socio-demographic index (SDI) levels. Trends were assessed by measuring the
35
36 41 annual percent change using the joinpoint regression. Inequalities with respect to between-country
37
38 42 health systems were measured using the Gini coefficients and concentration indices.
39
40 43 Results: Countries with higher SDI levels had a worse disease incidence burden in 2016, while
41
42 44 the health inequality in breast cancer incidence decreased since 1990. The mortality rate showed
43
44 45 opposite trends between high and low SDI countries, with the concentration indices declining and
45
46 46 even turning negative in the 15-49 and 50-69 age groups, suggesting an increase in the mortality
47
48 47 burden in undeveloped regions. Conversely, inequality related to the MI ratio increased. In 2016,
49
50 48 the MI ratios showed distinct gradients from high to low SDI regions in all age groups.
51
52 49 Conclusions: Patterns and trends in breast cancer incidence and mortality closely correlated with
53
54 50 SDI levels. Our findings highlighted that the two pressing needs in the next decades are the
55
56 51 primary prevention of breast cancer in high SDI countries with high incidence and the
57
58
59
60

1
2
3
4 52 development of cost-effective diagnosis and treatment interventions in low SDI countries with
5
6 53 poor MI ratios.
7

8 54
9

10 55
11

12
13 56 **Keywords:** breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini
14
15 57 coefficient, concentration index
16

17 58
18

19 59
20

21 60 Article summary

22
23
24
25 61 Strengths and limitations of this study :

- 26
27
28 62 ● This study was the first overview of the current global patterns and long-term period trends
29
30 63 in breast cancer burden, stratified according to the levels of socio-demographic development.
31
32 64 ● Gini coefficient and concentration index were used to evaluate the extent, trend and
33
34 65 concentration of health inequality caused by breast cancer.
35
36 66 ● The study is limited by the use of secondary estimated data from the Global Burden of
37
38 67 Disease database, as the estimates for some countries with poor-quality raw data could be
39
40 68 biased.
41

42 69
43

44 70
45

46 71 Introduction

47
48
49 72 Breast cancer is the most common cancer and the first leading cause of cancer death among
50
51 73 women, with an estimated 2.4 million new cases and 523,000 deaths worldwide in 2015¹. Where
52
53 74 and in which socioeconomic status women live can significantly affect their odds of developing
54
55 75 breast cancer and whether she will ultimately survive¹. The incidence rate in high-income
56
57 76 countries is higher than in low- and middle-income countries (LMICs)¹⁻³. Because of better
58
59
60

1
2
3
4 77 awareness of the risk factors, regular mammography screening and sufficient and effective
5
6 78 medical services, the breast cancer mortality rates in many high-income countries significantly
7
8 79 declined in the last decades, and the incidence rates kept stable or even decreased since the 2000.
9
10 80 Breast cancer is not confined to high-income countries. The cancer-related mortality rates in
11
12 81 LMICs do not correspond to their low incidence rates³⁻⁵. In many resource-poor settings or
13
14 82 countries undergoing rapid transition, both the incidence and mortality rates of breast cancer
15
16 83 increased, partially due to changes in the reproductive patterns and delayed diagnosis and
17
18 84 treatments, independently from the increase in breast cancer awareness^{6, 7}.

21 85 Disparities do exist in the global burden of breast cancer, especially among counties with
22
23 86 different development levels. Understanding the exact correlations between the disease burden
24
25 87 and the socioeconomic status is critical for the world's health policymakers to formulate
26
27 88 appropriate measures according to local conditions. The Socio-demographic Index (SDI) was first
28
29 89 introduced in the Global Burden of Disease Study 2015 (GBD 2015) by the Institute for Health
30
31 90 Metrics and Evaluation to quantitatively measure the development of a country or region⁸.
32
33 91 Through combining the latest SDI data with breast cancer incidence and mortality data between
34
35 92 1990 and 2016, this study aimed to describe the current patterns and trends in breast cancer
36
37 93 incidence and mortality according to the country-level wellbeing. This approach will enable a
38
39 94 comprehensive investigation on the distributions and changes in the breast cancer-associated
40
41 95 health inequalities, according to the spectrum of countries' development.
42
43
44
45
46
47
48

49 98 Material and Methods

51 99 Breast cancer was defined by the International Classification of Disease-Revision 10 with code
52
53 100 C50. Incidence and mortality data between 1990 and 2016 from 195 individual countries,
54
55 101 belonging to 5 predefined SDI groups were collected from the Global Health Data Exchange
56
57 102 database⁵. The annual incidence and mortality rates, stratified in 5-year age bracket from age 15
58
59
60

1
2
3
4 103 to 95+, were extracted for each involved country. Detailed methods for the estimation of age-
5
6 104 standardized incidence and mortality rate (ASIR and ASMR, respectively) per 100,000
7
8 105 population had been previously described in the GBD 2016 reports^{3,4}. Women aged between 50
9
10 106 and 69 years constituted the major population participating in regular screening programs. We
11
12 107 further calculated the age-specific incidence and mortality rates per 100,000 population into three
13
14 108 subgroups: 15-49, 50-69 and 70+ years of age, which were adjusted following the new world
15
16 109 population age-standard³. Mortality-to-incidence (MI) ratio was calculated by dividing the breast
17
18 110 cancer mortality rate for a given year, age-group, country, and SDI group by its corresponding
19
20 111 incidence rate.
21
22

23 112

25 113 Patient and Public Involvement

27 114 Patients or public were not involved in the recruitment and conduct of this study.

29 115

31 116 Ethics approval

33 117 Ethical approval was not obtained because the data included in this study were publicly available.

35 118

37 119 Socio-demographic index (SDI)

39 120 SDI is a comparable metric of overall development calculated using an equal weighting of lag-
41 121 distributed income per capita, average years of education in the population over 15 years, and
42 122 total fertility rate⁹. SDI is expressed on a scale of 0 to 1. A greater value of SDI implies a higher
43 123 level of development. SDI data from 1990 to 2016 for the 195 countries involved in the study
44 124 were obtained from the Global Health Data Exchange database⁵. Countries were grouped into the
45 125 following quintiles, based on their SDI values in 2016: high, high-middle, middle, low-middle
46 126 and low SDI. Detailed methods describing the SDI computation as well as the choice of the
47 127 quintile cutoffs were reported elsewhere^{1,3}.

49 128

1
2
3
4 129 Gini coefficient and concentration index
5

6 130 The Gini coefficient and concentration index, used in the economics field, were adopted to
7
8 131 measure breast cancer-associated health inequalities in our study^{10, 11}. The Gini coefficient was
9
10 132 calculated based on the Lorenz curve. It ranges between 0 and 1, with 0 representing perfect
11
12 133 equality and 1 total inequality¹¹. Annual ASIRs, ASMRs, age-specific incidence, age-specific
13
14 134 mortality rates and MI ratios of breast cancer from 195 countries were used to calculate the Gini
15
16 135 coefficients and to describe the health inequality trend between countries from 1990 to 2016. The
17
18 136 concentration index, derived from the concentration curve, is commonly used to measure
19
20 137 socioeconomic-related health inequality¹². Concentration indices were computed by relating the
21
22 138 abovementioned breast cancer metrics to the corresponding national SDIs. The value of the index
23
24 139 varies between -1 and +1. A positive (negative) value of the concentration index indicated that
25
26 140 the breast cancer disease burden was more concentrated in countries with high (low) levels of
27
28 141 development, as measured by the SDI¹². The absolute value is related to the degree of a “pro-
29
30 142 developed” or “pro-underdeveloped” distribution in health limitations. A value of zero means an
31
32 143 absence of inequality associated with the socioeconomic gradient, rather than an absolute absence
33
34 144 of inequality.
35
36
37
38
39

40 146 Statistical analyses
41

42 147 For comparing data with a normal distribution but heterogeneity in variances, such as the
43
44 148 incidence, mortality and MI ratio across 5 SDI-based country groups, we performed the one-way
45
46 149 ANOVA, followed by pairwise comparisons using the Tamhane T2 test¹³. The liner regression
47
48 150 model was used to test the correlation between the indicators for breast cancer burden and SDI
49
50 151 values. The joinpoint piecewise linear regression analysis was performed to identify the time
51
52 152 points where significant changes occurred as well as to identify temporal trends for the age-
53
54 153 standardized and age-specific incidence and mortality rates between 1990 and 2016¹⁴. Default
55
56 154 parameters were used, except the minimum number of data points between two joints and at either
57
58
59
60

1
2
3
4 155 end of the data, which was set to 5. To avoid over-fitting at the truncating points, the maximum
5
6 156 number of joinpoints was defined as 2. The best-fit point where the rate had significantly changed
7
8 157 was assessed with a permutation test, and the *P* value for each permutation test was estimated
9
10 158 using Monte Carlo methods¹⁴. Statistics on the annual percent change (APC) for each segment
11
12 159 and the average annual percent change (AAPC) for the overall period were summarized using the
13
14 160 optimal joinpoint model. All joinpoint trend analyses were performed using the joinpoint
15
16 161 statistical software (Version 4.5.0.1) from the surveillance research program of the United States
17
18 162 National Cancer Institute¹⁵. The Gini coefficient was computed using the AINEQUAL module¹⁶,
19
20 163 and the concentration index with the CONINDEX module¹⁷ by the Stata 14.0 software (Stata Corp,
21
22 164 Texas, USA). Other statistical analyses were performed with the SPSS 20.0 software (IBM Corp,
23
24 165 Chicago, USA).
25
26
27
28
29

30 167 Results

31 168 Current profiles in breast cancer incidence and mortality rates according to SDIs

32
33 169 Figure 1 showed the year 2016 distribution of counts and proportions of new cases and deaths
34
35 170 due to breast cancer in the 5 SDI groups. There were 719,000 new cases in high SDI countries,
36
37 171 about 20 times higher than the 37,000 in low SDI countries. The number of deaths in these two
38
39 172 groups were 162,000 and 32,000, respectively. About half of the new cases occurred in women
40
41 173 aged between 50 and 69 years across all SDI groups. In countries belonging to the middle, low-
42
43 174 middle, and low SDI group, more than one-third of the new cases appeared in the 15-49 age group,
44
45 175 along with higher death proportion in this age group. By contrast, deaths in the age of 70 or older
46
47 176 accounted for 50.9% of the total breast cancer-related deaths in high SDI countries.
48
49

50
51 177 The one-way ANOVA analysis suggested significant differences for both the age-standardized
52
53 178 and the age-specific incidence rates and MI ratios ($P < 0.01$), but not for the mortality rates among
54
55 179 countries belonging to different SDI groups. Pairwise comparisons indicated lower MI ratios in
56
57 180 countries representing the highest level of development based on SDI, where the mortality rates
58
59
60

1
2
3
4 181 were not proportional to their high incidence rates (Figure 2). The Incidence rates in all age groups
5
6 182 were shown to have a positive relationship with SDI, while we observed a negative relationship
7
8 183 between MI ratios and SDI (Figure 3). Moreover, the MI ratios exhibited well-fitting linear
9
10 184 relationships in all age groups, whereas the incidence and mortality rates in the elder age groups
11
12 185 were more scattered across countries with different SDIs.
13
14
15 186

17 187 Temporal trends in breast cancer incidence and mortality across SDI groups

18
19 188 According to the joinpoint trend analysis (Table 1), the ASIR in high and high-middle SDI groups
20
21 189 reached a plateau after a quick increase in the early 1990s. The ASIR in the high SDI group even
22
23 190 showed a declining trend of 0.1% per year since the year 2000. In contrast, significant increases
24
25 191 were found in the middle, low-middle and low SDI groups through the whole period
26
27 192 (Supplementary figure 1A). The ASIR AAPC for the middle SDI group was 2.1%, the highest
28
29 193 increase among the SDI groups. The trend of incidence rates changes in the 15-49, 50-69, and
30
31 194 70+ age groups was comparable with the ASIR values across SDI groups (Supplementary table 1
32
33 195 and supplementary figure 1B).
34
35

36 196 Changes in ASMR were contradictory across SDI groups, as shown in table 2 and
37
38 197 supplementary figure 2A. In the high SDI group, the ASMR continuously decreased from 24.2 in
39
40 198 1990 to 17.6 in 2016, with an AAPC of -1.3%. The ASMR in the high-middle SDI group began
41
42 199 to decline in 1994, and we observed an accelerated decrease (APC: -1.9%) between 2004 and
43
44 200 2016. The ASMR in the middle SDI group also slightly diminished from 2002 to 2016, with an
45
46 201 average decrease of 0.5% per year. Opposite trends were instead observed in the low-middle
47
48 202 (2002-2016, APC: 0.7%) and low SDI groups (2009-2016, APC: 0.8%), especially in recent years.
49
50 203 The change patterns in the 3 age groups were similar to the ASMR in each SDI group, but the
51
52 204 degree of change differed (Supplementary table 2 and supplementary figure 2B). For example,
53
54 205 our results showed, among the 70+ age group, a lower decrease in more developed regions and a
55
56 206 higher increase in less developed regions in the mortality rate.
57
58
59
60

207

208 Global health inequality related to breast cancer

209 The Gini coefficients for the incidence of breast cancer decreased continuously from 1990 to 2016
210 (Figure 4A). The values calculated from the ASIRs and the incidence rate in the 15-49, 50-69 and
211 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
212 0.43 in 1990, respectively. Similarly, the Gini coefficients calculated with mortality rates showed
213 markedly declining trends during the same period in all age groups, except the 15-49 group. On
214 the contrary, the Gini coefficients calculated with the MI ratios distribution increased, reaching a
215 value of 0.29 in 2016 from the 0.23 in 1990.

216 The concentration indices according to the breast cancer age-standardized and age-specific
217 incidence and mortality rates were all above zero in 1990, suggesting that the inequalities
218 associated with socioeconomic development were more concentrated in countries with a higher
219 level of development, as measured by SDI. Moreover, the concentration indices for the 70+ group
220 were higher than those for the other groups. Both the concentration indices of incidence and
221 mortality rate decreased between 1990 and 2016, with the decrease rate accelerating since late
222 1990s, as shown in figure 4B. The mortality rate concentration indices in the age groups of 15-49
223 and 50-69 crossed the zero and became negative in 1998 and 2013, respectively. In contrast, the
224 concentration indices based on age-standardized and age-specific MI ratios were already below
225 zero in 1990, with values of -0.21, -0.22, -0.22 and -0.18. By 2016, the values had decreased to -
226 0.28, -0.31, -0.30 and -0.25.

227

228

229 Discussion

230 The socioeconomic development-associated inequality in the global incidence of breast cancer
231 has been decreasing since 1990. However, countries with higher levels of development according
232 to the SDI had a worse incidence burden by 2016. Consistently with the opposite trends between

1
2
3
4 233 countries with high and low SDI regarding the mortality rate, in recent years the mortality
5
6 234 concentration index turned to be negative in the 15-49 and 50-69 age groups. This observation
7
8 235 points towards a transition in the concentration of mortality burden from developed to
9
10 236 undeveloped countries. Conversely, both the overall inequality and the inequality correlated with
11
12 237 socioeconomic development calculated using the MI ratio increased from 1990 to 2016. In 2016,
13
14 238 the MI ratio distribution showed a distinct gradient from high to low SDI countries among all age
15
16 239 groups.

17
18
19 240 Thanks to the availability of epidemiological data from individual countries, the prevailing
20
21 241 perception has been that inequalities existed in breast cancer incidence worldwide, especially
22
23 242 between the high-income countries and LMICs¹⁸⁻²¹. However, quantitative evidence about the
24
25 243 relationship between the global breast cancer burden and national socioeconomic development
26
27 244 were still limited. According to the GLOBOCAN 2012 estimates, the breast cancer incidence
28
29 245 burden was distributed with obvious disparities among countries with different levels of human
30
31 246 development index (HDI)². This is consistent with our results, which were based on the SDI and
32
33 247 data from the GBD 2016 study. We observed that the overall inequality in breast cancer incidence
34
35 248 had not yet been eliminated and is still concentrated in countries with high SDI levels. The higher
36
37 249 prevalence of breast cancer is somewhat associated with the so-called western lifestyle (i.e.,
38
39 250 specific reproductive patterns and excessive body weight)^{22, 23}, making it a marker for the extent
40
41 251 of development. Trend analyses in our study demonstrated a fast increase in the breast cancer
42
43 252 incidence rate in countries belonging to the middle SDI group. This result might suggest that
44
45 253 countries with middle levels of SDI were undergoing rapid social and economic transitions in the
46
47 254 period considered in the study²⁴. In many LMICs, the burden of infection-related cancers, such as
48
49 255 cervical, gastric and liver cancer, remained higher than that of breast cancer^{1, 2}. Mammographic
50
51 256 screening programs were generally implemented in high-income countries, especially for women
52
53 257 aged between 50 and 69 years²⁵⁻²⁷. Consistently, our subgroup analysis based on the age
54
55 258 confirmed a transient rise in the incidence for women in this age group and a subsequent fall in
56
57 259 the 70+ group in high SDI countries.
58
59
60

1
2
3
4 260 The mortality rates did not differ significantly from low to high SDI countries. Inequalities in
5
6 261 breast cancer deaths were possibly offset by better clinical outcomes in more developed countries
7
8 262 because of early diagnosis and the development of advanced treatments, while a small scale of
9
10 263 incidence but a limited access to health care existed in most LMICs^{28,29}. Therefore, mortality rates
11
12 264 could not well represent the exact trends and current status of cancer-related death burden. Cancer
13
14 265 survival is another important indicator for evaluating the malignancies-related death burden.
15
16 266 According to the data from 59 countries used in the CONCORD-2 study³⁰, the 5-year survival
17
18 267 rate for patients diagnosed with breast cancer during the 2005-2009 period was 85% or higher in
19
20 268 North America, Australia, Israel, Brazil, and most Northern and Western European countries,
21
22 269 while it remained 60% or lower in many LMICs, such as India, Mongolia, Algeria and South
23
24 270 Africa. However, the availability of comprehensive survival data was scarce in most countries,
25
26 271 especially in those with limited resources. Thus, calculating the role of socioeconomic
27
28 272 development-associated inequalities in the survival rate of breast cancer patients and comparing
29
30 273 the current survival status in each country across the world remained critical issues. In the present
31
32 274 study, we analyzed the trends of inequalities for breast cancer MI ratios, which is a marker that
33
34 275 estimate the departure of mortality in relation to incidence from expectation and is suggested as
35
36 276 an approximation for cancer survival³¹⁻³³. Our results suggest a widening disparity according to
37
38 277 the breast cancer MI ratios among countries with different levels of development.
39
40

41
42 278 HDI was a metric composed by life expectancy at birth, mean and expected years of schooling
43
44 279 and gross national income per capita³⁴. It was used to investigate how macro-socioeconomic
45
46 280 determinants correlated with national disease burdens^{2,28,35}. However, the use of this index is not
47
48 281 ideal to evaluate how socioeconomic development influences health, because the measure of
49
50 282 overall health (life expectancy at birth) is one important component of the index and can introduce
51
52 283 a bias. In the GBD 2015 study, the SDI was first developed to identify where countries or
53
54 284 geographic areas sit on the spectrum of social development⁸. As reproductive patterns were
55
56 285 proved to be risk factors for breast cancer²², the SDI, a yardstick based on income, education, and
57
58 286 fertility rate measurements, might be more appropriate than HDI to weigh the influence of
59
60

1
2
3
4 287 socioeconomic status on the global patterns and trends in health inequality of breast cancer.
5

6 288 To our knowledge, this study is the first overview of the global patterns and trends in breast
7
8 289 cancer incidence and mortality in relation to SDI levels. However, the following limitations
9
10 290 should be considered when interpreting the results of our investigation. First, this study is subject
11
12 291 to the limitations of the GBD 2016 study, such as data sources and statistical assumptions, which
13
14 292 are detailed in the GBD 2016 reports^{3, 4}. Estimates for most LMICs could be biased due to poor-
15
16 293 quality raw data, especially for MI ratios. Better primary data from nation-wide observational
17
18 294 studies or cancer registries in these countries are needed for future studies. Second, the joinpoint
19
20 295 analysis is particularly sensitive to the parameter settings. The pattern trends of incidence and
21
22 296 mortality may change if parameters are set differently or more data are analyzed. Third, regional
23
24 297 data within each country, information on disease stage and histopathological characteristics were
25
26 298 unavailable in the GBD 2016 database. In the United States, for example, nation-wide
27
28 299 distributions and trends in breast cancer burden can differ by ethnicity, state, disease stage, and
29
30 300 intrinsic subtype^{36, 37}. Thus, more studies are needed to further understand the disparities
31
32 301 worldwide and eliminate the biases in the data.
33
34
35
36
37

38 303 Conclusions

39
40 304 The socioeconomic development-associated health inequality in breast cancer incidence has been
41
42 305 declining since 1990. Countries undergoing an economic and lifestyle transition were
43
44 306 experiencing a growing incidence of breast cancer. Nonetheless, in 2016 the incidence burden
45
46 307 still concentrated in countries with a higher SDI. These findings highlighted that public health
47
48 308 clinicians and cancer control specialists should pay more attention to the primary prevention of
49
50 309 breast cancer, especially in high-incidence countries. In less developed countries, breast cancer
51
52 310 mortality greatly deviated from the expectation based on their low incidence. Furthermore, this
53
54 311 situation deteriorated in the considered period, with an ever-increasing rate ratio inequality
55
56 312 between countries from 1990 to 2016. Public health planners should carry out more sensitive and
57
58
59
60

1
2
3
4 313 cost-effective detection and treatment interventions, particularly in low and low-middle SDI
5
6 314 settings with limited healthcare resources, to counteract the premature deaths caused by breast
7
8 315 cancer.
9

10 316

11
12 317

13 14 15 318 **Funding**

16
17 319 This work was supported by the National Natural Science Foundation of China (Grant Number,
18
19 320 81602716 and 81802628).
20

21 321

22
23 322

24 25 26 323 **Competing interests**

27
28 324 The authors declared no conflict of interest.
29

30 325

31
32 326

33 34 35 327 **Data sharing statement**

36
37 328 The data used in this study is collected from the Global Health Data Exchange database. Available
38
39 329 from: <http://www.healthdata.org/gbd-results-tool>.
40

41 330

42
43 331

44 45 46 332 **Authors' contributions**

47
48 333 Kaimin Hu designed the study, extracted and analyzed the data and prepared the figures. Peili

49
50 334 Ding and Yinan Wu wrote the first draft of the manuscript. Tao Pan and Wei Tian revised the

51
52 335 paper critically. Suzhan Zhang was the principle investigator and designed the study. All authors

53
54 336 commented on manuscript drafts and approved the final version.
55

56
57 337
58
59
60

338

339 Acknowledgement

340 The authors would like to thank Editage (www.editage.cn) for English language editing.

341

342

343 References

- 344 1. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, et al. Global, Regional, and
345 National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and
346 Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for
347 the Global Burden of Disease Study. *JAMA Oncol.* 2017;3(4):524-548.
- 348 2. Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand
349 challenge in global health. *Lancet.* 2017;389(10071):847-860.
- 350 3. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence,
351 and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a
352 systematic analysis for the Global Burden of Disease Study 2016. *Lancet.*
353 2017;390(10100):1211-1259.
- 354 4. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264
355 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study
356 2016. *Lancet.* 2017;390(10100):1151-1210.
- 357 5. Global Health Data Exchange. GBD Results Tool. Available from:
358 <http://www.healthdata.org/gbd-results-tool>. Accessed Sep 26, 2017.

- 1
2
3
4 359 6. Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive
5
6
7 360 epidemiology of female breast cancer: an international comparison of screening, incidence,
8
9
10 361 survival and mortality. *Cancer Epidemiol*. 2012;36(3):237-248.
11
12
13 362 7. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global Cancer in Women: Burden and
14
15
16 363 Trends. *Cancer Epidemiol Biomarkers Prev*. 2017;26(4):444-457.
17
18
19 364 8. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause
20
21
22 365 mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic
23
24
25 366 analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459-1544.
26
27
28 367 9. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD
29
30
31 368 2016) Socio-demographic Index (SDI) 1970–2016. Seattle, United States: Institute for Health
32
33
34 369 Metrics and Evaluation (IHME), 2017.
35
36
37 370 10. Bleichrodt H, van Doorslaer E. A welfare economics foundation for health inequality
38
39
40 371 measurement. *J Health Econ*. 2006;25(5):945-957.
41
42
43 372 11. Pan American Health Organization. Measuring health inequalities: Gini coefficient and
44
45
46 373 concentration index. *Epidemiol Bull*. 2001;22(1):2.
47
48
49 374 12. Costa-Font J, Hernandez-Quevedo C. Measuring inequalities in health: What do we know?
50
51
52 375 What do we need to know? *Health Policy*. 2012;106(2):195-206.
53
54
55 376 13. Shingala MC, Rajyaguru A. Comparison of Post Hoc Tests for Unequal Variance.
56
57 377 *International Journal of New Technologies in Science and Engineering*. 2015;2:22-33.
58
59
60

- 1
2
3
4 378 14. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with
5
6
7 379 applications to cancer rates. *Stat Med.* 2000;19(3):335-351.
8
9
10 380 15. National Cancer Insititute. Surveillance Epidemiology and end results (SEER) program.
11
12
13 381 methods & tools: joinpoint trend analysis. Available from:
14
15
16 382 <https://surveillance.cancer.gov/joinpoint>. Accessed Oct 10, 2017.
17
18
19 383 16. Kerm PV. INEQUAL7: Stata module to compute measures of inequality. *Statistical Software*
20
21
22 384 *Components S416401, Boston College Department of Economics.* 2001.
23
24
25 385 17. O'Donnell O, O'Neill S, Van Ourti T, Walsh B. conindex: Estimation of concentration indices.
26
27
28 386 *Stata J.* 2016;16(1):112-138.
29
30
31 387 18. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin.*
32
33
34 388 2014;64(1):52-62.
35
36
37 389 19. Lundqvist A, Andersson E, Ahlberg I, Nilbert M, Gerdtham U. Socioeconomic inequalities in
38
39
40 390 breast cancer incidence and mortality in Europe-a systematic review and meta-analysis. *Eur*
41
42
43 391 *J Public Health.* 2016;26(5):804-813.
44
45
46 392 20. Li T, Mello-Thoms C, Brennan PC. Descriptive epidemiology of breast cancer in China:
47
48
49 393 incidence, mortality, survival and prevalence. *Breast Cancer Res Treat.* 2016;159(3):395-406.
50
51
52 394 21. Lukong KE, Ogunbolude Y, Kamdem JP. Breast cancer in Africa: prevalence, treatment
53
54
55 395 options, herbal medicines, and socioeconomic determinants. *Breast Cancer Res Treat.*
56
57 396 2017;166(2):351-365.
58
59
60

- 1
2
3
4 397 22. Porter P. "Westernizing" women's risks? Breast cancer in lower-income countries. *N Engl J*
5
6
7 398 *Med.* 2008;358(3):213-216.
8
9
10 399 23. Lahmann PH, Schulz M, Hoffmann K, et al. Long-term weight change and breast cancer risk:
11
12
13 400 the European prospective investigation into cancer and nutrition (EPIC). *Br J Cancer.*
14
15
16 401 2005;93(5):582-589.
17
18
19 402 24. Bray F. Transitions in human development and the global cancer burden. In: Steward BW,
20
21
22 403 Wild CP, eds. World Cancer Report 2014. *Lyon: International Agency for Research on Cancer,*
23
24
25 404 2014.
26
27
28 405 25. Gotzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. *Cochrane*
29
30
31 406 *Database Syst Rev.* 2013(6):CD001877.
32
33
34 407 26. Narod SA. Reflections on screening mammography and the early detection of breast cancer:
35
36
37 408 A Countercurrents Series. *Curr Oncol.* 2014;21(5):210-214.
38
39
40 409 27. Loberg M, Lousdal ML, Bretthauer M, Kalager M. Benefits and harms of mammography
41
42
43 410 screening. *Breast Cancer Res.* 2015;17:63.
44
45
46 411 28. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the
47
48
49 412 Human Development Index (2008-2030): a population-based study. *Lancet Oncol.*
50
51
52 413 2012;13(8):790-801.
53
54
55 414 29. Coughlin SS, Ekwueme DU. Breast cancer as a global health concern. *Cancer Epidemiol.*
56
57
58 415 2009;33(5):315-318.
59
60

- 1
2
3
4 416 30. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009:
5
6
7 417 analysis of individual data for 25,676,887 patients from 279 population-based registries in 67
8
9
10 418 countries (CONCORD-2). *Lancet*. 2015;385(9972):977-1010.
11
12
13 419 31. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and
14
15
16 420 prevalence across five continents: defining priorities to reduce cancer disparities in different
17
18
19 421 geographic regions of the world. *J Clin Oncol*. 2006;24(14):2137-2150.
20
21
22 422 32. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods
23
24
25 423 Part II. Completeness. *Eur J Cancer*. 2009;45(5):756-764.
26
27
28 424 33. Asadzadeh Vostakolaei F, Karim-Kos HE, Janssen-Heijnen ML, Visser O, Verbeek AL,
29
30
31 425 Kiemeny LA. The validity of the mortality to incidence ratio as a proxy for site-specific cancer
32
33
34 426 survival. *Eur J Public Health*. 2011;21(5):573-577.
35
36 427 34. Programme UND. Human development report. Available from:
37
38
39 428 <http://hdr.undp.org/en/content/human-development-index-hdi>. Accessed Nov 16, 2017.
40
41
42 429 35. Fidler MM, Soerjomataram I, Bray F. A global view on cancer incidence and national levels
43
44
45 430 of the human development index. *Int J Cancer*. 2016;139(11):2436-2446.
46
47
48 431 36. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer
49
50
51 432 statistics, 2015: Convergence of incidence rates between black and white women. *CA Cancer*
52
53
54 433 *J Clin*. 2016;66(1):31-42.
55
56
57 434 37. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017,
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

435 racial disparity in mortality by state. *CA Cancer J Clin.* 2017;67(6):439-448.

436

437

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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*

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

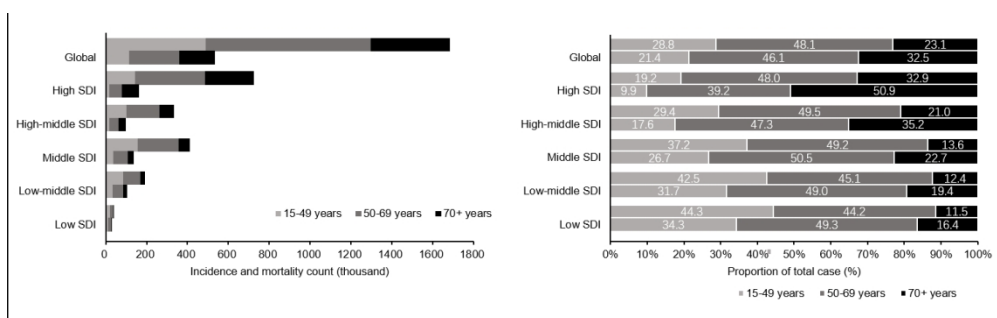


Figure 1

256x79mm (150 x 150 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

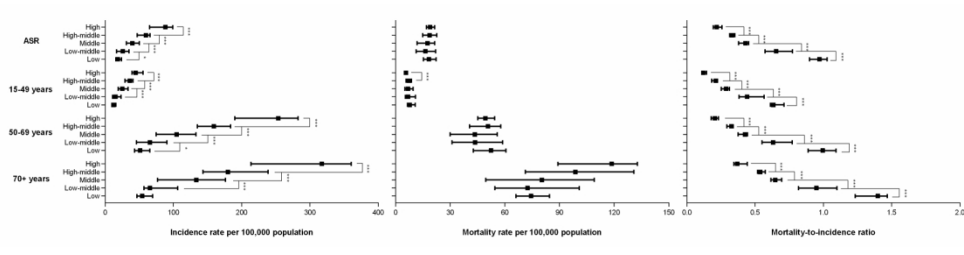


Figure 2

361x91mm (150 x 150 DPI)

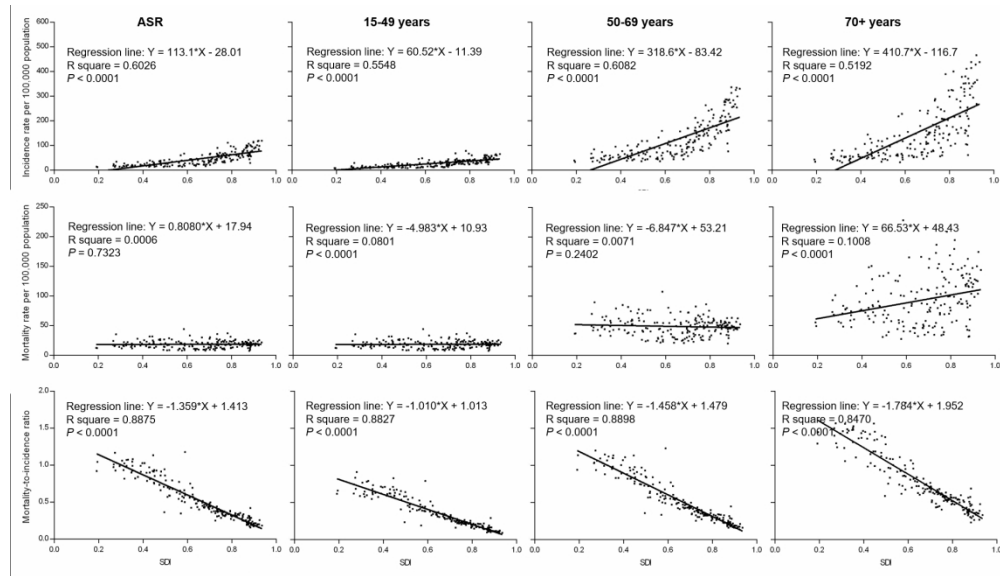


Figure 3

343x196mm (150 x 150 DPI)

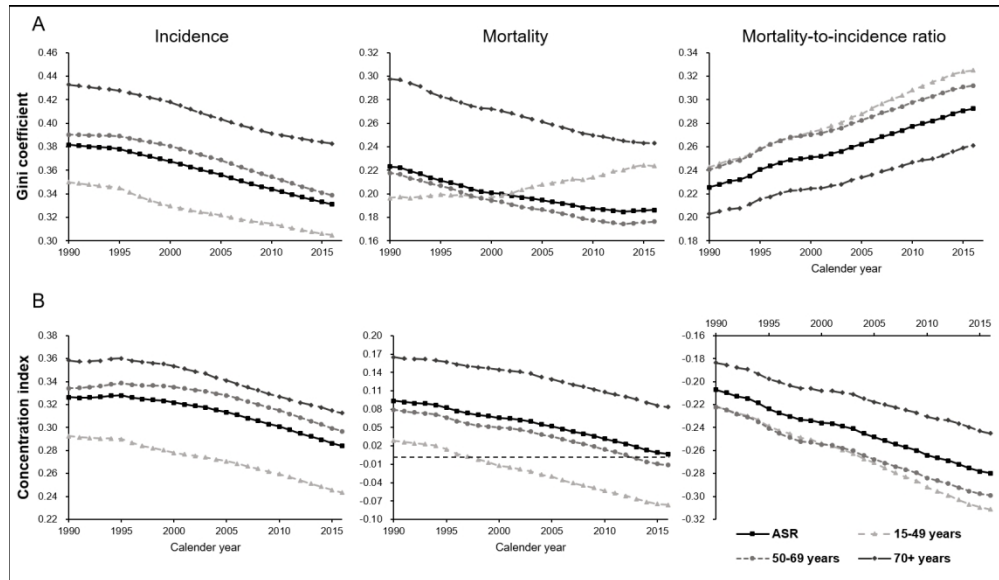


Figure 4

283x163mm (150 x 150 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

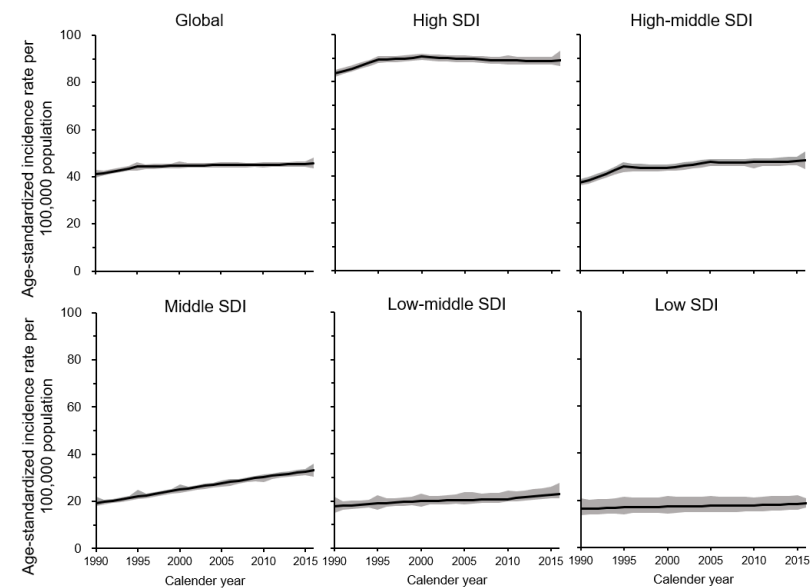
Supplementary figures and tables

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

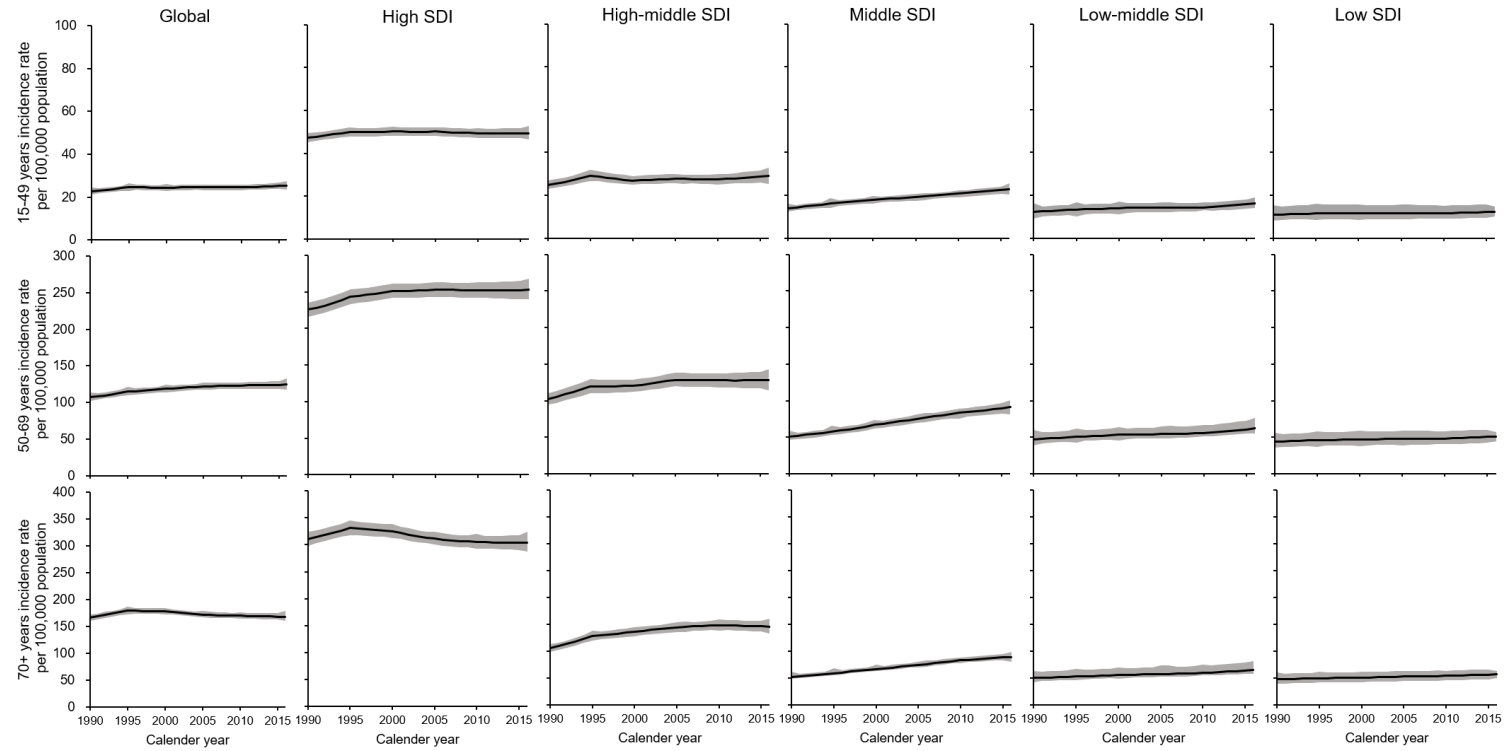
	Age	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
		Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	248.2	22.7	21.0-24.6	484.0	25.4	23.6-27.5	1990-1995	1.6*	1995-2011	0	2011-2016	0.7*	0.4*
	50-69 years	372.8	107.0	102.4-113.5	809.6	124.4	117.4-132.8	1990-1995	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.

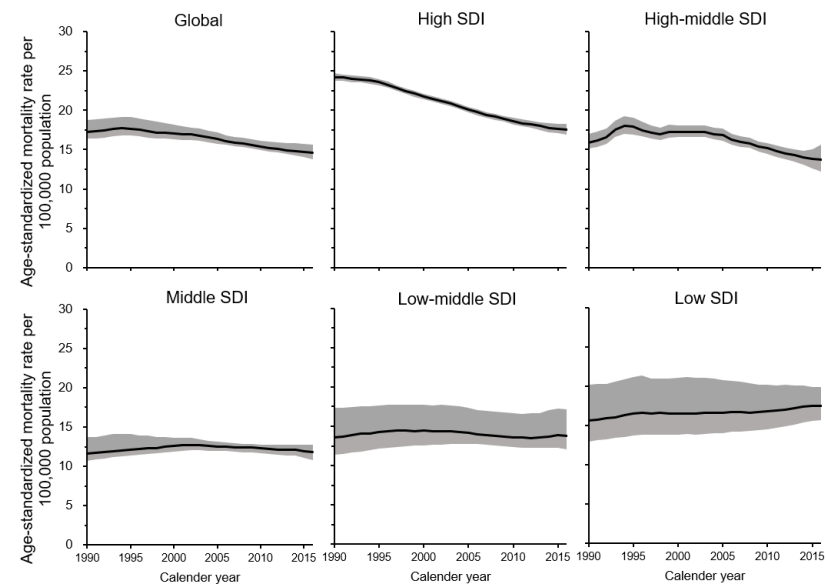
	Age	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
		Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	80.7	7.4	6.6-8.4	114.3	6.0	5.6-6.6	1990-1995	0.8*	1995-2012	-1.4*	2012-2016	-0.3*	-0.8*
	50-69 years	156.5	44.9	42.2-49.4	246.9	38.0	35.6-41.4	1990-1994	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*



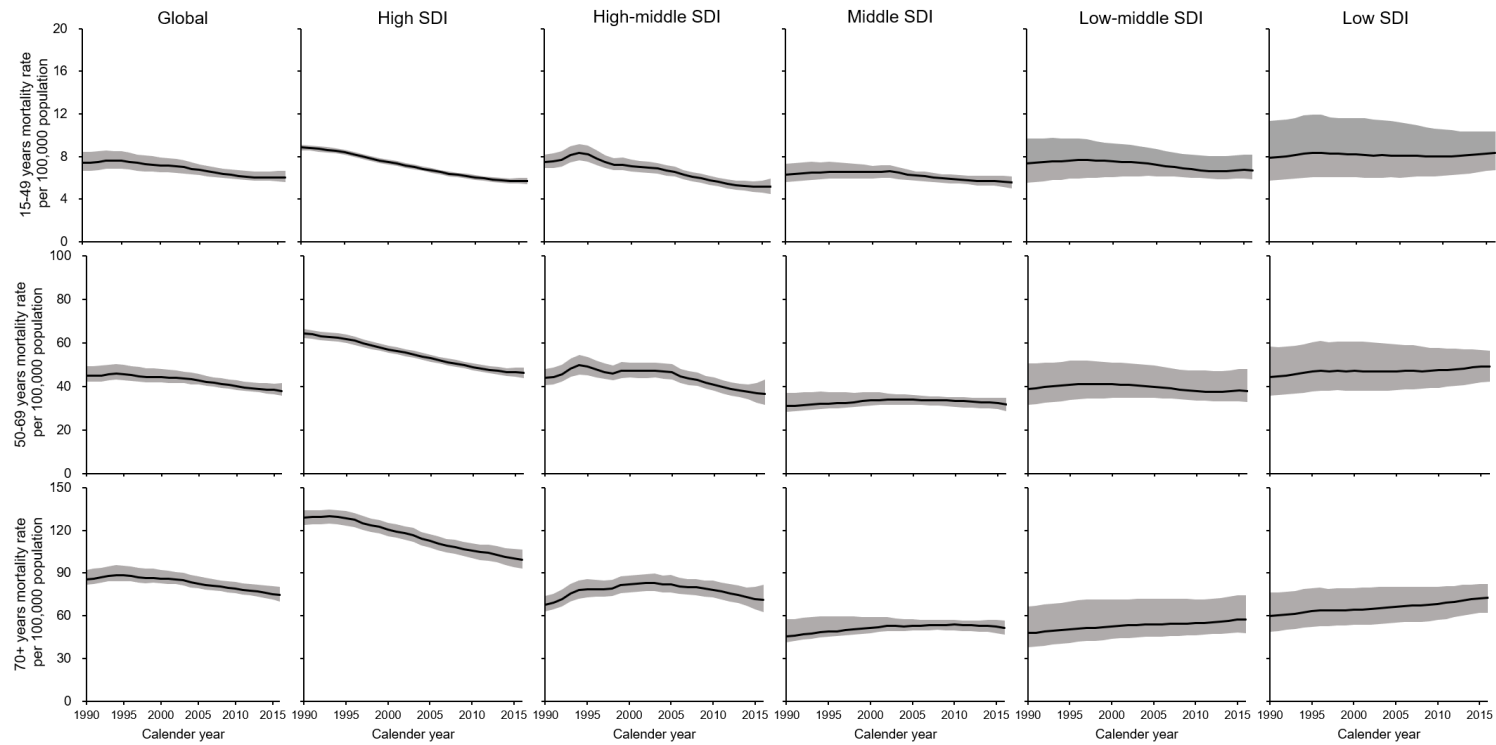
Supplementary figure 1A. Trends in breast cancer age-standardized incidence rate (ASIR) according to SDI settings, 1990-2016. The black lines represent the estimated ASIRs, and areas shaded in gray represent 95% uncertainty intervals.



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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028461.R3
Article Type:	Original research
Date Submitted by the Author:	28-Aug-2019
Complete List of Authors:	Hu, Kaimin; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Ding, Peili; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Wu, Yinan; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Tian, Wei; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Pan, Tao; Cancer Institute, the 2nd affiliated hospital of Zhejiang university Zhang, Suzhan; Cancer Institute, the 2nd affiliated hospital of Zhejiang university
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Oncology, Global health
Keywords:	breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini coefficient, concentration index

SCHOLARONE™
Manuscripts

1
2
3
4
5 1 Title page:
6
7

8 2 Global Patterns and Trends in the Breast Cancer Incidence and
9
10 3 Mortality According to Socio-demographic Indices: An
11
12 4 Observational Study Based on the Global Burden of Diseases
13
14
15
16
17
18

19 6 Kaimin Hu ^{1,2,#}

20 7 Peili Ding ^{1,#}

21 8 Yinan Wu ¹

22 9 Wei Tian ^{1,2}

23 10 Tao Pan ^{1,2}

24 11 Suzhan Zhang ¹

25
26
27
28
29
30
31
32
33 13 ¹ Cancer Institute, the Second Affiliated Hospital of Zhejiang University, College of Medicine,
34 Hangzhou, Zhejiang, China.

35
36
37 15 ² Department of Breast Surgery, the Second Affiliated Hospital of Zhejiang University, College
38 of Medicine, Hangzhou, Zhejiang, China.

39
40
41 17 # These authors contributed equally to this work.
42
43
44
45

46 19 Corresponding Author:

47
48 20 Suzhan Zhang

49
50 21 Cancer Institute

51
52 22 The Second Affiliated Hospital of Zhejiang University, College of Medicine

53
54 23 Jiefang Road 88, Hangzhou, 310009, China.

55
56 24 Telephone: +86-5718778-4501

57
58 25 Fax: +86-5718721-4404
59
60

1
2
3
4 26 Email: zrsj@zju.edu.cn
5
6
7 27
8
9 28

10 29 Word count: 3160
11
12
13 30
14
15 31

16
17 32 **Abstract:**

18
19
20 33 Objectives: Disparities in the global burden of breast cancer have been identified. We aimed to
21
22 34 investigate recent patterns and trends in the breast cancer incidence and associated mortality. We
23
24 35 also assessed breast cancer-related health inequalities according to socioeconomic development
25
26 36 factors.

27
28 37 Design: An observational study based on the Global Burden of Diseases.

29
30 38 Methods: Estimates of breast cancer incidence and mortality during 1990–2016 were obtained
31
32 39 from the Global Health Data Exchange database. Subsequently, data obtained in 2016 were
33
34 40 described using the age-standardized and age-specific incidence, mortality and mortality-to-
35
36 41 incidence (MI) ratios according to socio-demographic index (SDI) levels. Trends were assessed
37
38 42 by measuring the annual percent change using the joinpoint regression. The Gini coefficients and
39
40 43 concentration indices were used to identify between-country inequalities.

41
42
43 44 Results: Countries with higher SDI levels had worse disease incidence burdens in 2016, whereas
44
45 45 inequalities in the breast cancer incidence had decreased since 1990. Opposite trends were
46
47 46 observed in the mortality rates of high and low SDI countries. Moreover, the decreasing
48
49 47 concentration indices, some of which became negative, among people aged 15–49 and 50–69
50
51 48 years suggested an increase in the mortality burdens in undeveloped regions. Conversely,
52
53 49 inequality related to the MI ratio increased. In 2016, the MI ratios exhibited distinct gradients
54
55 50 from high to low SDI regions across all age groups.

56
57 51 Conclusions: The patterns and trends in breast cancer incidence and mortality closely correlated
58
59
60

1
2
3
4 52 with the SDI levels. Our findings highlighted the primary prevention of breast cancer in high SDI
5
6 53 countries with a high disease incidence and the development of cost-effective diagnostic and
7
8 54 treatment interventions for low SDI countries with poor MI ratios as the two pressing needs in the
9
10 55 next decades.
11

12 56

13 57

14
15
16
17 58 **Keywords:** breast cancer, mortality-to-incidence ratio, socio-demographic index, Gini
18
19 59 coefficient, concentration index
20

21 60

22 61

23 62 Article summary

24
25
26
27 63 Strengths and limitations of this study:

- 28
29
30
31 64 ● This study provides the first overview of current global patterns and long-term trends in
32
33 65 breast cancer burdens stratified according to socio-demographic development.
34
35 66 ● The Gini coefficient and concentration index were used to evaluate the extent, trend, and
36
37 67 concentration of health inequalities caused by breast cancer.
38
39 68 ● The study was limited by the use of secondary estimated data from the Global Burden of
40
41 69 Disease database, as the estimates for some countries with poor-quality raw data may have
42
43 70 been biased.
44

45 71

46 72

47 73 Introduction

48
49
50
51 74 Breast cancer is the most common type of cancer worldwide and the leading cause of cancer-
52
53 75 related deaths among women, with an estimated 2.4 million new cases and 523,000 deaths
54
55 76 reported in 2015¹. A woman's place of residence and socioeconomic status are significant
56
57 77 determinants of the odds of developing breast cancer and the ultimate survival outcome¹. The
58
59
60

1
2
3
4 78 breast cancer incidence rate is higher in high-income countries than in low- and middle-income
5
6 79 countries (LMICs)¹⁻³. In many high-income countries, a better awareness of the risk factors,
7
8 80 regular mammography screening, and sufficient and effective medical services have led to
9
10 81 significant decrease in breast cancer mortality rates in recent decades and stable or even
11
12 82 decreasing incidence rates since 2000. However, breast cancer is not restricted to high-income
13
14 83 countries. The low cancer incidence rates in LMICs have not necessarily translated to lower
15
16 84 cancer-related mortality rates³⁻⁵. Both the breast cancer incidence and related mortality have
17
18 85 increased in many resource-poor settings or countries, partially due to changes in reproductive
19
20 86 patterns and delays in diagnosis and treatment, which are independent of an increase in breast
21
22 87 cancer awareness^{6,7}.

23
24
25 88 Disparities in the global burden of breast cancer have been identified, especially among
26
27 89 countries with different levels of development. Global health policy makers rely on understanding
28
29 90 of the exact correlations between the disease burden and socioeconomic status to formulate
30
31 91 appropriate measures according to local conditions. The Institute for Health Metrics and
32
33 92 Evaluation first introduced the socio-demographic index (SDI) in the Global Burden of Disease
34
35 93 Study 2015 (GBD 2015) as a quantitative measure of development in a country or region⁸. This
36
37 94 study aimed to describe current patterns and trends in breast cancer incidence and mortality
38
39 95 among countries according to national-level wellbeing by combining the latest SDI data with
40
41 96 breast cancer incidence and mortality data collected between 1990 and 2016. This approach would
42
43 97 enable a comprehensive investigation of the distribution of breast cancer-associated health
44
45 98 inequalities and related changes according to the level of national development.

46
47
48 99

49
50 100

51 101 Materials and Methods

52
53
54
55 102 Breast cancer was defined using code C50 from the International Classification of Disease-
56
57 103 Revision, 10th edition. Incidence and mortality data from 195 individual countries across 5
58
59
60

1
2
3
4 104 predefined SDI groups during 1990–2016 were collected from the Global Health Data Exchange
5
6 105 database⁵. The annual incidence and mortality rates for subjects aged 15 to 95+ years were
7
8 106 extracted for each involved country and stratified into 5-year age brackets. Detailed methods for
9
10 107 estimating the age-standardized incidence and mortality rates (ASIR and ASMR, respectively)
11
12 108 per 100,000 women in a population were described in the GBD 2016 reports^{3,4}. Women aged 50–
13
14 109 69 years comprised the largest population participating in regular screening programs. We further
15
16 110 calculated the age-specific incidence and mortality rates per 100,000 women into three age
17
18 111 subgroups: 15–49, 50–69 and 70+ (including 70) years, and these rates were adjusted according
19
20 112 to the new world population age-standard³. The mortality-to-incidence (MI) ratio was calculated
21
22 113 by dividing the breast cancer mortality rate for a given year, age group, country, and SDI group
23
24 114 by the corresponding incidence rate.
25
26
27
28
29

115

116 Patient and Public Involvement

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

118

119 Ethics approval

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

121

122 SDI

123 The SDI, a comparable metric of overall development, was calculated using the lag-distributed
124 income per capita, average years of education in the population older than 15 years, and total
125 fertility rate, with equal weighting of these variables⁹. The SDI is expressed using a scale of 0 to
126 1, with a greater value indicating a higher level of development. SDI data from the 195 countries
127 involved in the study during 1990–2016 were obtained from the Global Health Data Exchange
128 database⁵. Countries were classified into the following quintiles based on their SDI values in 2016:
129 high, high-middle, middle, low-middle, and low SDI. Detailed methods describing the calculation

1
2
3
4 130 of SDI and the selection of the quintile cutoffs have been previously reported^{1, 3}.

5
6 131

7
8 132 Gini coefficient and concentration index

9
10 133 We adopted the Gini coefficient and concentration index, which are used in the field of economics,

11
12 134 to measure breast cancer-associated health inequalities in our study^{10, 11}. The Gini coefficient is

13
14 135 calculated based on the Lorenz curve. The coefficient ranges between 0 and 1, with 0 and 1

15
16 136 representing perfect equality and total inequality, respectively¹¹. The annual ASIRs, ASMRs, age-

17
18 137 specific incidence rates, age-specific mortality rates, and MI ratios of breast cancer from the 195

19
20 138 included countries were used to calculate the Gini coefficients and describe trends in health

21
22 139 inequality between countries from 1990 to 2016. The concentration index, which is derived from

23
24 140 the concentration curve, is a common measure of socioeconomic-related health inequality¹². The

25
26 141 concentration indices were calculated by correlating the abovementioned breast cancer metrics

27
28 142 with the corresponding national SDIs. The concentration index values range between -1 and +1.

29
30 143 A positive or negative concentration index value indicated that the breast cancer disease burden

31
32 144 was more concentrated in countries with high or low levels of development, respectively, as

33
34 145 measured by the SDI¹². The absolute index value was related to the degree of a “pro-developed”

35
36 146 or “pro-underdeveloped” distribution of health limitations. A value of zero indicated an absence

37
38 147 of inequality associated with the socioeconomic gradient rather than an absolute absence of

39
40 148 inequality.

41
42 149

43
44 150 Statistical analyses

45
46 151 We performed one-way ANOVA, followed by pairwise comparisons with the Tamhane T2 test

47
48 152 to compare variables with normal distributions but heterogeneous variances, such as the incidence,

49
50 153 mortality and MI ratio, across five SDI-based country groups¹³. A linear regression model was

51
52 154 used to test the correlations between indicators of the breast cancer burden and the SDI values. A

53
54 155 joinpoint piecewise linear regression analysis was performed to identify the time points

1
2
3
4 156 corresponding to significant changes and identify temporal trends in the age-standardized and
5
6 157 age-specific incidence and mortality rates between 1990 and 2016¹⁴. Default parameters were
7
8 158 used for all analyses except for the minimum number of data points between two joints or at either
9
10 159 end of the data; these two values were set to 5. The maximum number of joinpoints was set to 2
11
12 160 to avoid over-fitting at the truncating points. The best-fit point corresponding to a significant
13
14 161 change in the rate was assessed using a permutation test, and the *P* value for each test was
15
16 162 estimated using Monte Carlo methods¹⁴. Statistics relating to the annual percent change (APC)
17
18 163 for each segment and average annual percent change (AAPC) for the overall period were
19
20 164 summarized using the optimal joinpoint model. All joinpoint trend analyses were performed using
21
22 165 joinpoint statistical software (Version 4.5.0.1; Surveillance Research Program of the United
23
24 166 States National Cancer Institute, Bethesda, MD, USA)¹⁵. The Gini coefficient and concentration
25
26 167 index values were computed using the AINEQUAL¹⁶ and CONINDEX modules¹⁷ of Stata 14.0
27
28 168 software (Stata Corp, College Station, TX, USA). Other statistical analyses were performed using
29
30 169 SPSS 20.0 software (IBM Corp., Armonk, NY, USA).
31
32
33
34
35

36 171 Results

37 172 Current profiles in breast cancer incidence and mortality rates according to SDIs

38
39 173 Figure 1 presents the distribution of counts and proportions of new breast cancer cases and related
40
41 174 deaths in the 5 SDI groups during the year 2016. Approximately 719,000 new cases were reported
42
43 175 in high SDI countries, and this value was about 20 times higher than the 37,000 new cases reported
44
45 176 in low SDI countries. Moreover, 162,000 and 32,000 deaths were reported in these groups,
46
47 177 respectively. Approximately half of all new breast cancer cases occurred in women aged 50–69
48
49 178 years across all SDI groups. In middle, low-middle, and low SDI countries, more than a third of
50
51 179 new breast cancer cases were identified in women aged 15–49 years, and this group also had a
52
53 180 higher proportion of related deaths. In contrast, in high SDI countries, people age 70+ years
54
55 181 accounted for 50.9% of all reported breast cancer-related deaths.
56
57
58
59
60

1
2
3
4 182 One-way ANOVA suggested significant differences in both the age-standardized and age-
5
6 183 specific incidence rates and MI ratios ($P < 0.01$) but not in the mortality rates among countries
7
8 184 belonging to different SDI groups. Pairwise comparisons showed the mortality rates were not
9
10 185 proportional to the corresponding high incidence rates in countries with higher level of
11
12 186 development indicated by SDI, and the lowest MI ratios were observed in high SDI countries
13
14 187 (Figure 2). In all age groups, positive relationships existed between the incidence rates and SDI
15
16 188 values, and negative relationships existed between the MI ratios and SDI values (Figure 3).
17
18 189 Moreover, the MI ratios exhibited well-fitting linear relationships in all age groups, whereas the
19
20 190 incidence and mortality rates in older age groups were more scattered among countries with
21
22 191 different SDIs.
23
24
25
26

27 193 Temporal trends in breast cancer incidence and mortality across SDI groups

28
29 194 According to the joinpoint trend analysis (Table 1), the ASIRs in high and high-middle SDI
30
31 195 groups plateaued after rapidly increasing in the early 1990s. In the high SDI group, the ASIR even
32
33 196 exhibited a declining trend of 0.1% per year since 2000. In contrast, significant increases in the
34
35 197 ASIRs were observed in the middle, low-middle and low SDI groups over the whole study period
36
37 198 (Supplementary Figure 1A). The AAPC in ASIR was 2.1% for the middle SDI group, and this
38
39 199 was the highest increase among the SDI groups. The trends in incidence rate changes among
40
41 200 women aged 15–49, 50–69, and 70+ years were comparable with the ASIR values across the SDI
42
43 201 groups (Supplementary Table 1 and Supplementary Figure 1B).
44
45

46 202 Changes in the ASMR varied across the SDI groups, as shown in Table 2 and Supplementary
47
48 203 Figure 2A. In the high SDI group, the ASMR decreased continuously from 24.2 in 1990 to 17.6
49
50 204 in 2016, with an AAPC of -1.3%. In the high-middle SDI group, the ASMR began to decline in
51
52 205 1994, with an accelerated decrease (APC: -1.9%) between 2004 and 2016. In the middle SDI
53
54 206 group, the ASMR also decreased slightly from 2002 to 2016, with an average decrease of 0.5%
55
56 207 per year. Opposite trends were observed in the low-middle (2002–2016, APC: 0.7%) and low SDI
57
58
59
60

1
2
3
4 208 groups (2009–2016, APC: 0.8%), especially in more recent years. Although the patterns of change
5
6 209 in the three age groups were similar to the ASMR in each SDI group, the degrees of change
7
8 210 differed among the groups (Supplementary Table 2 and Supplementary Figure 2B). For example,
9
10 211 among subjects aged 70+ years, we observed lesser decreases and greater increases in the
11
12 212 mortality rate in more and less developed regions, respectively.
13
14
15 213

16 214 Global health inequality related to breast cancer

17
18
19 215 The Gini coefficients for the incidence of breast cancer continuously decreased from 1990 to 2016
20
21 216 (Figure 4A). The values calculated from the ASIRs and incidence rates among women aged 15–
22
23 217 49, 50–69, and 70+ years decreased to 0.33, 0.30, 0.34 and 0.38 by 2016, respectively, from
24
25 218 starting values of 0.38, 0.35, 0.39, and 0.43 in 1990, respectively. Similarly, the Gini coefficients
26
27 219 calculated using the mortality rates exhibited markedly declining trends over the same period in
28
29 220 all age groups, except those aged 15–49 years. In contrast, the Gini coefficients calculated using
30
31 221 the age-standardized MI ratio distributions increased, from 0.23 in 1990 to 0.29 in 2016.

32
33
34 222 In 1990, all the concentration indices based on the breast cancer age-standardized and age-
35
36 223 specific incidence and mortality rates exceeded zero, suggesting that the inequalities associated
37
38 224 with socioeconomic development were more concentrated in countries with higher levels of
39
40 225 development (as indicated by SDI). Moreover, the concentration indices were higher among
41
42 226 subjects aged 70+ years than in other groups. Both the concentration indices for the incidence and
43
44 227 mortality rate decreased between 1990 and 2016, and the rate of decrease began to accelerate in
45
46 228 the late 1990s (Figure 4B). The concentration indices for mortality rates in the age groups of 15–
47
48 229 49 and 50–69 years decreased below zero and became negative in 1998 and 2013, respectively.
49
50
51 230 In contrast, the concentration indices based on age-standardized MI ratios and age-specific rate
52
53 231 ratios for age groups of 15–49, 50–69, and 70+ years were already below zero in 1990, with values
54
55 232 of -0.21, -0.22, -0.22, and -0.18, respectively. By 2016, these values had decreased to -0.28, -0.31,
56
57 233 -0.30, and -0.25, respectively.
58
59
60

1
2
3
4 2345
6 2357
8
9 236 Discussion

10
11 237 Socioeconomic development-associated inequalities in the global incidence of breast cancer have
12
13 238 continued to decrease since 1990. However, countries with higher levels of development
14
15 239 according to the SDI reported a worse burden of breast cancer incidence by 2016. Consistent with
16
17 240 the opposite trends in mortality rates between countries with high and low SDI values, the
18
19 241 mortality concentration indices among women aged 15–49 and 50–69 years have become
20
21 242 negative in recent years. This phenomenon suggests a shift in the concentration of the mortality
22
23 243 burden from developed to undeveloped countries. Conversely, both the overall inequality and
24
25 244 inequality associated with socioeconomic development, which was calculated using the MI ratio,
26
27 245 increased from 1990 to 2016. In 2016, the MI ratio distribution exhibited a distinct gradient from
28
29 246 high to low SDI countries across all age groups.

30
31
32 247 The availability of epidemiological data from individual countries has led to a prevailing
33
34 248 perception that inequalities exist in the global breast cancer incidence, especially between high-
35
36 249 income countries and LMICs^{18–21}. However, there remains a paucity of quantitative evidence
37
38 250 regarding the relationship between the global breast cancer burden and national levels of
39
40 251 socioeconomic development. According to the GLOBOCAN 2012 estimates, the breast cancer
41
42 252 incidence burden was distributed among countries at different human development index (HDI)
43
44 253 levels, with obvious disparities². The results of that report are consistent with our results, which
45
46 254 were based on the SDI and data from the GBD 2016 study. We observed that the overall inequality
47
48 255 in the breast cancer incidence had not yet been eliminated and remained concentrated in countries
49
50 256 with high SDI levels. This higher prevalence of breast cancer is somewhat associated with the so-
51
52 257 called western lifestyle (i.e., specific reproductive patterns and excessive body weight)^{22, 23}, and
53
54 258 thus can be used as a marker of the extent of development. Our trend analyses demonstrated rapid
55
56 259 increases in the breast cancer incidence rates of countries classified in the middle SDI group. This
57
58
59
60

1
2
3
4 260 result suggests that countries with SDI levels near the middle of the spectrum were undergoing
5
6 261 rapid social and economic changes during the study period²⁴. In many LMICs, the burdens of
7
8 262 infection-related cancers, including cervical, gastric, and liver cancer, remained higher than those
9
10 263 of breast cancer^{1, 2}. Moreover, high-income countries have generally implemented
11
12 264 mammographic screening programs, especially for women aged 50–69 years^{25–27}. Consistently,
13
14 265 our age-based subgroup analysis confirmed a transient increase in the incidence of breast cancer
15
16 266 among women aged 50–69 years and a subsequent decrease among those aged 70+ years in
17
18 267 countries with high SDI values.

21 268 The mortality rates did not differ significantly between low and high SDI countries. Inequalities
22
23 269 in breast cancer deaths were possibly offset by better clinical outcomes in more developed
24
25 270 countries due to early diagnosis and the development of advanced treatments; in contrast, the
26
27 271 situation in most LMICs were characterized by a low incidence of breast cancer but limited access
28
29 272 to health cares^{28, 29}. Therefore, the mortality rates do not represent the exact trends and current
30
31 273 statuses of the burdens of cancer-related death. Cancer survival is another important indicator
32
33 274 used to evaluate the malignancy-related death burden. According to data from 59 countries in the
34
35 275 CONCORD-2 study³⁰, the 5-year survival rates of patients diagnosed with breast cancer during
36
37 276 2005–2009 were $\geq 85\%$ in North America, Australia, Israel, Brazil, and most Northern and
38
39 277 Western European countries but $\leq 60\%$ in many LMICs, such as India, Mongolia, Algeria and
40
41 278 South Africa. However, little comprehensive survival data were available from most countries,
42
43 279 especially those with limited resources. Accordingly, the determination of the effects of
44
45 280 socioeconomic development-associated inequalities on the survival rates of breast cancer patients
46
47 281 and comparisons of current survival statuses among various countries across the world remained
48
49 282 critical issues. In this study, we analyzed the trends in inequality of the breast cancer MI ratio, a
50
51 283 marker used to estimate the extent to which actual mortality differs from the expected mortality
52
53 284 relative to disease incidence; the marker has been suggested as an approximation of cancer
54
55 285 survival^{31–33}. Our results suggest increasing disparities according to breast cancer MI ratios among
56
57
58
59
60

1
2
3
4 286 countries with different levels of development.

5
6 287 The HDI, a metric comprising the life expectancy at birth, mean and expected years of
7
8 288 education, and gross national income per capita³⁴, was used to investigate the correlations between
9
10 289 macro-socioeconomic determinants and national disease burdens^{2, 28, 35}. However, this index is
11
12 290 not ideal for evaluating the effects of socioeconomic development on health because the measure
13
14 291 relies on the overall health (i.e., life expectancy at birth), which could introduce bias. The SDI
15
16 292 was initially developed in the GBD 2015 study, to determine the placement of countries or
17
18 293 geographic areas on the spectrum of social development⁸. Given the role of reproductive patterns
19
20 294 as risk factors for breast cancer²², the SDI, a measure based on measures of income, education,
21
22 295 and fertility rate, might be more appropriate than the HDI when assessing the degree of influence
23
24 296 of the socioeconomic status on global patterns and trends in health inequality associated with
25
26 297 breast cancer.

27
28
29 298 To our knowledge, this study provides the first overview of global patterns and trends in breast
30
31 299 cancer incidence and mortality according to the SDI. However, our results should be interpreted
32
33 300 in light of the following limitations. First, this study is subject to the limitations of the GBD 2016
34
35 301 study such as the data sources and statistical assumptions, as detailed in the related reports^{3, 4}. For
36
37 302 most LMICs, the estimates, particularly the MI ratios, might have been biased due to poor-quality
38
39 303 raw data. Future studies will require better primary data from nation-wide observational studies
40
41 304 or cancer registries. Second, the joinpoint analysis is particularly sensitive to parameter settings.
42
43 305 Accordingly, trends in the patterns of incidence and mortality may change if the parameters are
44
45 306 changed or more data are analyzed. Third, the GBD 2016 database did not provide regional data
46
47 307 within each country or information about disease stages and histopathological characteristics. In
48
49 308 the United States, for example, nation-wide distributions and trends in breast cancer burden can
50
51 309 differ by ethnicity, state, disease stage and intrinsic subtype^{36, 37}. Therefore, more studies are
52
53 310 needed to understand the global disparities more fully and to eliminate biases in the data.
54
55

56
57 311
58
59
60

312 Conclusions

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

325

326

327 Funding

328 This work was supported by the National Natural Science Foundation of China (Grant Number,
329 81602716 and 81802628).

330

331

332 Competing interests

333 The authors declared no conflict of interest.

334

335

336 Data sharing statement

1
2
3
4 337 The data used in this study is collected from the Global Health Data Exchange database. Available
5
6 338 from: <http://www.healthdata.org/gbd-results-tool>.
7

8 339
9

10 340
11

12 341 Authors' contributions

13
14
15 342 Kaimin Hu designed the study, extracted and analyzed the data and prepared the figures. Peili

16
17 343 Ding and Yinan Wu wrote the first draft of the manuscript. Tao Pan and Wei Tian revised the

18
19 344 paper critically. Suzhan Zhang was the principle investigator and designed the study. All authors

20
21 345 commented on manuscript drafts and approved the final version.
22

23 346
24

25 347
26

27 348 Acknowledgement

28
29 349 The authors would like to thank Editage (www.editage.cn) for English language editing.
30

31 350
32

33 351
34

35 352 References

36
37 353 1. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, et al. Global, Regional, and

38
39 354 National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and

40
41 355 Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for

42
43 356 the Global Burden of Disease Study. *JAMA Oncol.* 2017;3(4):524-548.
44

45
46 357 2. Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand

47
48 358 challenge in global health. *Lancet.* 2017;389(10071):847-860.
49

50
51 359 3. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence,
52

- 1
2
3
4 360 and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a
5
6
7 361 systematic analysis for the Global Burden of Disease Study 2016. *Lancet*.
8
9
10 362 2017;390(10100):1211-1259.
11
12
13 363 4. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264
14
15
16 364 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study
17
18
19 365 2016. *Lancet*. 2017;390(10100):1151-1210.
20
21
22 366 5. Global Health Data Exchange. GBD Results Tool. Available from:
23
24
25 367 <http://www.healthdata.org/gbd-results-tool>. Accessed Sep 26, 2017.
26
27
28 368 6. Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive
29
30
31 369 epidemiology of female breast cancer: an international comparison of screening, incidence,
32
33
34 370 survival and mortality. *Cancer Epidemiol*. 2012;36(3):237-248.
35
36
37 371 7. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global Cancer in Women: Burden and
38
39
40 372 Trends. *Cancer Epidemiol Biomarkers Prev*. 2017;26(4):444-457.
41
42
43 373 8. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause
44
45
46 374 mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic
47
48
49 375 analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459-1544.
50
51
52 376 9. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD
53
54
55 377 2016) Socio-demographic Index (SDI) 1970–2016. Seattle, United States: Institute for Health
56
57 378 Metrics and Evaluation (IHME), 2017.
58
59
60

- 1
2
3
4 379 10. Bleichrodt H, van Doorslaer E. A welfare economics foundation for health inequality
5
6
7 380 measurement. *J Health Econ.* 2006;25(5):945-957.
8
9
10 381 11. Pan American Health Organization. Measuring health inequalities: Gini coefficient and
11
12
13 382 concentration index. *Epidemiol Bull.* 2001;22(1):2.
14
15
16 383 12. Costa-Font J, Hernandez-Quevedo C. Measuring inequalities in health: What do we know?
17
18
19 384 What do we need to know? *Health Policy.* 2012;106(2):195-206.
20
21
22 385 13. Shingala MC, Rajyaguru A. Comparison of Post Hoc Tests for Unequal Variance.
23
24
25 386 *International Journal of New Technologies in Science and Engineering.* 2015;2:22-33.
26
27
28 387 14. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with
29
30
31 388 applications to cancer rates. *Stat Med.* 2000;19(3):335-351.
32
33
34 389 15. National Cancer Insititute. Surveillance Epidemiology and end results (SEER) program.
35
36 390 methods & tools: joinpoint trend analysis. Available from:
37
38
39 391 <https://surveillance.cancer.gov/joinpoint>. Accessed Oct 10, 2017.
40
41
42 392 16. Kerm PV. INEQUAL7: Stata module to compute measures of inequality. *Statistical Software*
43
44
45 393 *Components S416401, Boston College Department of Economics.* 2001.
46
47
48 394 17. O'Donnell O, O'Neill S, Van Ourti T, Walsh B. conindex: Estimation of concentration indices.
49
50
51 395 *Stata J.* 2016;16(1):112-138.
52
53
54 396 18. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin.*
55
56
57 397 2014;64(1):52-62.
58
59
60

- 1
2
3
4 398 19. Lundqvist A, Andersson E, Ahlberg I, Nilbert M, Gerdtham U. Socioeconomic inequalities in
5
6
7 399 breast cancer incidence and mortality in Europe-a systematic review and meta-analysis. *Eur*
8
9
10 400 *J Public Health*. 2016;26(5):804-813.
11
12
13 401 20. Li T, Mello-Thoms C, Brennan PC. Descriptive epidemiology of breast cancer in China:
14
15
16 402 incidence, mortality, survival and prevalence. *Breast Cancer Res Treat*. 2016;159(3):395-406.
17
18
19 403 21. Lukong KE, Ogunbolude Y, Kamdem JP. Breast cancer in Africa: prevalence, treatment
20
21
22 404 options, herbal medicines, and socioeconomic determinants. *Breast Cancer Res Treat*.
23
24
25 405 2017;166(2):351-365.
26
27
28 406 22. Porter P. "Westernizing" women's risks? Breast cancer in lower-income countries. *N Engl J*
29
30
31 407 *Med*. 2008;358(3):213-216.
32
33
34 408 23. Lahmann PH, Schulz M, Hoffmann K, et al. Long-term weight change and breast cancer risk:
35
36
37 409 the European prospective investigation into cancer and nutrition (EPIC). *Br J Cancer*.
38
39
40 410 2005;93(5):582-589.
41
42
43 411 24. Bray F. Transitions in human development and the global cancer burden. In: Steward BW,
44
45
46 412 Wild CP, eds. World Cancer Report 2014. Lyon: International Agency for Research on Cancer,
47
48
49 413 2014.
50
51
52 414 25. Gotzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. *Cochrane*
53
54
55 415 *Database Syst Rev*. 2013(6):CD001877.
56
57
58 416 26. Narod SA. Reflections on screening mammography and the early detection of breast cancer:
59
60

- 1
2
3
4 417 A Countercurrents Series. *Curr Oncol*. 2014;21(5):210-214.
5
6
7 418 27. Loberg M, Lousdal ML, Bretthauer M, Kalager M. Benefits and harms of mammography
8
9
10 419 screening. *Breast Cancer Res*. 2015;17:63.
11
12
13 420 28. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the
14
15
16 421 Human Development Index (2008-2030): a population-based study. *Lancet Oncol*.
17
18
19 422 2012;13(8):790-801.
20
21
22 423 29. Coughlin SS, Ekwueme DU. Breast cancer as a global health concern. *Cancer Epidemiol*.
23
24
25 424 2009;33(5):315-318.
26
27
28 425 30. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009:
29
30
31 426 analysis of individual data for 25,676,887 patients from 279 population-based registries in 67
32
33
34 427 countries (CONCORD-2). *Lancet*. 2015;385(9972):977-1010.
35
36
37 428 31. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and
38
39
40 429 prevalence across five continents: defining priorities to reduce cancer disparities in different
41
42
43 430 geographic regions of the world. *J Clin Oncol*. 2006;24(14):2137-2150.
44
45
46 431 32. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods
47
48
49 432 Part II. Completeness. *Eur J Cancer*. 2009;45(5):756-764.
50
51
52 433 33. Asadzadeh Vostakolaei F, Karim-Kos HE, Janssen-Heijnen ML, Visser O, Verbeek AL,
53
54
55 434 Kiemeny LA. The validity of the mortality to incidence ratio as a proxy for site-specific cancer
56
57
58 435 survival. *Eur J Public Health*. 2011;21(5):573-577.
59
60

- 1
2
3
4 436 34. Programme UND. Human development report. Available from:
5
6
7 437 <http://hdr.undp.org/en/content/human-development-index-hdi>. Accessed Nov 16, 2017.
8
9
10 438 35. Fidler MM, Soerjomataram I, Bray F. A global view on cancer incidence and national levels
11
12
13 439 of the human development index. *Int J Cancer*. 2016;139(11):2436-2446.
14
15
16 440 36. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer
17
18
19 441 statistics, 2015: Convergence of incidence rates between black and white women. *CA Cancer*
20
21
22 442 *J Clin*. 2016;66(1):31-42.
23
24
25 443 37. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017,
26
27
28 444 racial disparity in mortality by state. *CA Cancer J Clin*. 2017;67(6):439-448.
29

445

446

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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*

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

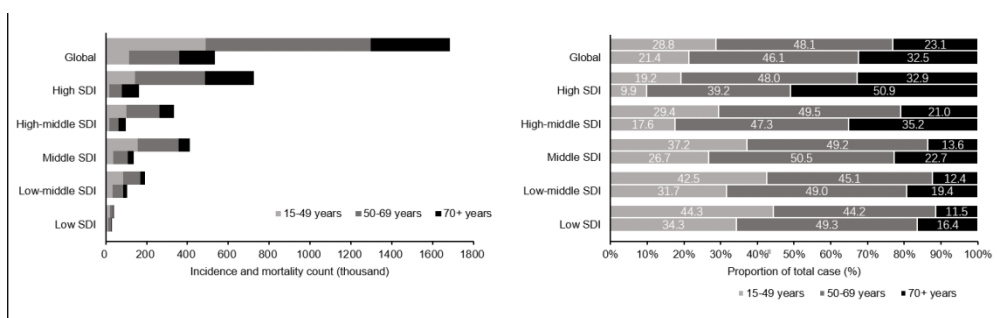


Figure 1

256x79mm (150 x 150 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

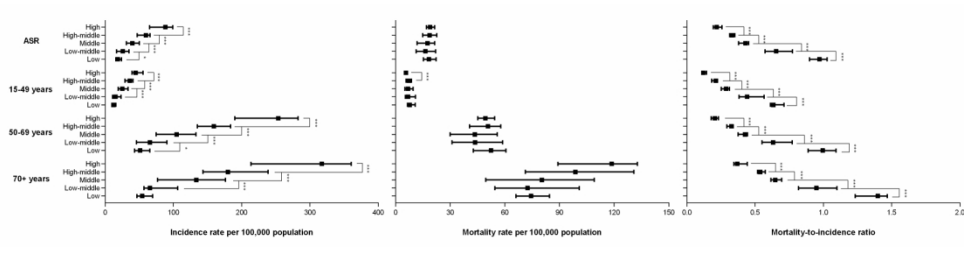


Figure 2

361x91mm (150 x 150 DPI)

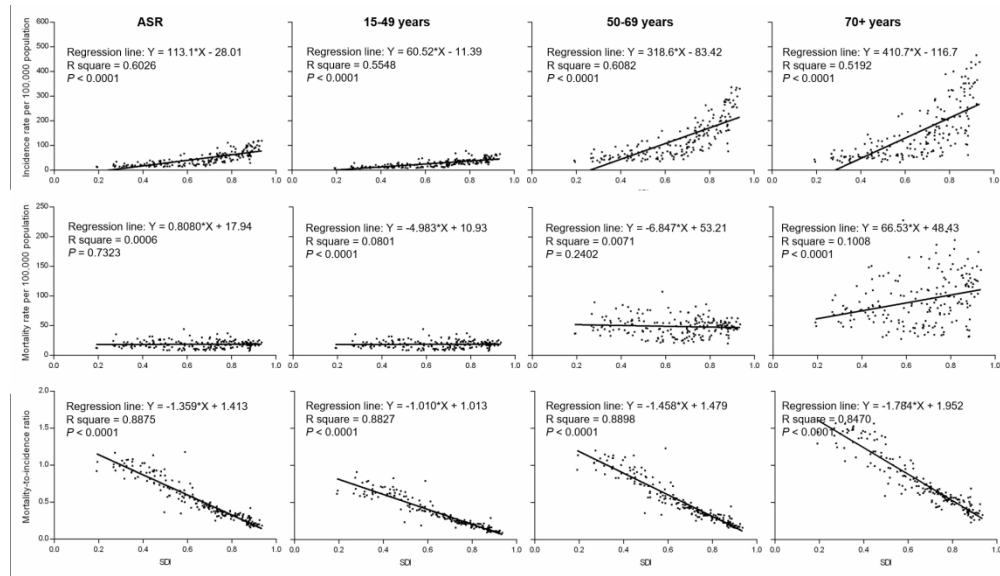


Figure 3

343x196mm (150 x 150 DPI)

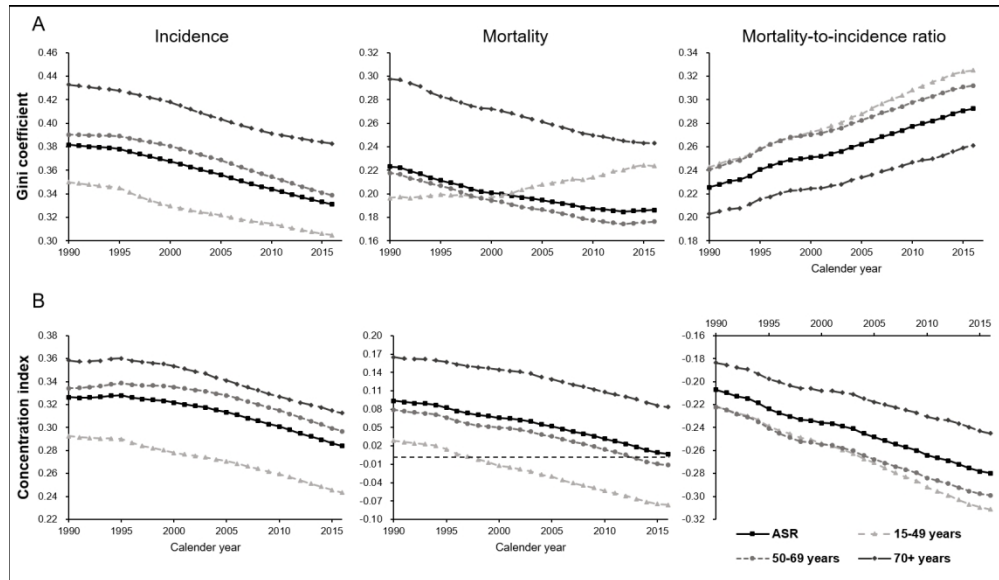


Figure 4

283x163mm (150 x 150 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

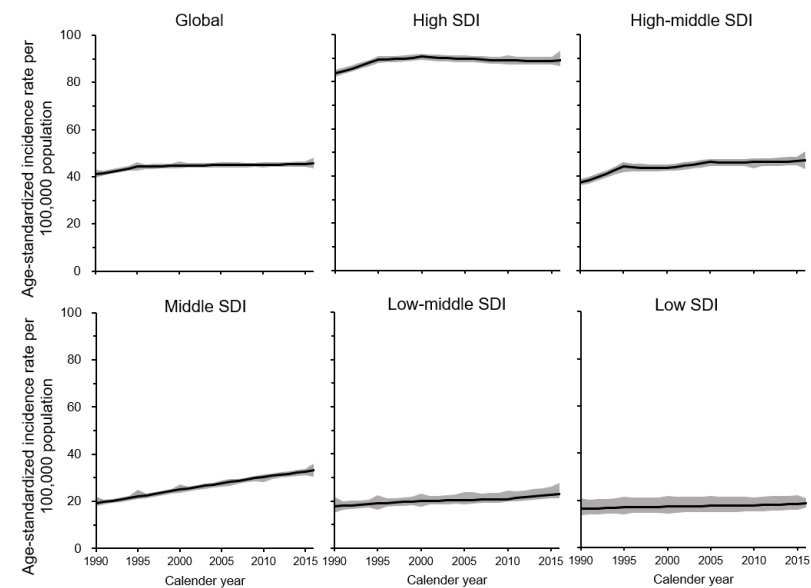
Supplementary figures and tables

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

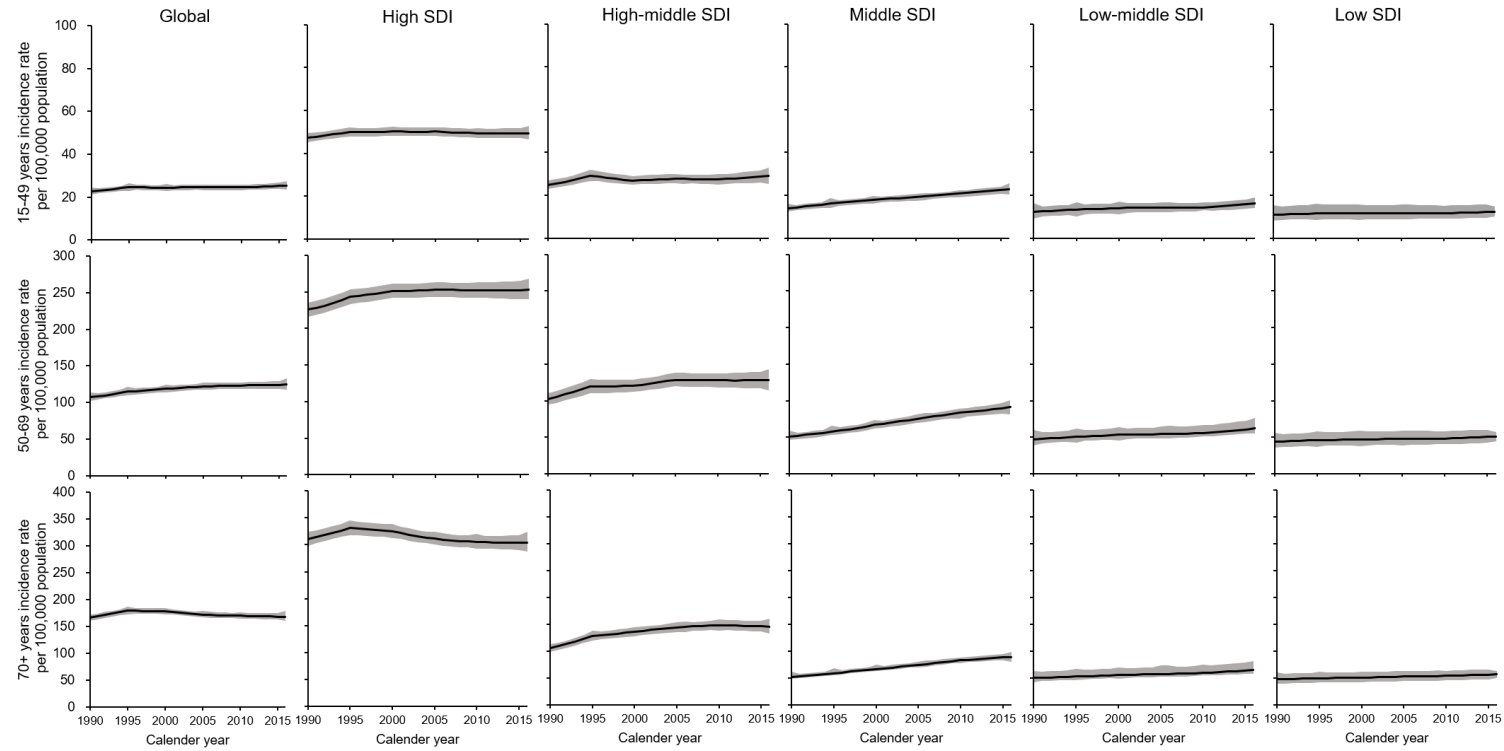
	Age	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
		Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	248.2	22.7	21.0-24.6	484.0	25.4	23.6-27.5	1990-1995	1.6*	1995-2011	0	2011-2016	0.7*	0.4*
	50-69 years	372.8	107.0	102.4-113.5	809.6	124.4	117.4-132.8	1990-1995	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.

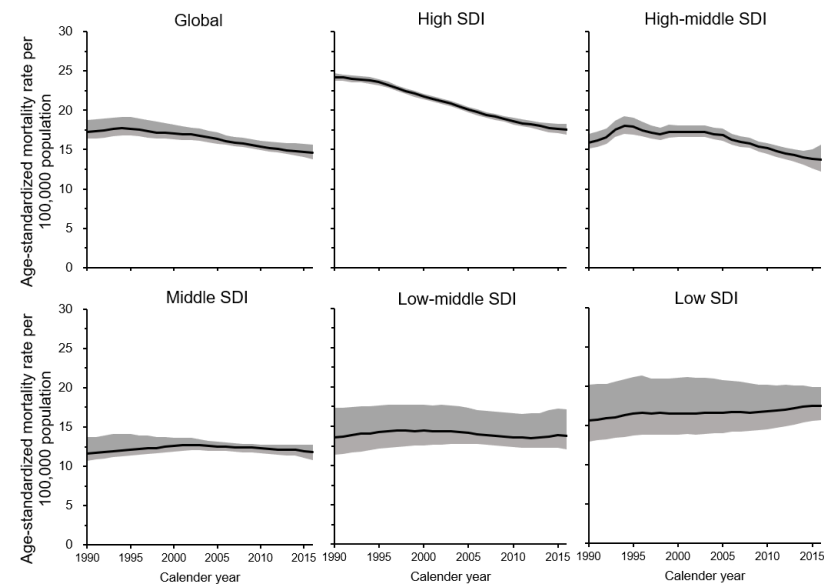
	Age	1990			2016			Trend1		Trend2		Trend3		AAPC (%)
		Case	ASR	95% UI	Case	ASR	95% UI	Period	APC (%)	Period	APC (%)	Period	APC (%)	
Global	15-49 years	80.7	7.4	6.6-8.4	114.3	6.0	5.6-6.6	1990-1995	0.8*	1995-2012	-1.4*	2012-2016	-0.3*	-0.8*
	50-69 years	156.5	44.9	42.2-49.4	246.9	38.0	35.6-41.4	1990-1994	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*



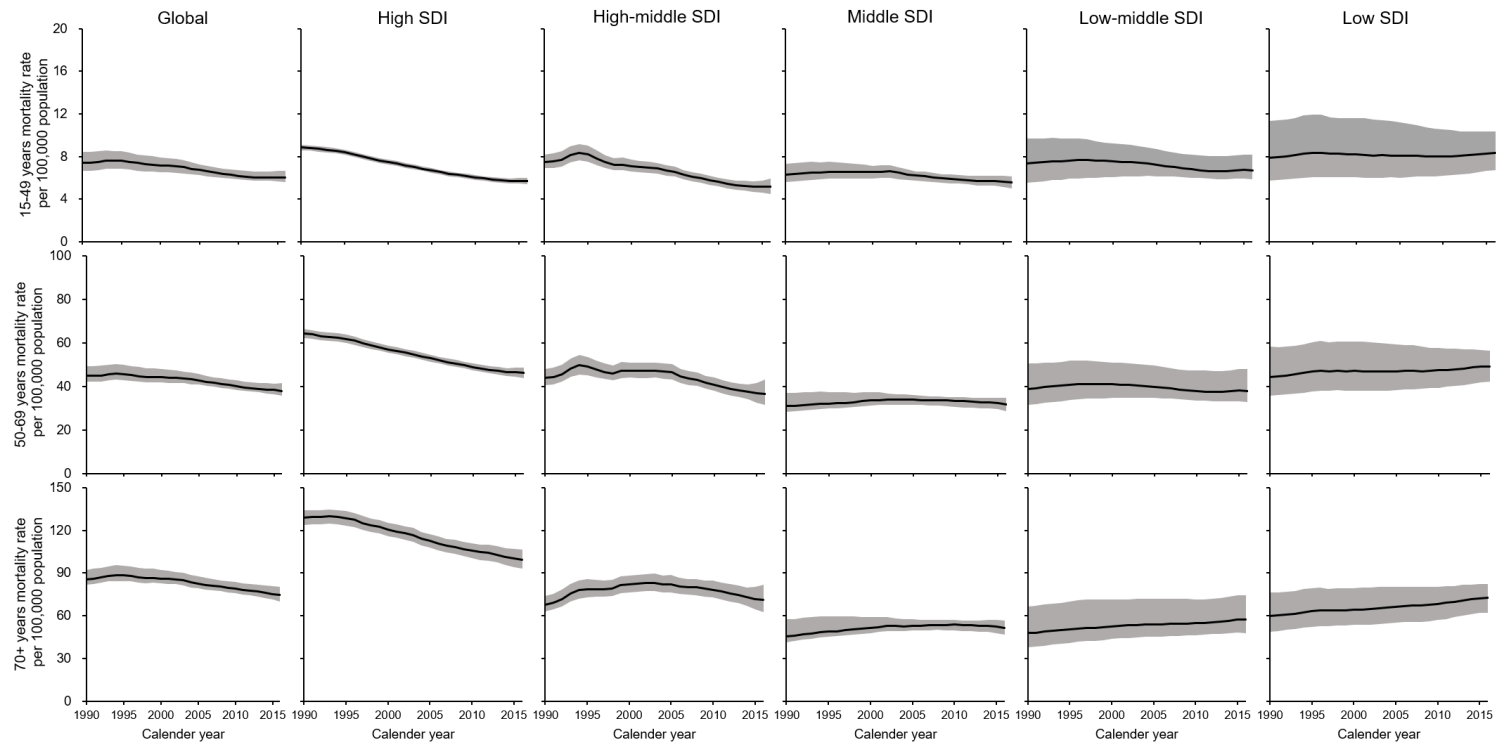
Supplementary figure 1A. Trends in breast cancer age-standardized incidence rate (ASIR) according to SDI settings, 1990-2016. The black lines represent the estimated ASIRs, and areas shaded in gray represent 95% uncertainty intervals.



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.