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Disparities in Breast Cancer Mortality Trends with Liver and Brain Metastases in the United States (1999-2020): A Population-Based Analysis Using the CDC WONDER Database

Hafsa Shahid, MD[1,2*], Fatima Sial, MBBS[3], Mazhar Ali Shah[3], Syed Muhammed Salman Hassan[4] and Khubaib Ahmad[5]

[1]Brigham and Women's Health Hospital, Boston, MA, USA
[2]King Edward Medical University, Lahore, Pakistan
[3]Khyber Medical College, Peshawar, Pakistan
[4]Nishtar Medical University Multan, Pakistan
[5]Marshfield Clinic Health System, Marshfield, Wisconsin, USA

[*]**Corresponding author:** Hafsa Shahid, MD, Brigham and Women's Health Hospital, Boston, MA, USA, E-mail: Hafsashahid786786@gmail.com

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1. Abstract

Background: Breast cancer remains the second leading cause of mortality among women in the United States. Metastasis to the liver and brain signifies advanced disease and is associated with significantly poorer outcomes. Understanding trends in mortality due to breast cancer with secondary liver and brain metastases is essential to addressing demographic and geographic disparities.

Methods: This population-based study utilized data from the CDC WONDER Multiple Cause of Death database from 1999 to 2020. Breast cancer cases with secondary liver and brain metastases were identified using ICD-10 codes. Age-adjusted mortality rates (AAMRs) per 100,000 individuals were calculated. Joinpoint regression analysis was performed to estimate Annual Percent Change (APC) and assess significance ($p < 0.05$). Data were stratified by sex, race/ethnicity, region, urban-rural status, and age groups.

Results: A total of 84,384 deaths were recorded, predominantly among women (83,643 vs. 741 males). Women had a higher overall AAMR (3.1) than men (0.028). AAMRs in women declined from 1999-2008 (APC: -4.16), then rose in successive phases through 2020. Men showed a steady trend (APC: 1.24). Black individuals had the highest AAMR (2.29), followed by White (1.74), Hispanic (1.31), American Indian/Alaska Native (1.20), and Asian/Pacific Islander (1.09). Notably, Asian/Pacific Islanders showed a sharp rise from 2011-2020 (APC: 7.10). The Southern region had the highest mortality (AAMR: 1.84), while the Northeast had the lowest (AAMR: 7.8). Non-metropolitan areas had slightly higher average AAMRs (1.86) than metropolitan areas (1.74). The 85+ age group had the highest mortality rate (6.67), while the 25-34 group had the lowest (0.14). States with the highest mortality included Arkansas (3.30), Mississippi (3.04), and West Virginia (1.83), whereas Massachusetts (1.04), Utah (1.27), and Hawaii (1.75) had the lowest rates.

Conclusion: Breast cancer mortality with secondary liver and brain metastasis exhibits concerning upward trends in specific demographics and regions. Black individuals, older adults, and residents of Southern and non-metropolitan areas face disproportionately higher mortality. These findings underscore the urgent need for targeted public health strategies to address these disparities and improve outcomes.

2. Introduction

Breast cancer is the second leading cause of mortality among women in the United States. Metastasis of a breast neoplasm to distant organs such as the brain and liver signifies an advanced stage of the disease and is associated with a significant decline in survival. The liver is the most common site for metastasis of solid malignant tumours and ranks as the third most frequent site of metastasis in breast cancer [1]. Brain metastases are also prevalent in patients with breast neoplasms, accounting for approximately 24% of all metastatic cases [2]. Prognosis in these patients is often poor due to the limited treatment options available for brain involvement.

Despite advances in surveillance, diagnostics, and screening methods such as mammography, significant disparities in breast cancer-related mortality persist, particularly among patients with metastasis to the liver and brain across different age groups and ethnicities. To better understand and address these disparities, a comprehensive analysis of national mortality trends using data from the CDC database is essential. Our study aims to analyse breast cancer mortality trends associated with secondary liver and brain metastasis from 1999 to 2020, identifying demographic and geographic disparities to guide future healthcare interventions.

3. Methods

This study examined breast cancer-related mortality with secondary liver and brain metastasis in the United States from 1999 to 2020 using death certificate data from the CDC WONDER Multiple Cause of Death database. Cases were identified using ICD-10 codes **C50, C50.1, C50.2, C50.3, C50.4, C50.5, C50.6, C50.8, C50.9** for primary breast neoplasms, and **C78.7, C79.3** for secondary liver and brain metastases, respectively. Age-Adjusted Mortality Rates (AAMRs) per 100,000 individuals were analyzed to identify trends over time. Joinpoint regression analysis was used to estimate the Annual Percent Change (APC) and determine statistical significance, with p-values < 0.05 considered statistically significant. Mortality patterns were further analyzed by stratifying data across sex, race/ethnicity, geographic regions, and age groups. This study was exempt from Institutional Review Board (IRB) approval as it utilized publicly available, de-identified government data in compliance with federal data use policies.

4. Results

Breast cancer and metastatic disease account for 84,384 deaths, predominantly among females (83,643 vs. 741 males). Women had higher overall AAMR i.e., 3.1 per 100,000 as compared to men i.e. 0.028 per 100,00 during the period 1999-2020.For Women, the AAMR initially decreased sharply from 1999 to 2008 (APC: -4.16; 95% CI: -4.72 to -3.58).Then the AAMR continued rising, first from 2008 to 2013 (APC: 1.14; 95% CI: -1.06 to 3.38), then from AAMR rapidly rose from 2013 to 2017 (APC: 6.99; 95% CI: 3.83 to 10.24) and continue rising modestly from 2017 to 2020 (APC: 2.21 95% CI: -0.57 to 5.08). For Men, the AAMR showed a steady pattern with (APC: 1.24; 95% CI: -0.75 to 3.26) as shown in Figure 1.

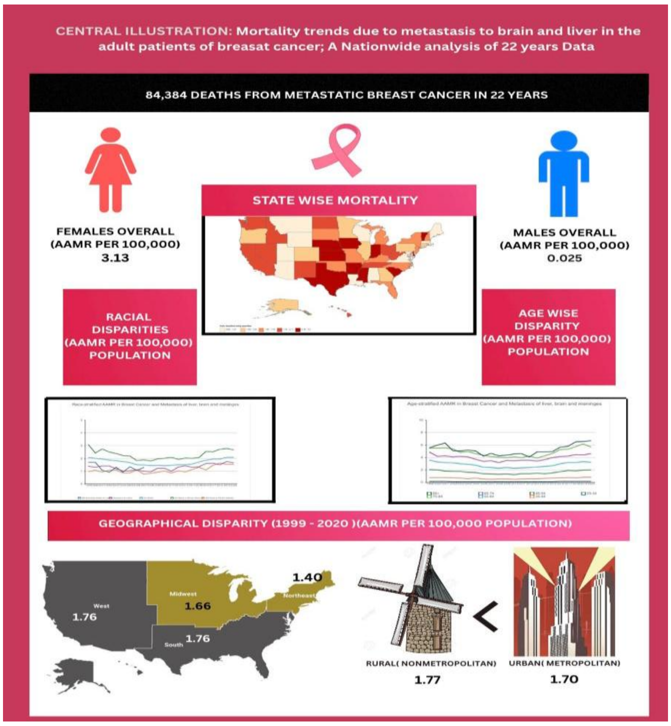

Figure 1: Trends in mortality related to brain and liver metastasis among breast cancer patients, stratified by gender, race, age and regions.

Between 1999 and 2020, the Black or African American population had the highest average AAMR (2.29), more than other groups. Followed by Whites' (1.74) then Hispanic or Latino (1.31) populations, while the American Indian or Alaska Native and Asian or Pacific Islander population had slightly lower average at (1.20) and (1.09) respectively.For American Indian or Alaska Native individuals, the Age-Adjusted Mortality Rate decreased gradually from 2005 to 2020 (APC: -1.32; 95% CI: -5.24 to 2.76). Among Asian or Pacific Islander individuals, the AAMR initially showed slow decline from 1999-2011 (APC: -0.92; 95% CI: -3.23 to 1.44). Then dramatic surge is observed from 2011 to 2020 (APC 7.10; 95% CI: 4.54 to 9.71). For Black or African American individuals, the AAMR initially declined sharply from 1999 to 2008 (APC: -5.43; 95% CI: -7.21 to -3.59). Then rose rapidly from 2008 to 2020, with an APC of 3.80 (95% CI: 2.64 to 4.95). Among White individuals, the AAMR showed four distinct segments. It decreased steeply from 1999 to 2008 (APC: -4.20; 95% CI: -4.87 to -3.51), then gradually maintained a steady phase from 2008 to 2013 (APC: 0.70; 95% CI: -1.82 to 3.28), then AAMR rapidly increased from 2013 to 2017 (APC: 6.90; 95% CI: 3.23 to 10.70), and rose further between 2017 and 2020 (APC: 2.59 ; 95% CI: 0.37 to 5.65).For Hispanic or Latino individuals, the AAMR significantly declined initially from 1999 to 2007 (APC: -4.06; 95% CI: -7.39 to -0.60), followed by a sharper reversal from 2007 to 2020 with APC 4.21 (95% CI: 2.93 to 5.50).

Over the course of the study period, the highest mortality rates were recorded in the Southern Region (AAMR: 1.84) , followed by Midwest Region (AAMR: 1.80),then Western Region (AAMR: 1.79) and lastly Northeast Region has the lowest AAMR of (7.8).In the Northeast, the AAMR sharply declined from 1999 to 2010 (APC: -5.40; 95% CI: -6.40 to -

4.39), then AAMR increase steadily from 2010 to 2020 (APC: 1.27; 95% CI: -0.01 to 2.57). The Midwest showed initially moderate decline from 1999 to 2006 (APC: -3.29; 95% CI: -4.29 to -2.28). From 2006 to 2010, the AAMR declined rapidly with APC of -6.19 (95% CI: -10.43 to -1.74), then from 2010 to 2014, there was a moderate increase in AAMR with APC: 3.19 (95% CI: -1.61 to 8.22). After that AAMR surged rapidly from 2014 to 2018 with (APC: 7.35; 95% CI: 3.19 to 11.67), then at last there was a minimal increase in AAMR from 2018 to 2020, with (APC: 0.65; 95% CI: -6.00 to 7.77). In the South, the AAMR initially showed sharp decline from 1999 to 2007 with APC -4.73 (95% CI: -5.98 to -3.45), then there is a stagnation phase from 2007 to 2012 (APC: 0.35; 95% CI: -3.14 to 3.97). After that, AAMR sharply rose from 2012 to 2017 (APC: 7.44; 95% CI: 4.06 to 10.92), and at last AAMR increased moderately from 2017 to 2020 (APC: 1.82; 95% CI: -2.66 to 6.50). The West also experienced a moderate decline in AAMR from 1999 to 2006 (APC: -3.67; 95% CI: -5.04 to -2.28), this was followed by a continued steady increase from 2006 to 2014 (APC: 2.29; 95% CI: 0.83 to 3.75). After that, the AAMR rose sharply from 2014 to 2017 (APC: 9.24 95% CI: 0.32 to 18.95). From 2017 to 2020 the AAMR showed a minimal increase (APC: 1.91; 95% CI: -1.68 to 5.64).

From 1999 through 2020, Non-Metropolitan adults experienced a slightly higher average age-adjusted mortality rate (1.86) than Metropolitan adults (1.74). Both groups began around 2.1 in 1999-2000, declined to a low of roughly 1.5 by 2006-2008, and then rose again, reaching peaks near 2.08-2.24 in 2019-2020. By 2020, Non-Metropolitan AAMR stood at 2.24-just above its urban counterpart (2.08)-indicating persistently higher mortality outside metropolitan areas.For Metropolitan areas, the AAMR initially decreased sharpy from 1999 to 2008 (APC: -4.55; 95% CI: -5.07 to -4.01). Then the AAMR began rising, first from 2008 to 2014 (APC: 1.58; 95% CI: 0.17 to 3.01), then from 2014 to 2017 the AAMR rose rapidly with (APC: 8.75; 95% CI: 3.21 to 14.57), and finally from 2017 to 2020 the AAMR showed minimal increase (APC: 1.48; 95% CI: -0.80 to 3.81). For Nonmetropolitan areas, the AAMR slightly decreased from 1999 to 2004 with APC: -1.21 (95% CI: -3.26 to 0.88). This was followed by even sharper decline from 2004 to 2007 (APC: -7.87; 95% CI: -16.31 to 1.43), even after that, the AAMR still showed slight decline from 2007 to 2011 with APC of -0.69 (95% CI: -5.75 to 4.64). Finally from 2011 to 2020 the AAMR sharply rose with APC: 4.94 (95% CI: 4.03 to 5.86).

The 85+ years age group had the highest mortality rate (6.67), followed by 75-84 years (5.68), 65-74 years (4.61), and 55-64 years (3.22). Middle-aged groups showed lower rates: 45-54 years (2.00), 35-44 years (0.81), and the lowest mortality was in 25-34 years (0.14). Mortality rates consistently increased with age, peaking in the oldest demographic (85+), while younger adults (25-34) had the smallest burden. 25-35 age group initially showed sharp decline from 1999 to 2004 (APC: -10.50; 95% CI: -17.99 to -2.31), followed by rapid increase in AAMR from 2014 to 2017 (APC: 22.92; 95% CI: -8.92 to 65.90) and then again decline in AAMR from 2017 to 2020 (-3.43; 95% CI: -17.85 to 13.52). 35-44 age groups first showed steady increase in AAMr with APC 4.79 (95% CI: -6.02 to -3.53) from 1999 to 2009, then continued increase in AAMR from 2009 to 2020 with APC of 4.87 (95% CI: 3.72 to 6.02). 45-54 age group initially showed steady decline in AAMR from 1999 to 2010 with APC of -4.52 (95% CI: -5.30 to -3.72) and then the AAMR continued to rise from 2010 to 2020 with APC: 5.30 (95% CI: 4.24 to 6.38). 55-64 age group showed steady decline in AAMR from 1999 to 2008 with APC: -4.72 (95% CI: -5.54 to -3.87) initially. Then minimal increase from 2008 to 2013 (APC: 0.89 (95% CI: -2.04 to 3.90) in AAMR. After that a sharp surge is noticed from 2013 to 2017 (APC: 7.04; 95% CI: 2.60 to 11.67)), and finally from 2017 to 2020 AAMR slightly increased (APC: 1.16; 95% CI: -2.70 to 5.17). 65-74 age group initially showed decline in AAMR from 1999 to 2008 (APC: -4.11; 95% CI: -5.25 to -2.94) and right after that it followed a slower increase in AAMR (APC: 2.96; 95% CI: 2.25 to 3.67) from 2008 to 2020. 75-84 age group have first sharp decline in AAMR (APC: -3.78; 95% CI: -4.73 to -2.81) from 1999 to 2008. After that AAMR remained stagnant from 2008 to 2013 with APC: -0.29 (95% CI: -3.87 to 3.43). From 2013 to 2018 a sharp rise is noticed in AAMR (APC: 7.96; 95% CI: 4.43 to 11.60), which is followed by a slight decline from 2018 to 2020 (APC: -0.36; 95% CI: -8.85 to 8.92). 85+ age group first showed decline in AAMR from 1999 to 2010 (APC: -3.28; 95% CI: -4.55 to -1.98) and then AAMR rapidly raised from 2010 to 2020 with APC: 5.07 (95% CI% CI: 3.74 to 6.40).

The highest mortality rates occur in Arkansas (3.30), Mississippi (3.04), and West Virginia (1.83), with Arkansas leading significantly. Southern states dominate the top tiers, including Alabama (1.73) and Kentucky (1.73), reflecting regional health disparities. Conversely, the lowest rates are in Massachusetts (1.04), Utah (1.27), and Hawaii (1.75), suggesting better health outcomes or systemic advantages in these states.

5. Discussion

Breast cancer is the most commonly reported tumor in the female population. There were more than 2 million new cases reported throughout the globe in 2020 alone [3]. Data shows that breast cancer is the most commonly reported cause of death among young females aged less than 50 in the United States. One in six cases of breast cancer occur in patients aged less than 40 [4]. The disease tends to progress to advanced stages, often involving metastasis to distant organs such as the brain and liver, which contributes significantly to poor prognosis and high mortality rates. Brain is the major organ involved in advanced stage breast cancer, and brain metastasis in a diagnosed female with breast cancer has a very poor prognosis. The median survival reported is only 45.6 months [5]. Liver is the second most commonly involved organ in the metastasis of breast cancer. Patients with ER-positive subtypes have reported good response to neoadjuvant chemotherapy and radiotherapy, though hepatic metastasis burden has also been reported [6].

Screening and targeted therapies have shown to decrease the burden of breast cancer. There is a reduction of 25% in the reported breast cancer cases with proper screening techniques like mammography being implemented [7]. The use of targeted therapy, early detection methods, and better awareness contributed to this downward trend in mortality till 2008. Moreover, advancements in multidisciplinary approaches to managing brain and liver metastasis-including surgery, radiotherapy, and neoadjuvant chemotherapy-provided options for disease control and prolonged survival. Temozolomide, an FDA-approved drug for glioblastoma, has shown positive results in the secondary prevention of brain metastasis in diagnosed breast cancer patients with HER2-positive etiology [8].

The sudden surge in cases post-2008 indicates a decline in the utilization of screening tools and a decrease in the use of targeted therapies. One of the major reasons behind the increase in the reported cases of breast cancer despite the availability of modern interventions is the progression to advanced metastatic stages. Both surgical and intracranial complications are dealt with while managing brain metastasis in breast cancer, including radiotherapy and surgery along with neoadjuvant chemotherapy. Despite these interventions, prognosis remains poor [9]. These limitations, combined with systemic healthcare disparities, have led to a reversal in the declining trend and a notable increase in mortality in recent years.

There is an increasing trend in mortality among younger female populations, particularly in the 35-44 age group, with a reported Annual Percentage Change (APC) of 4.87%. The increased exposure to carcinogens like Dichlorodiphenyltrichloroethane (DDT) raises the risk of developing breast cancer [10]. Genetic mutations and predisposition are also key contributing factors. BRCA1, BRCA2, ATM, BARD1, CHEK2, PALB2, RAD51C, and RAD51D are some of the genes involved in hereditary predisposition to breast cancer [11]. The Black population has a significantly higher proportion of breast cancer-related deaths compared to other ethnicities, with a reported AAMR of 2.29, reflecting systemic barriers in healthcare access. The alarming rise in mortality among Black African Americans demands urgent investigation. Vickii Coffey et al. reported that African American men and women are more susceptible to receiving lower-quality healthcare compared to other ethnicities [12]. A stark mortality gap exists between genders, with females reporting an AAMR of 3.1 compared to 0.028 in males. This large difference highlights the female predominance in the disease. The Southern USA has reported higher AAMR compared to other regions, primarily due to poverty and unequal distribution of healthcare resources. States like Alaska, Mississippi, and Louisiana have high poverty levels and the shortest life expectancy in the country [13]. Inhabitants in these regions are more likely to experience medical and financial hardships compared to residents in other parts of the country [14]. Similarly, rural areas show a significantly higher mortality trend compared to urban areas, which highlights a lack of equitable healthcare resources. N. Douthit, et al. reported significant differences in healthcare access between rural and urban populations [15]. The lack of infrastructure, coupled with hesitancy in consulting oncologists, is a primary contributor to higher mortality in rural areas.

The reliance on ICD codes and death certificates significantly impacts the accuracy of mortality reporting. These data sources are limited to specific disease classifications and lack detailed information about clinical findings and laboratory results, making it challenging to determine the exact cause of death. Additionally, many underserved and underprivileged populations who lack access to healthcare may not be adequately represented or documented in the CDC database. The manual entry of data further increases the risk of human error, potentially affecting the reliability of the recorded information.

6. Conclusions

Breast cancer mortality reveals significant disparities and inequities across race, geography, and socioeconomic status. Populations in the Southern and rural regions, Black communities, and older adults continue to bear the highest burden. Meanwhile, the rising mortality rates among younger individuals and Asian/Pacific Islanders signal an emerging public health concern. Addressing these disparities requires targeted screening efforts, increased investment in metastatic breast cancer research, and the development of policies aimed at dismantling structural barriers to care. Prioritizing equity in healthcare access and innovation is essential to curbing the rising trend in breast cancer mortality.

7. Policy Statements

Funding statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Statement: Ethical approval was not required for this study.

Author's Contribution Statement: HS and FS were responsible for conceptualising the study idea. **HS** reviewed and edited the final draft, and **KA** conducted the analysis. **MSHS and MAS** contributed to writing the original draft. **MAS** contributed to making visualisations. All authors contributed to the critical revision of the manuscript for intellectual content and approved the final version.

Competing Interests Policy Statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Dual Publication Statement: The authors affirm that the submitted manuscript is original and has not been published elsewhere in the same or substantially similar form.

Data Availability: All data used in this study are publicly available through the CDC WONDER (Wide-ranging Online Data for Epidemiologic Research) database, which can be accessed at https://wonder.cdc.gov. No proprietary or confidential data were used.

Clinical Trial Number: Not applicable.

Consent to Participate Declaration: Not applicable.

Consent to Publish Declaration: We, the authors, consent to the publication of our manuscript titled **"Disparities in Breast Cancer Mortality Trends with Liver and Brain Metastases in the United States (1999-2020): A Population-Based Analysis Using the CDC WONDER Database"** and confirm that all authors have approved the final version and agree to its submission and publication in **KOS Journal of Public Health and Integrated Medicine.**

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