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# Comparison of the trend of incidence and mortality rates of male breast cancer in Iran with SDI regions: 1990-2021

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## Abstract

Despite advancements in breast cancer research, the incidence and mortality of male breast cancer (MBC) continue to rise worldwide and in Iran. This study aimed to investigate the temporal trend of the incidence and mortality rates of MBC in Iran, with a particular focus on regional disparities based on the Socio-Demographic Index (SDI) over 30 years (1990-2021).

This ecologic study employed an analytic approach to investigate temporal trends in MBC incidence and mortality rates in Iran and six SDI regions. Data from the GBD 2021 study were used to compare trends across the six SDI regions. Joint point regression analysis was conducted to estimate the annual percent change (APC) and average annual percent change (AAPC).

MBC incidence rates (ASIR) showed an overall upward trend (1990–2021), with significant regional variations. Middle and high-middle SDI regions had the highest increases (AAPC = 3.61 and 2.59, respectively), while low-middle SDI regions also showed consistent growth (AAPC = 2.17). High SDI regions displayed fluctuating trends, with increases during the 1990s, followed by declines. In Iran, ASIR rose significantly until 2019 (AAPC = 2.19), with a notable peak in 2004 (APC = 7.87) and a reversal in 2019 (APC = -3.92). The mortality (ASDR) trends were more variable. The high SDI regions saw significant declines (AAPC = -0.45), whereas Iran (AAPC = 0.65) and the middle and low-middle SDI regions experienced increases. The sharpest increases in both incidence and mortality in Iran were observed in men aged ≥ 70 years, with rates tripling over the study period.

This study revealed significant regional and temporal variations in male breast cancer (MBC) incidence and mortality, driven by socioeconomic, behavioral, and healthcare-related factors. Urgent public health efforts focusing on early detection, awareness, and equitable healthcare access are critical to address the rising MBC burden, especially in the low and low-middle SDI regions.

**Keywords:** Male Breast Cancer, Incidence, Mortality, Global Burden of Disease, Iran

## Introduction

Breast cancer, while predominantly a female disease, also occurs in men and accounts for approximately 1.0% of all breast cancer cases (1) and approximately 0.1% of cancer mortality in men (2, 3). The lifetime risk is substantially lower for men, estimated at about 1 in 1,000, compared to approximately 1 in 8 for women (4). However, while breast cancer in men was previously thought to be constant, the incidence of male breast cancer (MBC) has now increased significantly from 0.86 to 1.06 per 100,000 in the past 26 years. MBC has biological differences compared with female breast cancer, including a high prevalence in certain parts of Africa, a higher incidence of oestrogen receptor positivity, and more aggressive clinical behavior (2). Consistent with other cancer types, the incidence of MBC increases with age. The average age at diagnosis for men is approximately five years older than that for women (67 years vs. 62 years, respectively) (5). Overall survival for male patients with breast cancer ranges from 36 to 75% at 5 years (6-8). A preponderance of stage III disease (22% in men versus 6% in women) and a higher incidence of lymph node positivity (60% in men versus 38% in women) have been linked to poorer prognosis (9-11).

Risk factors contributing to breast cancer in men include demographic characteristics (e.g., age, race, family history) (12, 13), genetic predispositions (14-16), environmental exposures (such as radiation)(17), and hormonal imbalances (e.g., elevated serum estradiol(18), Klinefelter's syndrome (19, 20), gynecomastia, liver disease, obesity, testicular abnormalities (21-23).

MBC represented 0.65% of all malignancies diagnosed in Iranian men in 2007(24). The prevalence of MBC in Iran increased with age and peaked in men aged 80(25). The incidence of MBC is rising, and men are diagnosed at later stages than women (26). Most studies have shown that the mean age at diagnosis and survival rate for MBC in Iran are lower than those in Western countries (27).

Breast cancer, traditionally perceived as a female disease, is also diagnosed in men. Although less common, the incidence of male breast cancer is increasing worldwide. By analyzing GBD data, this study aimed to investigate the trend of incidence and mortality rates of MBC in Iran, with a specific focus on the disparities between regions with varying levels of socioeconomic development (SDI). By comparing regions with different SDI, we aimed to identify potential risk factors and disparities in healthcare access that may contribute to the observed differences in cancer outcomes. The findings of this study will provide valuable insights for the development of targeted prevention and screening programs, as well as inform clinical decision-making and improve the overall quality of care for Iranian men with breast cancer.

## Method

*Data source*

The Global Burden of Disease (GBD) 2021 study, drawing on an extensive dataset of 328,938 data sources from 204 countries and territories, provides a comprehensive assessment of global health trends (28). One of the key factors in our study was the Socio-Demographic Index (SDI), a development measure ranging from 0 (lowest) to 1 (highest), based on three dimensions: economic status, as measured by lagged income per capita; educational attainment, as reflected in average years of schooling among the population aged 15 and over; and total fertility rate for females under the age of 25 (29).

*Statistical analysis*

Data on age-standardized incidence and mortality rates for MBC were obtained from the GBD 2021study. Data for Iran and the six Socio-Demographic Index (SDI) regions (high SDI, high income, high middle SDI, low SDI, low middle SDI, and middle SDI) from to 1990-2021 were extracted and analyzed separately.

To assess the temporal trends in breast cancer incidence and mortality, a trend analysis was performed using joint point regression software. In brief, by using incidence and mortality rates as inputs, this method identifies the year(s) when a trend change is produced, calculates the annual percentage change (APC) in rates between trend-change points, and estimates the average annual percentage change (AAPC) in the whole period studied(30, 31). When there are no join points (i.e., no changes in trend), the APC is constant; therefore, it equals the AAPC. Otherwise, the entire period is segmented by the points with trend change. Then, the AAPC is estimated as a weighted average of the estimated APC in each segment using the segment lengths as weights (32).

## Result

Our analysis revealed a general upward trend in Age-Standard Incidence Rates (ASIR) across the study period, with notable variations among regions. In the middle and high-middle SDI areas, ASIR experienced substantial increases, particularly between 2003 and 2009 in the high-middle SDI areas (APC = 6.8) and between 2004 and 2010 in the middle SDI areas (APC= 9.5). The positive and statistically significant AAPC for both the middle (AAPC = 3.61, 95% CI: 3.77, 3.85) and high-middle SDI regions (AAPC = 2.59, 95% CI: 2.08-3.10) underscored this trend, marking the highest AAPCs among all SDI categories.

In contrast, the high-SDI and high-income regions exhibited more fluctuating ASIR trends. For instance, areas with a high SDI experienced a significant increase in ASIR between 1990 and 2000 (APC= 2.99), followed by a substantial decrease between 2000 and 2003 (APC= -2.86). However, the rate of decrease declined significantly between 2003 and 2014 (APC= -0.5), and a further significant decrease occurred between 2017 and 2021 (APC= -2.15). Importantly, given the statistically non-significant AAPC for the period 1990-2017 (AAPC= 0.4, 95% CI:-0.59, 1.40), we cannot definitely conclude an overall increasing trend in high SDI regions.

In low-middle SDI regions, the overall trend in ASIR was consistently upward and statistically significant from 1990 to 2021 (AAPC= 2.17, 95% CI: 2.13, 2.22). Conversely, the low SDI areas exhibited a more complex pattern. While ASIR was initially higher than that in other regions in 1990, the trend reversed in 2007 (APC= -0.47) before increasing again until 2021. Nevertheless, the overall AAPC for low SDI areas was positive and statistically significant (AAPC = 0.37, 95% CI: 0.28, 0.46).

Iran showed an upward trend from 1990 to 2019, with a marked shift in 2004 (APC = 7.87). However, the trend reverses in 2019 (APC= -3.92). Even so, looking at the whole period from 1990 to 2021, the overall trend was still upwards (AAPC=2.19, 95% CI: 1.93, 2.44) (Table 1 and Figure 1).

**Table 1. Average Annual Percent Change (AAPC) in the incidence of male breast cancer across SDI Regions from 1990 to 2021**

| Cohort | Range | Lower Endpoint | Upper Endpoint | AAPC | Lower CI | Upper CI | Test Statistic~ | P-Value~ |
|---|---|---|---|---|---|---|---|---|
| High SDI - 4 Joinpoints | Full Range | 1990.000 | 2021.000 | 0.40 | -0.59 | 1.40 | 0.79 | 0.431 |
| High-income - 3 Joinpoints | Full Range | 1990.000 | 2021.000 | 0.63 | -0.22 | 1.49 | 1.45 | 0.148 |
| High-middle SDI - 5 Joinpoints | Full Range | 1990.000 | 2021.000 | 2.59* | 2.08 | 3.10 | 10.07 | < 0.001 |
| Iran (Islamic Republic of) - 4 Joinpoints | Full Range | 1990.000 | 2021.000 | 2.19* | 1.93 | 2.44 | 17.10 | < 0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Low SDI - 4 Joinpoints | Full Range | 1990.000 | 2021.000 | 0.37* | 0.28 | 0.46 | 8.04 | < 0.001 |
| Low-middle SDI - 1 Joinpoint | Full Range | 1990.000 | 2021.000 | 2.17* | 2.13 | 2.22 | 95.20 | < 0.001 |
| Middle SDI - 5 Joinpoints | Full Range | 1990.000 | 2021.000 | 3.61* | 3.37 | 3.85 | 29.96 | < 0.001 |

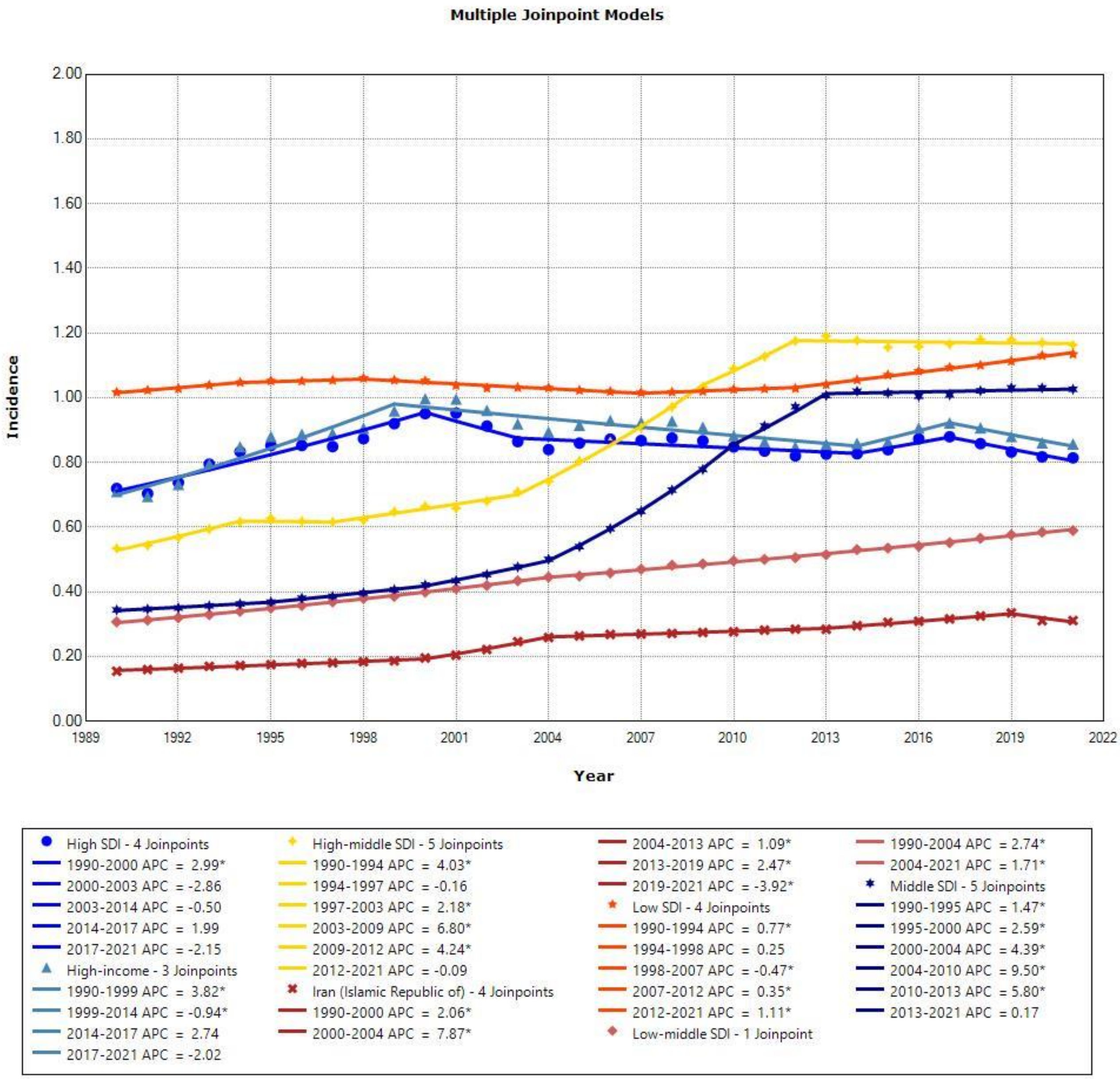


**Figure 1. Trend of male breast cancer incidence in Iran compared to different SDI Regions from 1990 to 2021**

Figure 2 illustrates the varying trends in the MBC Age-Standard Death Rate (ASDR) across different SDI regions from 1990 to 2021. As shown, the low SDI regions exhibit the highest ASDR in 1990 and continue to have the highest ASDR in 2021 compared to the other SDI regions. In Iran, the ASDR increased significantly between 2001 and 2004, with an

APC of 7.77. However, a decline in the ASDR was observed between 2019 and 2021 (APC=-4.75). Overall, Iran's mortality rate generally follows a downward trend, albeit with fluctuations, as indicated by the APC values.

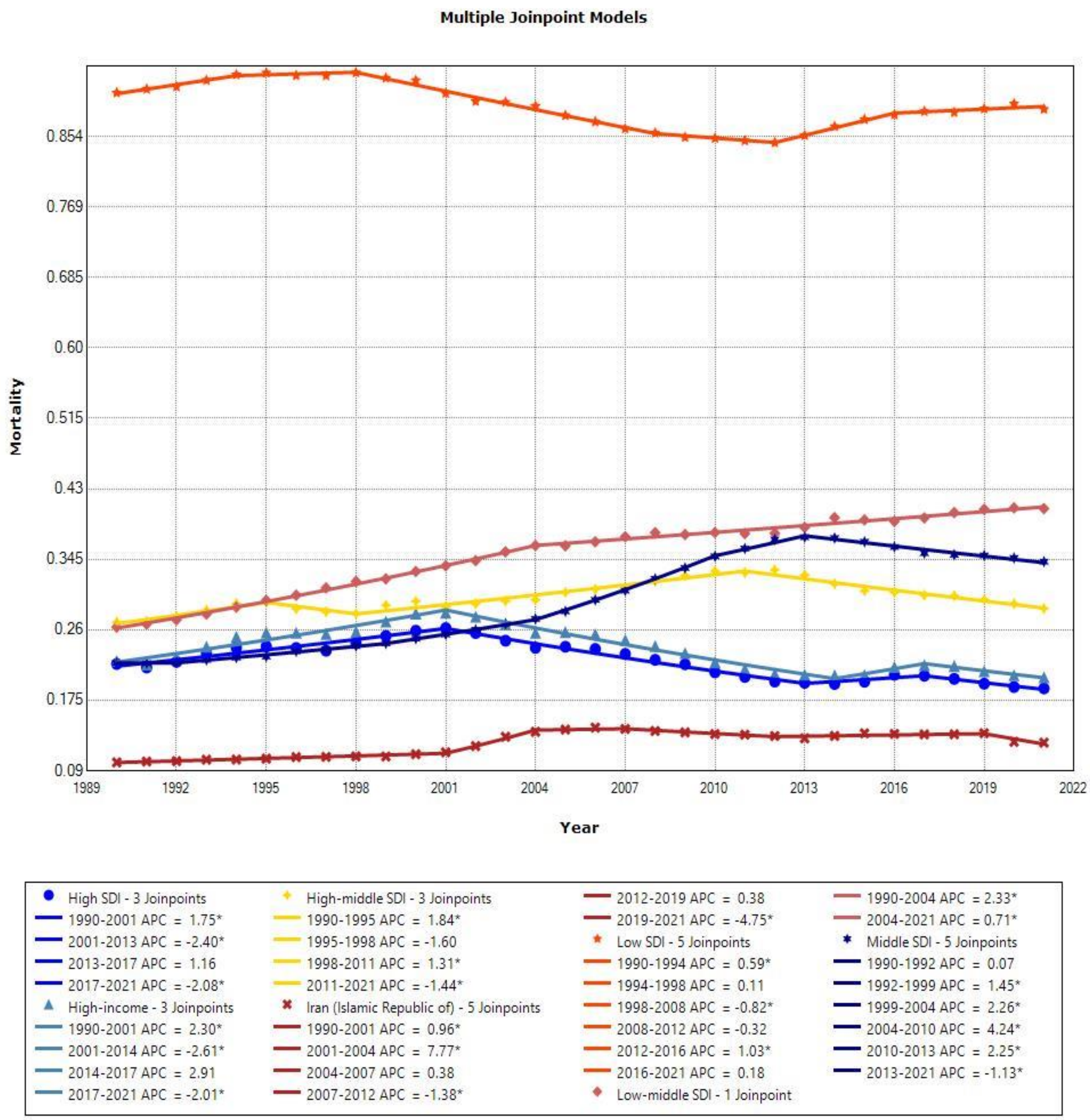


**Figure 2. Trend of male breast cancer mortality in Iran compared to different SDI regions from 1990 to 2021**

Notably, high SDI regions consistently demonstrated the most substantial reductions in ASDRs (AAPC= -0.45, 95% CI: -0.86,-0.04), while several regions, particularly Iran (AAPC= 0.65, 95% CI: 0.28, 1.02), low-middle (AAPC= 1.44, 95% CI: 1.38, 1.50), and middle SDI regions (AAPC= 1.43, 95% CI: 1.22, 1.64), witnessed statistically significant increases. Despite a small reduction in ASDR in Low SDI regions, the difference was not statistically significant (AAPC= -0.06, 95% CI: -0.17, 0.06) (Table 2).

Figures 3 and 4 illustrate the age-specific incidence and mortality of MBC in Iran from 1980 to 2021, respectively. Both figures reveal a concerning upward trend in both the incidence and mortality rates over the study period. For example, the incidence rate for men aged 65-69 nearly doubled, rising from approximately 0.6 cases per 1000 in 1990 to over 1.2 cases per 1000 cases in 2021. The most significant increase was observed in the +70 years age group, where the incidence rate more than tripled over the study period. Similarly, mortality rates have escalated significantly, particularly among individuals aged > 70 years.

**Table 2. Average Annual Percent Change (AAPC) in the mortality of male breast cancer across SDI Regions from 1990 to 2021**

| Cohort | Range | Lower Endpoint | Upper Endpoint | AAPC | Lower CI | Upper CI | Test Statistic~ | P-Value~ |
|---|---|---|---|---|---|---|---|---|
| High SDI - 3 Joinpoints | Full Range | 1990.000 | 2021.000 | -0.45* | -0.86 | -0.04 | -2.13 | 0.033 |
| High-income - 3 Joinpoints | Full Range | 1990.000 | 2021.000 | -0.29 | -0.94 | 0.37 | -0.86 | 0.387 |
| High-middle SDI - 3 Joinpoints | Full Range | 1990.000 | 2021.000 | 0.22 | -0.18 | 0.62 | 1.07 | 0.286 |
| Iran (Islamic Republic of) - 5 Joinpoints | Full Range | 1990.000 | 2021.000 | 0.65* | 0.28 | 1.02 | 3.42 | 0.001 |
| Low SDI - 5 Joinpoints | Full Range | 1990.000 | 2021.000 | -0.06 | -0.17 | 0.06 | -0.95 | 0.341 |
| Low-middle SDI - 1 Joinpoint | Full Range | 1990.000 | 2021.000 | 1.44* | 1.38 | 1.50 | 44.96 | < 0.001 |
| Middle SDI - 5 Joinpoints | Full Range | 1990.000 | 2021.000 | 1.43* | 1.22 | 1.64 | 13.42 | < 0.001 |

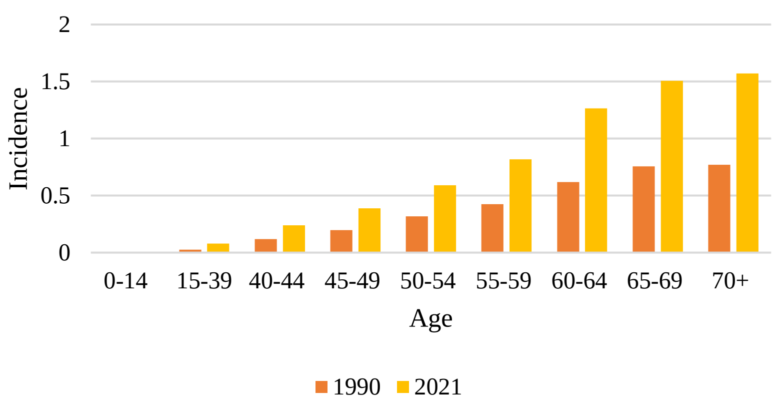


**Figure 3. Comparison of male breast cancer incidence in different age groups in Iran for the years 1990 and 2021**

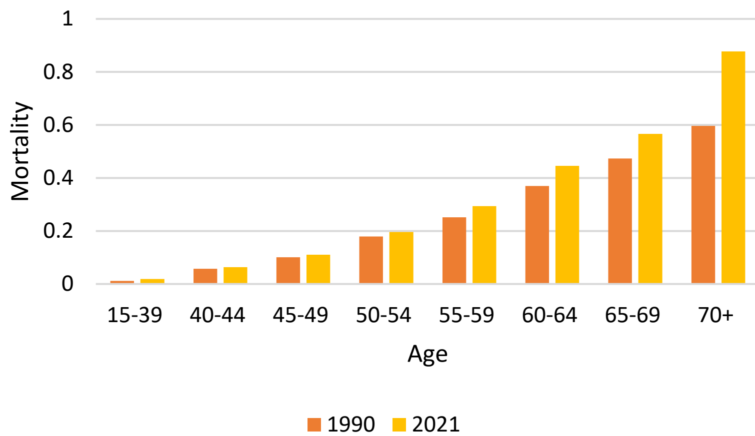


**Figure 4. Comparison of male breast cancer mortality in different age groups in Iran for the years 1990 and 2021**

## Discussion

This study examined temporal trends in MBC incidence rates across various SDI regions, with a particular focus on Iran. Regional variations in the trends were observed. Some areas exhibited a sustained increase, whereas others experienced an initial decline followed by a rise. Additionally, the temporal dimension played a significant role, with distinct periods showing divergent trends. For instance, certain regions experienced a sharp increase in a specific timeframe followed by a decrease. Furthermore, the level of development was found to have a substantial impact on the trajectory of the index, which is consistent with the findings of other studies (33, 34).

SDI is a composite index calculated based on the total fertility rate of women under the age of 25, the per capita lagged distribution income, and the average education level of individuals aged 15 and above (35). Our results show that middle and high-middle SDI areas have the highest AAPC in ASIR between 1990 and 2021, compared to other SDI regions. Notably, from 2008 onwards, high-middle SDI regions surpassed low SDI regions, which had previously exhibited the highest ASIR. This suggests a complex interplay of factors, including increased rates of smoking, alcohol consumption, physical inactivity, obesity, and a low-fiber/high-fat diet (36). Additionally, improved access to screening and treatment programs may have contributed to this trend (37).

Our results showed that despite an upward trend in incidence, during the 1990s in high SDI regions, a shift towards a declining trend was evident thereafter. One possible explanation is that the ASR of MBC incidence in these regions was higher in the past, with limited room for increase. Furthermore, owing to the general increase in the education level of the population in these areas, people's awareness of health has been continuously strengthened, which has limited the growth of MBC to a certain extent (38).

While Iran and the low-middle SDI regions exhibit similar overall AAPC values, the trajectory of this trend differs notably. While low-middle SDI regions have consistently shown an increasing AAPC, albeit with a slight deceleration since 2004, Iran's trend has been more variable, with a marked shift in 2004 (APC= 7.87), followed by a reversal in 2019 (APC= -3.92). Our finding, consistent with previous research, revealed a significant upward trend in MBC incidence rates in Iran between 2000 and 2005, the ASIR nearly quintupled over this period, rising from 0.1 to 0.5 cases per 100,000 individuals. This rise is likely attributable to a combination of factors, including increased prevalence of risk factors, improved cancer registry coverage, and dietary shifts towards high-fat, high-calorie diets (39). A decline in MBC in Iran between 2019 and 2021 may be partially explained by substantial disruptions to healthcare systems caused by the COVID-19 pandemic, leading to reduced cancer screening and diagnosis tests (40-42).

It is important to consider that in low and low-middle SDI regions, where population growth and demographic shifts are often pronounced, epidemiological trends may be influenced by factors beyond the underlying disease processes. Changes in ASIR and APCs in these settings can be attributed to improvements in healthcare access, sociodemographic development, demographic transitions, and increased body mass index (38).

While MBC incidence has been on the rise, mortality trends have displayed a more heterogeneous pattern. High SDI regions have generally experienced declines or stabilization in mortality rates, potentially due to widespread mammography for early stage breast cancer and advancements in treatment modalities, such as chemotherapy, radiation therapy, and targeted therapies (43-45).

While high SDI areas demonstrated a relatively stable ASDR from MBC, the lower and middle SDI regions experienced a marked increase. This trend may be attributed to factors such as increased mammogram utilization, often opportunistic, heightened public awareness, and expanded healthcare access (38, 46). Nevertheless, research suggests that the financial burden associated with severe illnesses can compel low-income individuals to prematurely cease treatment, resulting in rapid disease deterioration and higher mortality rates(47). Moreover, a previous study demonstrated that metabolic factors, such as elevated blood glucose levels and obesity, significantly contribute to the increased breast cancer mortality rate in low- and middle-income regions(38, 48). These findings highlight the complex interplay between socioeconomic, behavioral, and metabolic factors in shaping breast cancer outcomes.

Between 1990 and 2019, Iran experienced a consistent increase in ASDR from breast cancer, with a notable shift in 2004 (APC= 7.77). This escalating mortality rate can be attributed to a combination of factors, including limited awareness of early symptoms (49), delayed diagnosis due to insufficient mammography screening(50), and the rising prevalence of obesity among men, which is associated with advanced disease stages and increased metastatic potential(50, 51).However, a subsequent reversal in the trend was observed in 2019 (APC= -4.75). This decreasing trend may have been influenced by the COVID-19 pandemic. Unfortunately, no definitive statistics are available on the impact of COVID-19 on breast cancer mortality in Iran (52), as 60% of breast cancer research programs have also been postponed due to funding being prioritized for the global COVID-19 pandemic (53).Despite this recent decline, considering the entire period from 1990 to 2021, the overall trend in Iran remains upward.

Our age-specific analysis demonstrated a progressive increase in both the incidence and mortality rates associated with MBC across all age categories in Iran, with the steepest increase found in the +70 age group.

The progressive increase in mortality and incidence rates observed in older age groups is likely due to the delayed diagnosis of male breast cancer. The average age at diagnosis for men is 67 years, with over 40% of cases presenting at advanced stages (III or IV)(54).

## Strengths and Limitations

This study examined temporal trends in MBC incidence and mortality rates across various SDI regions, providing a comprehensive overview of the issue. Although the GBD study provides high-quality estimates of the global burden of diseases and injuries, certain limitations persist (55). The study relies heavily on data from vital and cancer registries, as well as epidemiological studies, and its results are contingent on the out-of-sample predictive validity of the models employed. In many parts of the world, especially in low-income regions, cancer registries may not be fully developed and thus reliable enough, which could influence the final results (56, 57). The early detection of new cases requires updated systems and advanced modalities that might not be effectively accessible in low-income regions. Based on previous reports, cancer registries began in Iran in 1999, but it did not cover all cancer data from pathology laboratories and departments all over the country during the first years, and it took years to develop to a higher standard level (58). Therefore, data from that period in the GBD study mostly rely on epidemiological studies and systematic reviews. The GBD study adopted advanced estimation models and methods to address the scarcity of data in such regions as much as possible (59).

## Conclusion

This study highlights significant temporal and regional variations in male breast cancer (MBC) incidence and mortality rates, underscoring the complex interplay of socioeconomic, behavioral, and healthcare-related factors. Regions with middle and high-middle Socio-Demographic Index (SDI) scores demonstrated the highest Annual Average Percentage Change (AAPC) in incidence rates, reflecting shifts in lifestyle, dietary habits, and improvements in cancer registry systems. Conversely, regions with high SDI experienced stabilization or a decline in mortality rates, likely due to advanced diagnostic and treatment interventions.

Iran exhibited unique trends, with a marked increase in incidence and mortality rates during the early 2000s, followed by recent declines potentially influenced by disruptions caused by the COVID-19 pandemic. Despite these shifts, the overall upward trajectory in both incidence and mortality rates across all age groups, particularly among older individuals, calls for urgent action.

Public health strategies should prioritize early detection programs, increase awareness of MBC symptoms, and improve access to timely diagnostic and therapeutic interventions, particularly in the low and low-middle SDI regions. Future research should explore the impact of modifiable risk factors, address gaps in healthcare delivery, and assess long-term outcomes of intervention programs to mitigate the growing burden of MBC globally.

## Abbreviations

AAPC: Average Annual Percent Change
APC: Annual Percent Change
ASDR: Age-Standard Death Rate
ASIR: Age-Standard Incidence Rate
ASDR: Age-Standard Death Rate
GBD: Global Burden of Disease
MBC: Male Breast Cancer
SDI: Socio-Demographic Index

## Data availability

The data that support the findings of this study are available from the corresponding author [HS] upon reasonable request.

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## Contributions

H.S. is the lead author and guarantor and contributed to interpreting the data and revising the manuscript. H.S. and M.V. planned the study and led the drafting and revision of the manuscript. H.S., M.V., H.G., and Z.S. interpreted the data and drafted and revised the manuscript. All authors approved the submitted version of the manuscript. All authors have contributed to the preparation of the manuscript and have read and approved the submitted manuscript. All listed authors meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors and agree with the manuscript. This work is original and is not under consideration by any other journal.

## Competing interests

The authors declare that they have no competing interests.

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