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RESEARCH ARTICLE

Trends in Pancreatic Cancer Related Mortality: A Retrospective Analysis using CDC WONDER Database

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Abstract

Background: Pancreatic cancer is 8th most prevalent cancer in the United States with a very high mortality rate. Understanding the epidemiology of Pancreatic cancer is important in identifying the causes and developing preventive strategies.

Methodology: Data from the death certificates spanning from 1999-2020, sourced from CDC WONDER (Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research) was analyzed. To quantify national annual trends in pancreatic cancer-related mortality, the Joinpoint Regression Program was used to determine the annual percent change (APC) with 95% CI in age-adjusted mortality rates (AAMRs) per 100,000 people for all ages stratified by year, gender and regions.

Results: Pancreatic neoplasm claimed about 847,589 lives across all age groups in the US from 1999-2000. The AAMR for pancreatic cancer peaked at 2020 with 11.7 [APC 0.2275 95% CI: 11.6-11.8]. The AAMR for pancreatic cancer-related deaths was 11(95%CI: 10.9=11.1) in 2003 and it increased to 11.3(95%CI: 11.2-11.3) in 2006 (APC 0.87* 95%CI: 11.2-11.4). Men had consistently higher AAMRs than women across all age groups throughout the study period of 1999-2000 (overall AAMR men: 13.2 (95% CI: 13.1-13.2); overall AAMR women: 9.9 (95% CI: 9.9-10)). Geographically; the lowest mortality was displayed by the Western regions (AAMR 10.5, 95% CI: 10.2-10.7), followed by Southern (AAMR 11.1, 95%CI: 10.9-11.4), followed by Midwestern (AAMR 11.7, 95%CI: 10.9 -11.4), followed by Northeast region (AAMR 11.9, 95%CI: 11.6-12.1).

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Conclusion: We observed an overall annual increase in mortality trends related to pancreatic cancer especially in men and certain regions like Northeast region of the United States. These results emphasize the immediate necessity for a comprehensive strategy to address this lethal illness, encompassing breakthroughs in medical research, focused public health initiatives, and extensive governmental reforms.

Key Words: *Pancreatic cancer; Mortality; Gender; Regional; Trends*

Introduction

Pancreatic cancer, ranks as the fourth leading cause of cancer-related deaths in the United States. The five-year survival rate in the U.S. is dismally low, ranging from 5% to 15%, with an approximate overall survival rate of 6% [1].

Globally, the incidence of pancreatic cancer is projected to rise to 18.6 per 100,000 people by 2050, reflecting an average annual growth of 1.1%. The pancreas's anatomical location often leads to late-stage diagnoses when symptoms become evident, underscoring the importance of understanding risk factors for prevention [2].

The disease is most prevalent among the elderly, with an average diagnosis age of 71 [3]. Risk factors contributing to pancreatic cancer can be classified as genetic (around 10%) and environmental (modifiable) [4], with common contributors including alcohol consumption, chronic pancreatitis, obesity, diabetes, family history, smoking, and diets high in red meat and fatty foods, among others. [5,6]. Regional and temporal variations in pancreatic cancer risk factors, such as diet, socioeconomic status, and smoking, significantly influence incidence rates. For localized pancreatic cancer, a multidisciplinary approach to treatment is essential. Systemic chemotherapy is increasingly employed in neoadjuvant settings, often combined with radiation therapy. Advancements in genomic testing have facilitated the development of targeted therapies, including PARP inhibitors and immune checkpoint inhibitors, improving disease management. [7].

Understanding the epidemiology of pancreatic cancer is crucial for identifying its causes and formulating preventive strategies. By quantifying mortality trends by gender and region, we can better appreciate these factors' micro-level effects, and identify areas that require focused research and healthcare resource allocation to reduce mortality rates effectively. This assessment of age-adjusted mortality rates over the past 20 years aims to clarify the impact of pancreatic cancer across the U.S. population.

Methodology

Study design and population

This is a retrospective observational study discussing trends in mortality rates due to all kinds of pancreatic cancers across United States of America (USA). Data from death certificates spanning from 1999-2020, accounting for two-decades was taken and all age groups from infants till old aged people were included. The data was sourced from CDC WONDER (Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research) [7]. This data set includes cause of death from death certificates including all 50 states and the state of Columbia, and disease identification on the database was done using International Statistical Classification of Diseases and Related Health Problems-10th Revision (ICD-10) codes. Following ICD-1O codes were used: C25, C25.1-C25.9, including all kind of pancreatic neoplasms.

Since the data set for this study was publicly available as provided by government related organizations, ensuring compliance with ethical standards regulations, thus ethical board review was deemed unnecessary.

Data extraction

Data were extracted for yearly mortality rates, gender specific mortality rates and regional mortality associated with pancreatic carcinomas. 21 years ranging from 1999-2020 were included. Genders were categorized as male and female. All Census regions of the United States were included, classified as Northeast, Midwest, South and West.

Statistical analysis

To investigate national trends in pancreatic cancer-related mortality, we calculated crude and age- adjusted mortality rates (AAMRs) per 100,000 population from 1999 to 2020 by year, sex and region with 95% CIs. Crude mortality rates were calculated by dividing the number of pancreatic cancer-related deaths by the corresponding U.S. population of that year. AAMRs were evaluated by standardising pancreatic cancer-related deaths to the year 2000 U.S. population.

To quantify national annual trends in pancreatic cancer-related mortality, the Joinpoint Regression Program (Joinpoint V 5.2.0.0, National Cancer Institute) was used to determine the annual percent change (APC) with 95% CI in AAMR [8]. This approach detects significant changes in AAMR overtime by applying log-linear regression models to periods with observed temporal variations. APCs were deemed to be increasing or decreasing if the slope representing the change in mortality was significantly different from zero, based on 2-tailed t-tests. A P value of, $P < 0.05$ was considered statistically significant (Figure1).

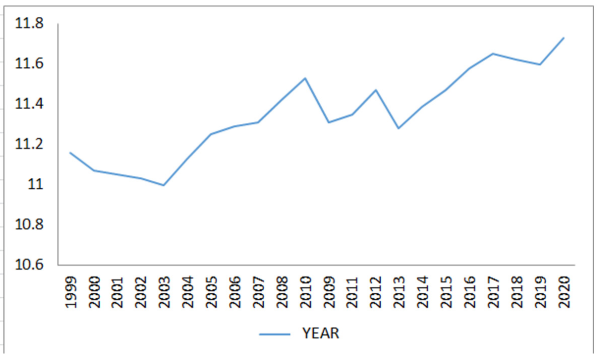

Figure 1) *AAMR of mortality trend of pancreatic cancer across US from 1999-2020.*

Results

Overall trends in pancreatic neoplasm-related mortality:

Pancreatic neoplasm claimed about 847,589 lives across all age groups in the US between 1999 to 2020. The AAMR for pancreatic cancer-related death was 11.2 (95%CI: 11-11.3) in 1999 and it dropped to 11(95%C: 10.9-11.1) in 2003 (APC= -0.42; 95% CI: -1.34-0.03). It then rose to 11.3 (95%CI: 11.2-11.3) in 2006 (APC= 0.87*; 95%CI: 11.2-11.4). A further increase of AAMR to 11.7 (95%CI: 11.6-11.8) was observed from 2006 to 2020 (APC= 0.23; 95% CI: 0.20-0.33).

Pancreatic neoplasm- related AAMRs stratified by sex:

Men had consistently higher AAMRs than women across all age groups throughout the study period of 1999-2000 (overall AAMR men: 13.2, 95% CI: 13.1-13.2; overall AAMR women: 9.9, 95% CI: 9.9-10).

The AAMR for pancreatic neoplasm in 1999 in men of all age groups was 12.9 (95%CI: 12.7 -13.2) and it decreased to 12.6(95%CI: 12.4-12.8) in 2003 (APC= -0.42; 95%CI: -1.68-0.38), followed by an increase in AAMR to 12.9 (95%CI: 12.8-13.1) in 2006 (APC= 0.65 95%CI:-0.20-1.21). The AAMR again increased to 13.6 (95%CI: 13.4-13.7) in 2020 (APC= 0.30; 95%CI: -0.64-1.17) (Figure2).

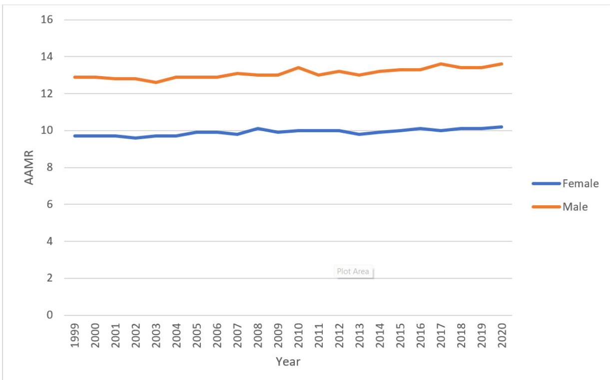

Figure 2) *AAMR rates for gender.*

In 1999, the AAMR for pancreatic neoplasm among women of all age groups was 9.7 (95%CI: 9.6-9.9) and it rose to 10.1 (95%CI: 9.9-10.1) in 2010 (APC= 0.37; 95%CI: -0.79-1.79), followed by a decreased to 9.8 (95%CI: 9.7 -10) in 2013 (APC= -0.42; 95%CI: -1.00-1.29). The AAMR then increased to 10.2 (95%CI: 10 -10.3) in 2020 (APC= 0.42; 95%CI:-0.25-1.58).

Pancreatic neoplasm- related AAMRs stratified by regions:

Over the course of the study period, geographically; the highest mortality was displayed by the Northeast region (AAMR 11.9, 95%CI: 11.6-12.1), followed by the Midwestern (AAMR 11.7, 95%CI: 10.9 -11.4), the Southern (AAMR 11.1, 95%CI: 10.9-11.4) and the Western (AAMR 10.5, 95% CI: 10.2-10.7) regions.

In the Northeast region, the AAMR modestly increased from 11.9(95%CI: 11.6-12.1) in 1999 to 12.0(95%CI: 11.7-12.2) in 2020 (APC= 0.13*; 95%CI: 0.04-0.23). The AAMR in the Midwestern region exhibited a rising trend from 11.1(95%CI: 10.9-11.4) in 1999 to 11.8 (95% CI: 11.5-12) in 2009 (APC= 0.63*; 95%CI: 0.42-1.44), which then proceeded to drop to 11.6 (95%CI: 11.4-11.9) in 2012 (APC= -0.44; 95%CI: -0.96-0.56). AAMR then increased to 12.6 (95%CI: 12.3-12.8) in 2020 (APC= 1.05*; 95%CI: 0.75-1.83). In the Southern region, the AAMR displayed a mild decrease from 11.1(95%CI: 10.9-11.4) in 1999 to 10 (95%CI: 10.6-11) in 2002 (APC= -0.63; 95%CI: -1.76-0.30). The AAMR then heightened to 11.6 (95%CI: 11.5-11.8) in 2020 (APC= 0.35*; 95%CI: 0.22- 0.80). In the Western region, the AAMR was observed to rise from 10.5(95%CI: 10.2-10.7) in 1999 to 11(95%CI: 10.7-11.2) in 2005 (APC= 0.67*; 95%CI: 0.17-2.81). This was followed by a sustained trend in AAMR from 2005 to 2020 (APC= -0.01; 95%CI:-1.11-0.13) (Figure 3-5) (Table 1-3).

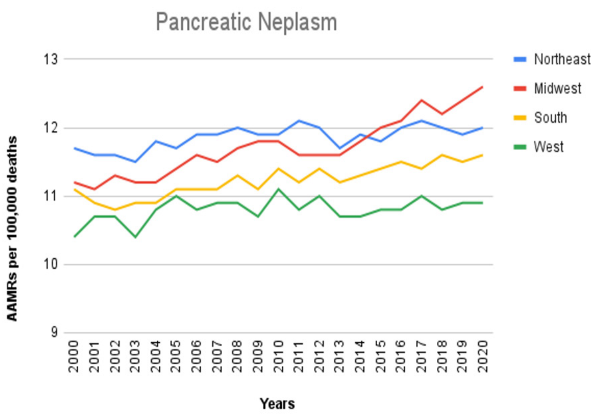

Figure 3) *AAMR by census region.*
Northeast: **1999 to 2020 APC:** 0.13* (95%CI: 0.04-0.23.
Midwest: **1999 to 2009 APC:** 0.63*(95%CI: 0.42-1.44) **2012 to 2020 APC:**1.05*(95%CI: 0.75-1.83).
South: **2002 to 2020 APC:** 0.35* (95%CI: 0.22-0.80).
West: **1999 to 2005 APC:** 0.67*(95%CI: 0.17-2.81).

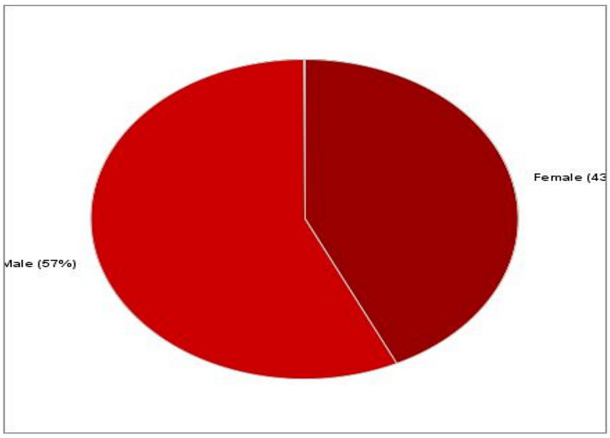

Figure 4) *AAMR rate by gender and year= 1999.*

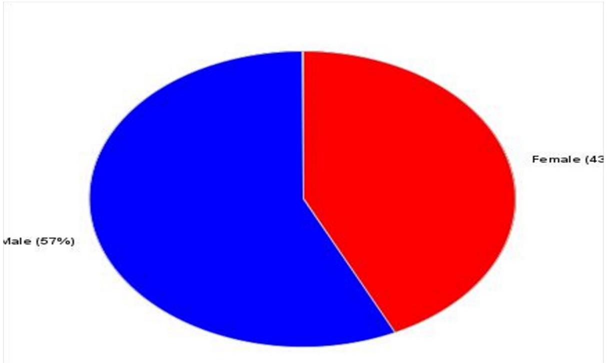

Figure 5) *AAMR rate by gender and year=2020.*

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TABLE 1
Overall and total deaths across genders.

Year total deaths	Population			
		Overall	Male	Female
1999	279040168	30523	14897	15627
2000	281421906	30702	15004	15699
2001	284968955	31157	15166	15992
2002	287625193	31585	15576	16010
2003	290107933	32059	15717	16342
2004	292805298	33045	16457	16589
2005	295516599	34029	16804	17226
2006	298379912	34832	17285	17547
2007	301231207	35550	17913	17637
2008	304093966	36685	18272	18415
2009	306771529	37134	18691	18443
2010	308745538	38413	19554	18859
2011	311591917	38870	19666	19204
2012	313914040	40414	20569	19845
2013	316128839	40671	20797	19875
2014	318857056	42214	21750	20465
2015	321418820	43482	22456	21026
2016	323127513	44815	23055	21760
2017	325719178	46213	24169	22045
2018	327167434	47243	24499	22746
2019	328239523	48249	25048	23202
2020	329484123	49690	25899	23791

TABLE 2
Age Adjusted rates with 96% CI for overall population, males and females.

Year	Age adjusted rate (95% CI)		
	Overall	**Male**	**Female**
1999	11.2 (11-11.3)	12.9 (12.7-13.2)	9.7 (9.6-9.9)
2000	11.1 (10.9-11.2)	12.9 (12.7-13.1)	9.7 (9.5-9.8)
2001	11.1 (10.9-11.2)	12.8 (12.6-13)	9.7 (9.6-9.9)
2002	11 (10.9-11.2)	12.8 (12.6-13)	9.6 (9.5-9.8)
2003	11 (10.9-11.1)	12.6 (12.4-12.8)	9.7 (9.5-9.8)
2004	11.1 (11-11.2)	12.9 (12.7-13.1)	9.7 (9.5-9.8)
2005	11.2 (11.1-11.4)	12.9 (12.7-13.1)	9.9 (9.8-10.1)
2006	11.3 (11.2-11.4)	12.9 (12.8-13.1)	9.9 (9.8-10.1)
2007	11.3 (11.2-11.4)	13.1 (13-13.3)	9.8 (9.7-10)
2008	11.4 (11.3-11.5)	13 (12.8-13.2)	10.1 (9.9-10.2)
2009	11.3 (11.2-11.4)	13 (12.8-13.2)	9.9 (9.8-10.1)
2010	11.5 (11.4-11.6)	13.4 (13.2-13.6)	10 (9.9-10.1)
2011	11.3 (11.2-11.5)	13 (12.8-13.2)	10 (9.8-10.1)
2012	11.5 (11.4-11.6)	13.2 (13-13.4)	10 (9.9-10.2)
2013	11.3 (11.2-11.4)	13 (12.8-13.2)	9.8 (9.7-10)
2014	11.4 (11.3-11.5)	13.2 (13-13.4)	9.9 (9.8-10)
2015	11.5 (11.4-11.6)	13.3 (13.1-13.5)	10 (9.8-10.1)
2016	11.6 (11.5-11.7)	13.3 (13.1-13.5)	10.1 (10-10.2)
2017	11.6 (11.5-11.8)	13.6 (13.4-13.8)	10 (9.9-10.2)
2018	11.6 (11.5-11.7)	13.4 (13.2-13.6)	10.1 (10-10.2)
2019	11.6 (11.5-11.7)	13.4 (13.2-13.6)	10.1 (10-10.2)
2020	11.7 (11.6-11.8)	13.6 (13.4-13.7)	10.2 (10-10.3)

TABLE 3
Total deaths across different regions.

	Northeast		Midwest		South		West	
Year	Population	Deaths	Population	Deaths	Population	Deaths	Population	Deaths
1999	53343775	6784	64100061	7202	99164460	10801	62431872	5737
2000	53594378	6759	64392776	7306	100236820	10848	63197932	5790
2001	53915522	6786	64776531	7296	101849575	10945	64427327	6131
2002	54143915	6857	65018293	7511	103150787	10973	65312198	6245
2003	54334453	6876	65276954	7559	104380188	11386	66116338	6238
2004	54423533	7161	65532305	7712	105883977	11527	66965483	6646
2005	54451230	7145	65751872	7921	107479771	12009	67833726	6955
2006	54522659	7332	66028555	8233	109076933	12315	68751765	6952
2007	54653362	7443	66293689	8256	110688742	12612	69595414	7239
2008	54875926	7617	66523935	8540	112184930	13118	70509175	7412
2009	55133101	7632	66748437	8738	113548615	13256	71341376	7508
2010	55317240	7777	66927001	8818	114555744	13904	71945553	7914
2011	55521598	7971	67158835	8846	116046736	14090	72864748	7963
2012	55761091	8091	67316297	9127	117257221	14812	73579431	8384
2013	55943073	8042	67547890	9289	118383453	14893	74254423	8448
2014	56152333	8322	67745108	9618	119771934	15552	75187681	8723
2015	56283891	8342	67907403	9924	121182847	16140	76044679	9076
2016	56209510	8628	67941429	10140	122319574	16723	76657000	9324
2017	56470581	8972	68179351	10562	123658624	16998	77410622	9682
2018	56111079	8972	68308744	10648	124753948	17811	77993663	9814
2019	55982803	8985	68329004	11013	125580448	18084	78347268	10168
2020	55849869	9238	68316744	11329	126662754	18746	78654756	10377

Discussion

The aim of this retrospective study was to conduct a comprehensive examination of mortality patterns associated with pancreatic cancer in the United States. The study utilized data acquired from the CDC WONDER database, covering the period from 1999 to 2020. The results not only showed the changes in death rates over time but also highlighted major differences across various demographic groups and geographies. These patterns can be crucial for influencing future studies, policy formation, and focused intervention initiatives.

Analysis of changing patterns over time and their significance

Our study began with an observation of a decline in the Age-Adjusted Mortality Rate (AAMR) between 1999 and 2003, followed by a subsequent rise in the following years until 2020. This oscillation might have been indicative of alterations in healthcare methodologies, breakthroughs in medical diagnostics, or changes in population demography. The initial decrease in AAMR could be linked to advancements in diagnostic tools and heightened screening. For instance, studies have shown that improvements in endoscopic ultrasounds and MRIs and the development of new biomarkers such as LRG1 and TIMP1 to further compliment the existing CA19-9 biomarker to improve diagnostic accuracy [9]. Nevertheless, the subsequent rise would suggest the appearance of elements that worsened mortality, such as a growing prevalence of risk factors such as metabolic risks [10] or obesity, or possible failures in efficient patient treatment measures. The risk of pancreatic cancer increased by two times in those with a history of binge drinking [11]. When compared to persons with a normal BMI, a meta-analysis revealed that those with a BMI of 25 to 30 kg/m2 and 30 to 35 kg/m2 had an increased risk of pancreatic cancer of thirteen percent and nineteen percent. Similar correlations for diabetes and high cholesterol were also noted [12,13].

Demographic inequalities: gender and age

The observed gender differences, wherein males continuously exhibited higher Age-Adjusted Mortality Rates (AAMR) than women, indicated a potential interplay of biological and lifestyle variables that may impact illness occurrence and death rates. Men exhibited a higher propensity for participating in high-risk activities, such as smoking and consuming diets rich in processed foods, both of which are established risk factors for pancreatic cancer. Given the inequality connected to gender, it was essential to implement public health programs that specifically targeted each gender. These interventions focused on lowering risky behaviours and promoting early screening and diagnosis.

Moreover, our study emphasized a rise in death rates linked to aging populations, highlighting the aggressive character of pancreatic cancer and its common occurrence in older individuals, which is explained by the physiological changes associated with aging such as more frequent mutations in KRAS, TP53 [14] and SMAD4 and generally lowered immunosenescence. This phenomenon necessitated the implementation of stronger geriatric oncology approaches to address the disease in older populations, including as enhanced palliative care and more assertive treatment of early-stage disease.) The increasing incidence of pancreatic cystic neoplasm (PCN) could be another factor contributing to its increased incidence. Over the past 20 years, there has been a rise in recognition of PCN, a novel disease entity [15].

Regional disparities in healthcare accessibility

Notable disparities were noted across different regions, with the Northeast area exhibiting the highest death rates despite its well-developed healthcare system [16]. This may have indicated underlying problems associated with socioeconomic inequalities, limited healthcare availability, and variations in lifestyle. Conversely, the death rates in the Western regions were lower, possibly due to the prevalence of better lifestyle choices or greater availability of healthcare facilities.

Socioeconomic disparities have a profound impact on the trends, as lower socio-economic conditions lead to limited access to quality health care, delayed diagnosis and reduced treatment options [17]. Additionally, differences in the available specialized medical services can lead to variations in the treatment options available [18]. Rural-urban variations are yet an important cause of the regional disparities as urban areas have advanced health care facilities and resources available to treat the disease at different stages of diagnosis [19]. Lastly, according to a study conducted over racial disparities, it was observed that African Americans have higher rate of mortality incidence in lieu to a combination of genetic susceptibility, socioeconomic factors and health care access [20].

Policy and Practice Implications

This study's findings highlighted the necessity for focused healthcare strategies that tackled both the medical and social factors that influenced health. It is crucial to develop strategies that enhanced healthcare access, particularly in areas with high mortality rates, and implemented public health campaigns that targeted lifestyle factors linked to a higher risk of pancreatic cancer. Implementing policies that promoted collaboration across states and regions to provide standardized care and improve accessibility to appropriate treatment might help alleviate the regional discrepancies that had been found.

Potential Areas for Future Research

Additional investigation was required to explore the molecular processes behind gender discrepancies in pancreatic cancer and the influence of socioeconomic variables on patient outcomes. Longitudinal studies had the potential to offer more profound understanding regarding the efficacy of public health interventions and healthcare policies that had been put into practice in the past twenty years. Furthermore, it was crucial to prioritize research on innovative therapeutic strategies that might be customized based on individual risk profiles and geographical features in order to improve the effectiveness of therapy and increase patient survival rates.

Conclusion

An annual increase in mortality trends related to pancreatic cancer, particularly in men and the Northeastern United States underscores the growing urgency to design a multifaceted approach to address this disease in these demographics. Identification of the novel biomarkers, improved early identification and development of targeted therapies that can improve the prognosis are necessary steps in this regard. The identification of suboptimal provision of healthcare facilities in these demographics is also needed for much-needed governmental reforms. The equitable distribution of healthcare resources and the streamlining of the treatment protocols across states and regions are necessary to reduce the disease burden.

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