

Trends and Projections of Pancreatic Cancer Mortality Attributable to Smoking and Alcohol Use in the U.S., 1999–2035.

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Abstract

Background:

This study's objective is to evaluate the 25-year mortality trends in the US population from pancreatic cancer that is exacerbated by alcoholism and smoking.

Pancreatic cancer is still one of the deadliest tumors in the United States, despite improvements in detection and treatment. Its known modifiable risk factors include alcohol consumption and smoking, which account for around 20–30% and less than 5% of cases, respectively. Given that almost 80% of smokers also drink, these two characteristics typically overlap. Although both are classified as contributory causes of mortality, the precise combined burden of smoking and alcohol-related pancreatic cancer fatalities has not been fully characterized.

Methodology:

For people over 45 with pancreatic cancer (ICD-10: C25), concomitant alcohol abuse (F10), and smoking abuse (F17), data from the CDC WONDER database (1999–2023) was studied. Age, sex, race, Hispanic origin, U.S. Census area, and 2013 urbanization categories were used to stratify age-adjusted mortality rates (AAMRs) per 100,000. Joinpoint regression (JPR) analysis was used to determine annual percentage changes (APCs). The significance level was set at $P < 0.05$. The Ljung-box test was used to assess the Autoregressive Integrated Moving Average (ARIMA: 1,1,0) models used to anticipate annual AAMRs through 2024.

Results:

Pancreatic cancer was the primary cause of 47,333 deaths in the US between 1999 and 2023; smoking and alcoholism were found to be contributory factors (overall AAMR = 14.09). By 2035, AAMR is predicted to be 30.61 with $p = 0.91$. Black people made up 10.94%, white people 87.23%, non-Hispanics 96.24%, and men 61.93%. Between 2001 and 2005, mortality increased significantly, with an APC of 63.96 ($p=0.001$). Males showed an even steeper significant rise from 2001 to 2004 with $APC = 82.90$, $p<0.001$, while females showed a dramatic significant surge from 2001 to 2005 with $APC = 63.90$ ($p = 0.003$). From 2001 to 2005, non-Hispanic people showed a sharply significant increase ($APC = 65.21$, $p = 0.00$). Significantly, the Northeast experienced a sharp increase between 2002 and 2004 ($APC = 164.77$, $p<0.001$). Among Urbanization categories, Medium Metro areas recorded the highest early $APC = 80.57$, $p = 0.003$. White individuals showed a significant surge 2001–2005 ($APC = 66.87$, $p = 0.0012$). Highest AAMRs were in Delaware (66.7), Michigan (51.5) and Vermont (50.5); lowest in California (0.9), Alabama (9.4), and Georgia (11.4)

Conclusion:

The findings indicate that, despite notable demographic and geographic variations, mortality rates have remained high over the past 20 years and will continue to grow by 2035. In order to reduce the significant estimated future mortality toll, targeted campaigns and new legislative initiatives are essential. These findings call for increased cessation and prevention efforts countrywide.

Introduction

Pancreatic cancer continues to be one of the most lethal cancers in the United States and exhibiting a five (5) year survival rate of under 12% and a consistently rising incidence during the last twenty years.^{1,2} It is a serious public health concern and numerous risk variables have been identified by epidemiological studies; with alcoholism and cigarette smoking being two well-known and modifiable contributions.^{3,4}

While excessive alcohol use can result in chronic pancreatitis, fibrosis, and ultimately malignant alteration of pancreatic tissue; smoking has been linked to pancreatic carcinogenesis through carcinogen induced DNA damage, chronic inflammation and oxidative stress.^{5,6,7} Additionally, the combined effects of drinking and smoking may worsen these pathological processes; raising the risk of cancer even more as demonstrated by U.S. population-based studies^{8,9,10}.

According to mortality estimates, pancreatic cancer outcomes will be influenced by the persistence of these risk behaviors beyond 2025 underscoring the necessity of focused public health initiatives.¹¹ The importance of smoking and alcohol use in preventative methods is highlighted by this large cohort analyses that consistently show a dose response association between these behaviors

and the risk of pancreatic cancer^{4,6} Differences in cancer outcomes and exposure prevalence indicate that some subpopulations may be disproportionately impacted; necessitating customized therapies.¹²

Few studies have rigorously assessed the impact of smoking and alcohol dependence to United States pancreatic cancer mortality rates over the lengthy periods.^{1,2} The purpose of this project is to evaluate the effects of smoking and alcohol on pancreatic cancer mortality in the United States between 1999 and 2025; offering data on trends over time, expected outcomes and potential risk reduction strategies.

Methodology

Study Setting and Population:

This retrospective, population-based mortality study was conducted using the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Cause of Death (MCOD) database. This is a publicly accessible surveillance system that compiles detailed U.S. mortality information from death certificates, coded using the International Classification of Diseases, Tenth Revision ICD-10. ICD-10 provides a highly standardized framework for coding diseases and causes of death, enhancing diagnostic accuracy, data consistency, and the validity of population-based mortality analyses¹³

The target population included adults aged 45 years and older who died between 1999 to 2023 with Pancreatic cancer (C25) and comorbid Smoking abuse related disorders (F17 and Alcohol abuse related disorders (F10) identified as contributing causes of death. These codes are consistent with the previous epidemiological studies of the mortality crises of pancreatic cancer, smoking and alcohol abuse^{14,4}

This investigation was exempt from institutional review board (IRB) oversight, and study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting standards.¹⁵

Data Abstraction:

Mortality records for each qualifying death, data on population size, year of death, place of death, demographic characteristics (age, sex, race /ethnicity), urban–rural classification, geographic region, and state were obtained. Racial and ethnic categories were classified as Hispanics, NH White, NH Black or African American, NH American Indian or Alaska Native, and NH Asian or Pacific Islander. Geographic assessments incorporated U.S. Census Bureau–defined regions (Northeast, Midwest, South, and West) and urbanization level into six-level urban–rural framework.¹⁶

Statistical Analysis:

We calculated crude mortality rates (CMRs) and AAMRs per 100,000 populations using the 2000 U.S. standard population as the reference¹⁶

Joinpoint Regression Program was used to estimate the annual percent change (APC) and Average annual percentage changes (AAPC) in AAMRs with 95% confidence intervals (CIs)¹⁶ By applying log-linear regression models. Trends were deemed statistically significant if the APC diverged from zero with a p-value < 0.05, based on two-tailed t-tests.

AAMRs were modeled using Autoregressive Integrated Moving Average (ARIMA) time-series methods. The analysis period was divided into a training cohort (1999–2017) and a validation cohort (2018–2023) to allow out-of-sample model evaluation. Stationarity of the training series was assessed using the Augmented Dickey–Fuller (ADF) test. Model adequacy was evaluated using residual diagnostics, including the Ljung–Box test to assess residual autocorrelation. ARIMA model was used to project AAMRs through 2035, with 95% confidence intervals.

Results

In the United States, 47,333 pancreatic cancer deaths related to smoking and alcohol dependence were reported from 1999 to 2023. 38.06% were female while 61.93% were male. Hispanic individuals had 3.75% of total deaths while non-Hispanic individuals had

96.24%. Racially, 87.23% of all deaths were Whites and 10.94% were Black. Mortality rate continues to rise between 2024 and 2035, with an increase in the AAMR of about 23.277 by 2024 to approximately 34.166 in 2035. Our mean absolute error (MAE), root mean square error (RMSE), and mean absolute percentage error (MAPE) were 2.45, 3.19, and 10.99%, respectively.

ANNUAL TRENDS:

In 1999, the AAMR was 1.50 per 100,000, rising to an AAMR of 21.8 in 2023. (Fig. 1, **Supplemental Tables 1 and 2**). There were enormous spikes from 2001 to 2005 and 2005 to 2018 with an APC value of 63.96 (95% CI: 44.21 to 83.98) and APC value of 6.12 (95% CI: 5.25 to 7.38) respectively. Between 2018 and 2023 only a minor decrease that was not statistically significant.

AAMR STRATIFIED BY SEX:

Men had consistently higher AAMRs than women throughout the study period (overall AAMR: 19.2; 95% CI: 18.11–20.29; vs :9.8; 95% CI:9.17–10.58) **as shown in Fig. 1. (supplemental table 2)**

From 1999 to 2001, women exhibited a non-significant slight increase in mortality (APC: 3.48; 95% CI: -15.80–53.82), whereas men displayed a non-significant slight decrease in mortality (APC: -15.97; 95% CI: -29.76 to 3.34). In women, a substantial rise in mortality was noted from 2001 to 2005 APC: 63.90 (95% CI: 5.45 to 85.00). A similar rising trend was noted from 2005 to 2018 (APC: 6.44; 95% CI:5.37 to 8.67).

Men also displayed a similar substantial rise in mortality from 2001 to 2004 (APC: 82.90; 95% CI: 59.25–102.56), which continued to rise between 2004 and 2008 (APC: 14.63; 95% CI:9.60–21.67) and between 2008 and 2019 (APC: 4.80;95% CI: 3.94 to 5.73). After 2019 Both show non significant trends.

AAMR STRATIFIED BY RACE/ETHNICITY:

Non-Hispanic populations had higher mortality (AAMR: 17.43; 95% CI: 16.68–18.18) than Hispanic populations (6.95; 95% CI: 5.43–8.68). Reliable Hispanic trend estimates were available only after 2003. (**supplemental table 3, Fig. 2**)

From 2003–2019, Hispanics showed a significant increase (APC: 6.03; 95% CI: 4.81–10.54), followed by a non-significant decline/plateau from 2019–2023 (APC: -5.14; 95% CI: -18.06 to 1.82). Non-Hispanic trends were stable from 1999–2001 (APC: -8.14; 95% CI: -23.76 to 21.48), followed by a sharp rise from 2001–2005 (APC: 65.21; 95% CI: 50.81–82.09) and continued increase from 2005–2018 (APC: 6.33; 95% CI: 5.50–7.42).

Between 1999 and 2023, mortality was highest among Black individuals (AAMR: 15.8/100,000), followed by Non-Hispanic Whites (14.6). Although American Indians/Alaska Natives showed the highest AAMR (17.9), this should be interpreted cautiously due to incomplete and inconsistent data. (Fig. 3)

Asian and American Indian/Alaska Native populations demonstrated similar non-significant declining trends in recent years; 2015 to 2023 and 2010 to 2023 with an APC - 1.064(95% CI: -11.06 to 10.16) and (APC: -1.66; 95% CI: -7.74 to 7.26, p = 0.56) respectively, though comparisons were limited by data gaps.

The AAMR remained stable for the White cohort from 1999 to 2001 after which it rose substantially till 2005 (APC:66.87; 95% CI: 47.74–86.94) with a persistent upward trend from 2005 to 2018 (APC:6.24; 95% CI: 5.40–7.41). Mortality rose from 2000 to 2008 for the Black or African American cohort with an APC value of 20.25(95% CI: 15.09 to 37.15) with a similar upward trend between 2008 and 2019(APC:5.37; 95% CI:3.81 to 8.37), followed by a downward, non-significant, reversal till 2023.

AAMR STRATIFIED BY CENSUS REGION:

The Midwest exhibited the highest overall AAMR at 20.2 deaths per 100,000, followed by the Northeast (14.02), the South (12.9), and the West (10.0). (Fig. 4) (**supplemental table 4**)

Mortality rose sharply in the Northeast region from 2002 to 2004 with an APC of 164.77(95% CI: 89.81-264.37), followed by a continued upward trend from 2004 to 2007 (APC:18.24;95% CI: 5.56–26.99) and from 2007 to 2020 (APC:2.99; 95% CI:1.95–4.34).

After 2020, the Northeast region exhibited a significant decline in mortality from 2020 to 2023 (APC: -5.41;95% CI: -14.49 to -0.37). Midwest exhibit a sharp and significant rise in trend between 2001 and 2004 (APC:112.61;95%CI:61.06-164.25), mortality rate continued to rise sharply through 2004 to 2011 with an APC value of 18.25(95%CI:13.42–22.98), whereas trend between 2011 to 2023 remained significant but relatively stable (APC:2.28;95% CI: 1.22–3.29). The South region in contrast exhibited a significant spike in rates from 1999 to 2005 (APC of 38.60(95% CI: 28.94–61.03)) with a similar significant upward trend between 2005 and 2019 (APC: 6.97; 95% CI: 5.92–8.77) and a significant decline from 2019 to 2023 with an APC value of -1.59(95% CI: -9.48 to 2.35). The mortality in the West region spiked significantly from 1999 to 2005 with an APC value of 34.88(95% CI: 25.21–56.77), followed by a continued but less steep upward trend from 2005 onward (APC:3.86; 95% CI: 2.94–4.92).

AAMR STRATIFIED BY URBANIZATION:

Non-metropolitan areas have a higher overall AAMR (Micropolitan AAMR: 20.1, Non-Core AAMR: 19.5) as compared to Metropolitan areas (Small Metro AAMR: 18.5; Medium Metro AAMR: 15.4; Large Fringe Metro AAMR: 13.2; Large Central Metro AAMR: 10.3). (Fig. 5, **supplemental table 5**)

Mortality rose significantly from 1999 to 2005 for the **Large Central Metro** with an APC 46.16 (95% CI: 33.52–110.13) and continued to rise from 2005 to 2010 (APC:11.82; 95% CI:4.25–29.12) trend stabilized and became non-significant till 2023. **Large Fringe Metro showed a significant rise from 1999 to 2006** (APC:42.35;95% CI: 28.61–70.76) with similar trends between 2006 and 2023 (APC: 3.54;95% CI: 2.42 to 4.74). **Medium metro** exhibited a non-significant rise in mortality between 1999 and 2002 with an APC value of 5.25(95% CI: -32.63 to 29.59), followed by a significantly sharp spike between 2002 and 2005 (APC:80.57;95% CI: 49.76–100.43) and continued to rise significantly from 2005 to 2017 (APC:6.22; 95% CI: 5.25–8.78). The **Small Metro** region showed a very large spike between 1999 and 2005 (APC:33.36;95% CI: 22.91–85.60) with a moderate but significant upward trend from 2005 to 2011 with an APC of 10.32(95% CI: 4.54–21.69) after which mortality became stable till 2023. The **Micropolitan** region displayed a significant rise in mortality from 1999 to 2008 (APC: 23.93;95% CI: 18.22–36.99) with a continued large upward trend from 2008 to 2023 (APC: 4.53;95% CI: 3.31–5.67). A very large significant spike in mortality was observed in the **non-core** region between 1999 to 2004 (APC:34.69; 95% CI: 23.66–65.98) with a continuous and significant upward trend from 2004 to 2016 (APC:9.46;95% CI: 7.73–11.69) than trend plateaued and became non-significant.

AAMR STRATIFIED BY GEOGRAPHIC REGION:

Between 1999 and 2023, AAMR have shown considerable variation between the states in the US. North Dakota exhibited the highest AAMR at 36.9, Idaho at 32.2, and Oregon at 29.4. In contrast, California showed the lowest AAMR at 1.5, Alabama at 3.6, and Mississippi at 3.9. (Fig. 6)

Discussion

Our 24-year analysis of pancreatic cancer mortality data from the Centers for Disease Control and Prevention demonstrated several significant mortality patterns associated with smoking and alcohol dependence. Our study highlighted the contribution of smoking and alcohol consumption to rising pancreatic cancer mortality since 1999. The apparent spike in mortality rates around 2001 to 2005 and then persistently increasing mortality trend until 2018 aligns with research suggesting that the rise in pancreatic cancer (PC) mortality may be attributed to improvements in diagnosis and certification in certain regions.^{17,18,19} The relatively stable period at the start may be due to underreporting of cases²⁰ as well as reflect demographic inertia, with the rising elderly population contributing more over time^{21,14}. Pancreatic cancer development is a process featured by a stepwise accumulation of genetic mutations.²² The progressive increase in driver gene mutations, combined with the cumulative effects of long-term tobacco exposure in older individuals, likely explains the rise in incidence with advancing age and the corresponding increase in mortality.²³

In contrast to other cancers in which the mortality rates have recently stabilized or even decreased, we noticed an increase in smoking and alcohol related pancreatic cancer mortality in the US, which favors the similar results by Tavakkoli et al. and Abboud et al.^{24,25} As the fourth leading cause of cancer-related mortality, pancreatic cancer has an overall 5-year relative survival rate of only 9%.²⁶

Tobacco smoking is one of the strongest modifiable risk factors for the development of PC^{27,28}. The relationship between smoking and pancreatic cancer has been shown in epidemiological studies, including case-control^{29,30} and cohort studies^{31,38}. Olsen et al

(2012) highlighted that smoking increases the pancreatic cancer risk by 75%, making it the strongest environmental risk factor³⁹. Smokers not only face a significantly higher risk of developing PC compared to non-smokers⁴⁰ but also experience an earlier onset of the disease⁴¹ (45) Heavy smokers have a higher risk of pancreatic cancer than light smokers. This dose-response relationship was observed in several case-control studies^{42,43,44} The relative risk (RR) of developing a PC is 1.8 for current smokers and 1.2 for former smokers. For those smoking more than 30 cigarettes a day, the relative risk increases to 2.2.⁴⁵

Chronic pancreatitis is also a significant risk factor for PC, with studies reporting PC incidence in chronic pancreatitis patients ranging from 0.68% to 2.94%.^{46,50} Tobacco smoking plays a dose-dependent role in the development of chronic pancreatitis.^{51,52} Alcohol consumption is the leading risk factor for chronic pancreatitis, responsible for 44–65% of cases^{53,54,55} While heavy alcohol consumption (around 80 g/day for six years) is considered the threshold for developing chronic pancreatitis, even lower levels of alcohol intake can contribute to disease progression when combined with other risk factors^{56,57}.

Higher pancreatic cancer mortality among smokers can be attributed to higher carcinogen exposure. Tobacco smoke contains carcinogens and nicotine that can activate survival signaling pathways in cancer cells and their microenvironment.^{2,58} Importantly, qualitative research suggests that patients who smoke may delay seeking medical care for symptoms due to misattribution, fear, or denial, which can contribute to diagnostic delays.⁵⁹ Alcohol also promotes inflammation, microbiome dysbiosis, production of reactive oxygen species (ROS), lipid peroxidation, and DNA damage⁶⁰ These mechanisms were suggested to cause pancreatic acinar cells injury, activate pancreatic stellate cells, and trigger pancreatic fibrosis in *in vitro* models^{62,2} Finally, alcohol consumption is strongly correlated with smoking habits, an established risk factor for pancreatic cancer²⁷

Obesity is a significant risk factor for both diabetes and PC. In the U.S., approximately 17% of PC cases are attributed to excess body weight. There is a well-established link between metabolism and cancer, with metabolic dysfunction being a key characteristic of cancer and obesity and diabetes representing the most common metabolic risk factors^{63,64} For every 1 mmol/L increase in blood glucose, individuals without diabetes had a 15% increased risk of PC (HR = 1.15)⁶⁵ The Fremantle Diabetes Study also highlighted that the incidence of PC was twice as high in adults with type 2 diabetes compared to those without it over a follow-up period of up to 25 years (Incidence Rate Ratio (IRR) = 2.06)⁶⁶ Additionally, Xia et al. (2020) showed that participants with metabolic syndrome (HR = 1.31), central obesity (HR = 1.24), and hyperglycemia (HR = 1.60) had a higher risk of developing PC⁶⁷ Considering the U.S. population, showing significantly increasing cases of pancreatic cancer in both men and women, a clear upward trend over time can be seen for diabetes as well, with age-standardized prevalence rising significantly from 9.8% in 1999–2000 to 14.3% in 2017–2018⁶⁹ This is mainly because obesity and diabetes are relatively more prevalent in high-income nations, which are both risk factors for pancreatic cancer.^{70,71,72}

We found a relatively stable mortality trend again between 2018 and 2023. There can be several plausible causes for that. Notably, the screening, diagnosis, and treatment of cancer have been postponed in many countries owing to disruptions caused by the COVID-19 pandemic⁷³ The WHO declared COVID-19 a global pandemic in March 2020⁷⁴, prompting widespread restructuring of healthcare systems to prioritize critically ill patients⁷⁵; as a result, oncology services were heavily disrupted^{76,77}, with delays in cancer screening, diagnosis, and treatment, particularly affecting high-risk patients such as those with severe comorbidities or active malignancies^{78,79,80} Cancer diagnosis rates were also lower than expected in the US in 2020 and 2021⁸¹ The UK CONTACT study (2023) and a retrospective multicenter study from Paris also highlighted similar results.^{82,83} Madge et al. reported that the median survival among pancreatic ductal adenocarcinoma patients diagnosed during the pandemic nearly halved compared to the pre-pandemic cohort (3.3 vs. 7.4 months), and this difference persisted even after excluding COVID-19-related deaths⁸²

Surgical resection (pancreatectomy) remains the only established curative approach for patients with pancreatic ductal adenocarcinoma⁸³ with multiple studies confirming that surgery is linked to improved survival^{84,85,86,87} Moreover, the evolution of enhanced recovery after surgery (ERAS) programs and treatment in certified cancer centers allows for a faster recovery, reducing complications and improving survival^{88,89} Additionally, the use of perioperative systemic therapy has enabled the downstaging of tumors, thereby rendering previously unresectable lesions operable, leading to higher rates of R0 resections and improved overall survival outcomes^{90,91} Moreover, neoadjuvant chemoradiation has significantly improved outcomes in patients with borderline resectable pancreatic cancer^{92,93}. The introduction of multi-agent chemotherapy regimens, including FOLFIRINOX and gemcitabine combined with nab-paclitaxel, has led to a significant improvement in overall survival compared to treatment with gemcitabine alone

^{94,95,96} Additionally, in borderline resectable and locally advanced pancreatic cancer, neoadjuvant chemotherapy, when combined with adjuvant chemotherapy following surgical resection, has shown significantly improved long-term survival outcomes. ^{97,98,99}

With respect to gender disparities, our study revealed consistently higher mortality rates in men than in women. These results are similar to many previous studies ^{14,21,99,100,101}. In addition, worldwide also, the incidence rate for pancreatic cancer is slightly higher for males (5.5/100,000 new cases/year in males, compared to 4.0/100,000 new cases/year in females) ¹⁰². The reason why there is a difference between the sexes is not entirely known, but this disparity is likely associated with the higher prevalence of high-risk behaviors among males, such as tobacco use, alcohol consumption, whereas unhealthy dietary patterns, and insufficient physical activity in women. ^{103,104,105,106,107,108}. The EPIC study (2025) reported that men had a 1.3-times greater risk of developing PC relative to women after multivariable adjustment ¹⁰⁹. The riskier behaviour in men, like smoking and drinking increase potential genetic susceptibility and the influence of sex steroids. These factors collectively affect metabolism, immunity, and inflammation, ultimately impacting the fidelity of genetic codes ¹¹⁰. Moreover, among carriers of BRCA2 mutations, males exhibit a higher incidence of pancreatic cancer ³⁷. Additionally, the prevalence of diabetes in males is higher than in females ¹¹¹, which may partly explain the higher pancreatic cancer mortality rate in males. Low mortality in women compared to men can be attributed to hormonal influences as studies report an inverse association between breastfeeding and pancreatic cancer risk ^{112,113} whereas others did not report this association ^{114,114,115,116,117,118,119}. The use of hormone replacement therapy (HRT) has also been extensively studied with mixed results ^{118–130}. However, most of these studies were not able to analyze the effect of specific types of HRT, making it difficult to generalize results across time and geographical regions as prescribing patterns and pharmaceutical formulations vary globally and over time ^{131,132}. Oestrogen exposure generally protects against developing PC, highlighting the rationale behind the lower pancreatic cancer risk for prolonged breastfeeding and prolonged HRT use ^{133,134,135}. The oestrogen receptors E_{α} and E_{β} are expressed in the exocrine tissue of the pancreas and might have an inhibitory effect on tumor growth ^{136,137} or have a moderating effect similar to what has been shown for the carcinogenesis of breast, colorectal, and ovarian cancers ^{138–141}. It has recently been reported that knocking out oestrogen-related receptor γ in acinar cells in mice results in acinar-ductal metaplasia, an early event in pancreatic carcinogenesis ¹³⁸. However, the exact role of oestrogen receptors in pancreatic tumor growths is not yet fully understood and is subject to ongoing research ^{142–146}. Early age at menarche may be directly associated with PC risk ^{147,148,149}, whereas older age at menopause may be inversely associated with PC. Similarly, women with at least one child have a significantly reduced risk of developing PC in comparison to nulliparous women ^{150,151}. However, some studies reported no association among these risk factors. ^{128–152}. The most recent meta-analysis identified a statistically significant association between having children and reduced risk of PDAC, with an RR of 0.91 (95% CI: 0.85–0.97) ¹²⁹.

Regarding racial disparities, our results are consistent with other studies reporting pancreatic cancer incidence or mortality trends in the US populations, highlighting that smoking and alcohol contributed to rising deaths in non-Hispanic Whites and Black populations. ¹⁵³ For instance, a study analyzing data from the National Program of Cancer Registries and the Surveillance, Epidemiology, and End Results program of cancer registries and the National Center for Health Statistics from 2001 through 2015 reported that pancreatic cancer incidence and mortality were higher among blacks than whites (incidence, 24.7 vs 19.4 per 100,000; IRR, 1.28; 95% CI, 1.26–1.29; mortality, 23.3 vs 18.4 per 100,000; IRR, 1.27; 95% CI, 1.26–1.28). ¹⁵⁴. Similarly, many other studies, including analysis of the National Inpatient Sample (NIS) database of 2016–2020, revealed that Black/African American individuals demonstrated significantly higher odds of mortality compared to White individuals (adjusted odds ratio (OR) = 1.339, 95% CI: 1.324–1.478, $p < 0.0001$) ^{24,130,155,156}. A study analyzing data from the California Health Interview Survey 2007 reported that binge drinking was most common among non-Hispanic Whites (11.9%), followed by Latinos (10.8%), American Indian/Alaska Natives (9.8%), Blacks (8.0%), and Asians (4.2%). ²⁴ CDC WONDER reported that non-Hispanic White adults have higher smoking prevalence (12.9%) than Blacks (11.7%) and Asian Americans (5.4%) ¹⁵⁷. Data analyzed from the 24 Californian residential SUD treatment programs highlighted that Non-Hispanic Whites smoked at a higher rate (68.7%) than both Hispanics (54.9%) and non-Hispanic Blacks (55.6%) and smoked more cigarettes per day ($M = 11.2$, $SD = 6.5$). Hispanics were more likely than non-Hispanic Whites to receive a referral to a cessation specialist (adjusted odds ratio; AOR = 2.34, 95% CI = 1.15, 4.78) and tobacco-cessation counseling (AOR = 2.68, 95% CI = 1.28, 5.62) ¹⁵⁸. An analysis from 30 prospective studies across Asia, Australia, Europe, and North America reported that a larger proportion of participants in the Asian cohorts were non-drinkers at baseline ¹⁵⁹.

A noteworthy point this analysis disclosed was the higher mortality rates in nonmetropolitan areas compared to metropolitan areas over 24 years of study. Previous studies from countries including the US, Denmark, Australia, Finland, and Canada have also reported

higher PC mortality rates in nonmetropolitan areas ^{160–166} Compared to many other common cancers, the diagnosis and management of PC require a higher level of expertise that is often unavailable in smaller or rural hospitals ¹⁶⁷ Previous studies have shown that individuals residing in rural areas have the lowest rates of local or locoregional stage diagnosis ¹⁶⁸. They also found that rural individuals receiving surgery live farther from major tertiary care high-volume academic medical centers and are operated on at low-volume hospitals, which have been associated with worse healthcare outcomes compared to higher volume hospitals ¹⁶⁹. Patients living in rural regions frequently face long travel distances to reach specialized cancer centers, and these barriers may ultimately prevent some individuals from receiving appropriate care at all ¹⁶⁹. Additionally, residents in rural areas often have lower socioeconomic status, reduced health insurance coverage ^{170–174}, and higher smoking rates, obesity rates, lack of exercise rates ¹⁷⁵, and lack of higher education ¹⁷⁶. Socioeconomic status is negatively correlated with the incidence of pancreatic cancer ¹⁷⁷. Those with lower socioeconomic status tend to detect pancreatic cancer later, have lower chances of surgical resection, and worse postoperative outcomes ¹⁷⁸. All these challenges can lead to late-stage diagnoses of PC, negatively affecting prognosis and increasing mortality rates.

Our geographical analysis demonstrated that the Midwest had the highest mortality, whereas the West had the lowest mortality from 1999 to 2023, which is consistent with other studies ¹⁷⁹. A recent study reported that smoking prevalence is geographically variable in the U.S., with the highest smoking rates in the Midwest and South ^{180,181}. Data by CDC also showed that smoking rates in the Midwest are higher 9(18%) than in the West (8.9%) ¹⁸² Midwest (33.9%) has the highest obesity prevalence as well ¹⁸³

While our state-level analysis identified North Dakota, Idaho, and Oregon as having the highest pancreatic cancer mortality attributable to smoking and alcohol dependence, whereas Alabama, Mississippi, and California had the lowest rates. These findings are in contrast with those of Didier et al. (2024) ¹⁸⁴. National surveys like the Behavioral Risk Factor Surveillance System (BRFSS) and the National Survey on Drug Use and Health (NSDUH) show higher smoking prevalence in some northern and northwestern states (e.g., North Dakota, Idaho, Oregon) and lower prevalence in some southern and western states (e.g., Alabama, Mississippi, California). Similarly, Northern states have higher rates of binge drinking and alcohol dependence compared to some southern and western states. ¹⁸⁵ States like North Dakota and Idaho have lower access to specialized care and higher rural populations, which can delay diagnosis and worsen outcomes. In contrast, California has better access to healthcare facilities and public health interventions that mitigate alcohol- and smoking-related risks ^{186,189}.

Our study predicted that mortality trend would climb over the coming decade, increasing from roughly 23 per 100,000 in the mid-2020s to nearly 34 per 100,000 by 2035. These projections are consistent with other studies. Historical data indicate that pancreatic cancer deaths attributable to smoking and alcohol were roughly 23 per 100,000 in the mid-2020s ¹⁹⁰, and projections suggest that rates will climb substantially over the next decade, with age-adjusted mortality rising nearly 50% by 2035 ^{191,192}.

Limitations:

Our study has several limitations. First, mortality data from the CDC WONDER database are derived from death certificates and may be affected by misclassification or coding errors, which may lead to potential bias. Moreover, residual confounding due to coexisting metabolic risk factors (e.g. obesity, DM) could not be accounted for and may have influenced the observed mortality trends. The lack of individual-level data on key risk factors might have introduced confounding bias. Second, determining whether observed mortality trends are driven by changes in incidence, survival, earlier detection, or treatment advances cannot be inferred from the given data. Fourth, mortality data for Asian or Pacific Islander and American Indian or Alaska Native populations were only available from 2015, and for Hispanics from 2003. This restricted time frame may limit the ability to assess long-term trends for these groups due to the small numbers of cases and inconsistencies in earlier mortality data. Fifth, subgroup comparisons may be influenced by migration and population structure changes over time.

Conclusion

In our study, we found gender, racial, geographical, and state-wise disparities in mortality trends. Mortality rates were highest in males, non-Hispanic Whites, the Midwest, and the state of North Dakota. Age-adjusted death rates are expected to increase steadily from the mid-2020s through 2035, underscoring a growing public health burden. Future studies should continue to explore the combined

effects of high-risk behaviour (harmful alcohol consumption and smoking), urbanization, and economic development level on the incidence of pancreatic cancer to develop more effective prevention and care interventions.

Declarations

Disclosure:

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 paper.

Ethical approval:

Ethical approval was not required because this study used publicly available, de-identified secondary data. No identifiable human participant information was accessed.

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Author Contribution

M.S. and A.N.M. conceived the research idea and supervised the study. M.K. drafted the introduction. A.Z. developed the methodology. W.A. performed data extraction and participated in the final compilation of the manuscript. P.K. conducted the analysis and prepared the results section. M.T. prepared the illustrations and figures. M.S. and M.W.A. wrote the discussion. M.A.K. drafted the conclusion. F.V., A.B., and J.K. critically reviewed the manuscript for intellectual content. A.N.M. and W.A. finalized and compiled the manuscript. All authors reviewed, revised, and approved the final version of the manuscript.

Data Availability

Data were obtained from the publicly available CDC WONDER Multiple Cause of Death database (1999–2023), available through the Centers for Disease Control and Prevention (CDC) at <https://wonder.cdc.gov/>. Data were analyzed for individuals aged ≥ 45 years with pancreatic cancer (ICD-10: C25) and coexisting tobacco use disorder (ICD-10: F17) and alcohol use disorder (ICD-10: F10). Age-adjusted mortality rates (AAMRs) per 100,000 population were stratified by age, sex, race, Hispanic origin, U.S. Census region, and 2013 urbanization categories. Annual percentage changes (APCs) were estimated using Joinpoint Regression Analysis (JPR), with statistical significance defined as $P < 0.05$. Future AAMRs were projected through 2035 using an Autoregressive Integrated Moving Average (ARIMA [1,1,0]) model, and model performance was assessed using the Ljung–Box test. As all data were publicly available and de-identified, institutional review board approval and informed consent were not required.

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Figures

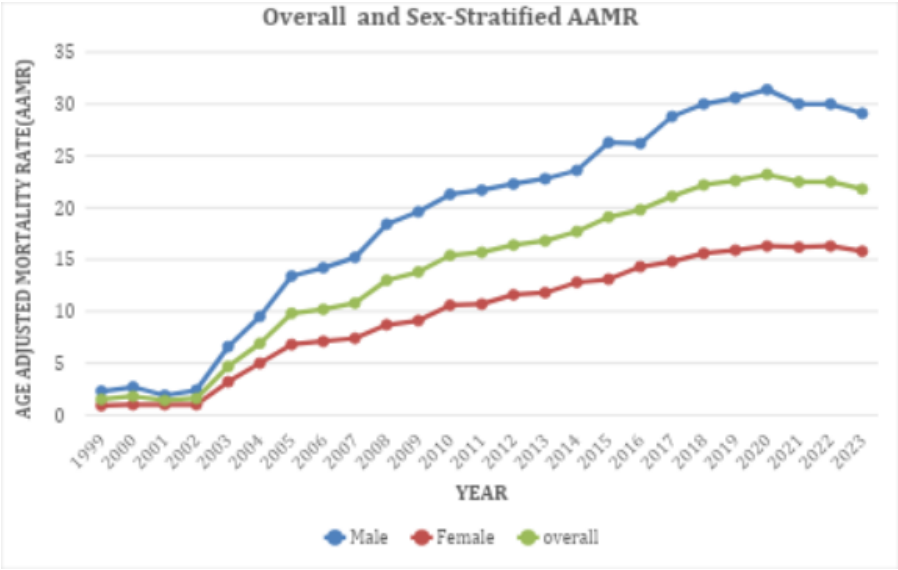


Figure 1

Trends in age-adjusted mortality rates due to Alcohol- and Smoking- Related Pancreatic Cancer stratified by sex in the United States, 1999-2023

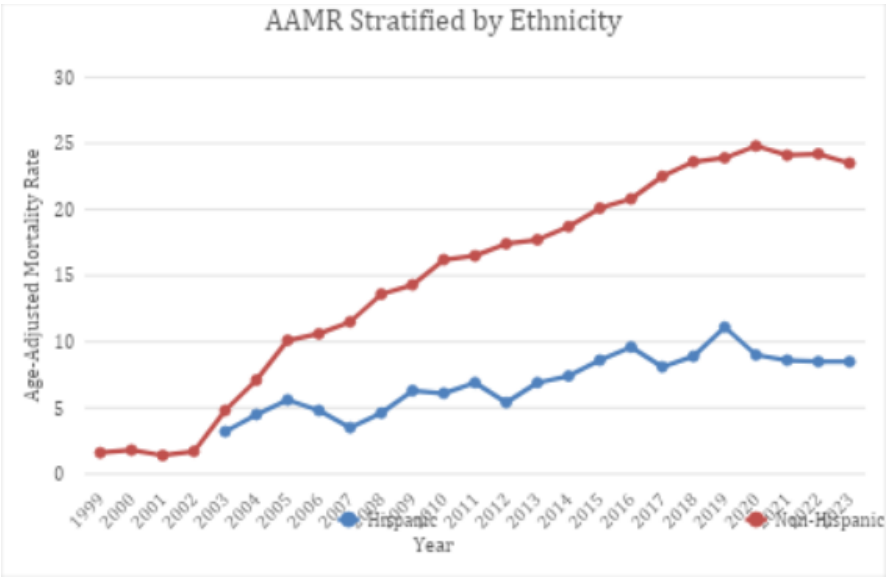


Figure 2

Trends in age-adjusted mortality rates due to Alcohol- and Smoking- Related Pancreatic Cancer stratified by ethnicity in the United States, 1999-2023

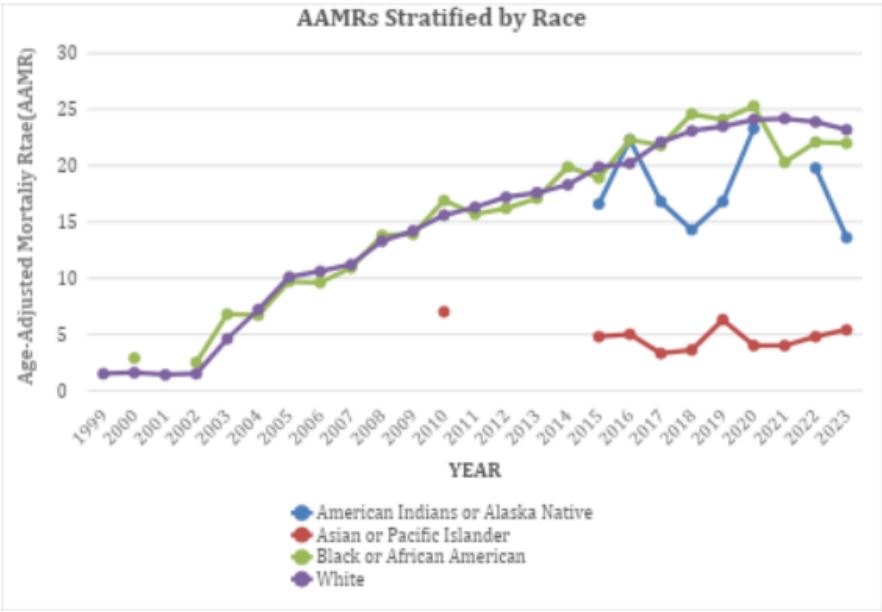


Figure 3

Trends in age-adjusted mortality rates due to Alcohol- and Smoking- Related Pancreatic Cancer stratified by race in the United States, 1999-2023

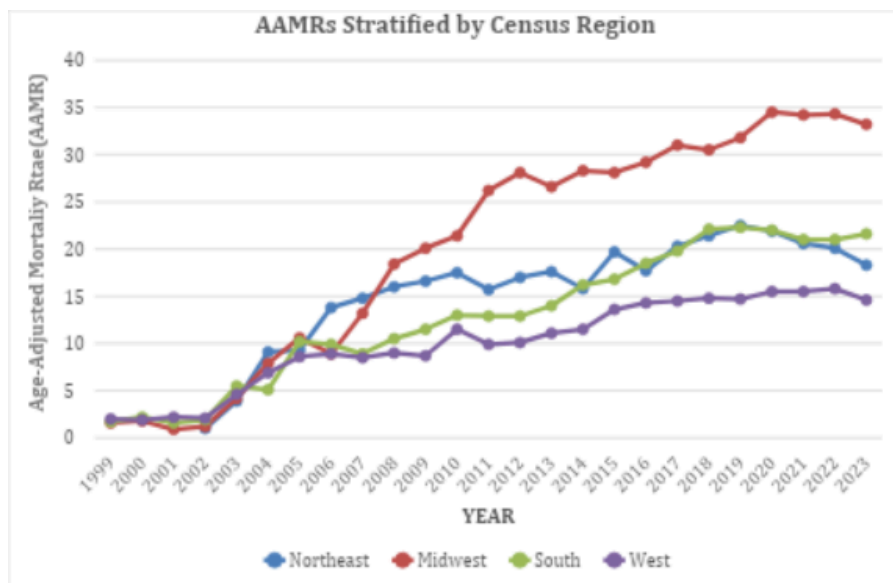


Figure 4

Trends in age-adjusted mortality rates due to Alcohol- and Smoking- Related Pancreatic Cancer stratified by census region in the United States, 1999-2023

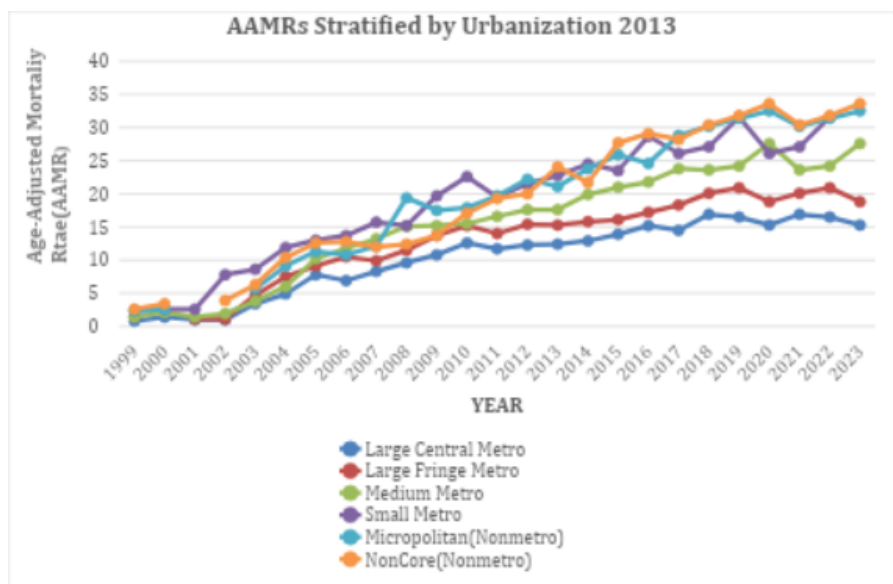


Figure 5

Trends in age-adjusted mortality rates due to Alcohol- and Smoking- Related Pancreatic Cancer stratified by urbanization in the United States, 1999-2023

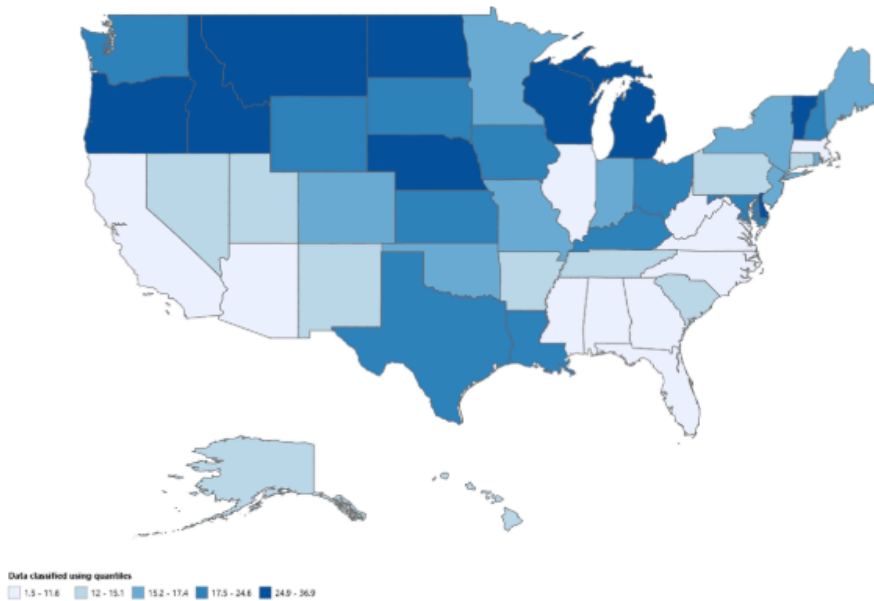


Figure 6

Trends in age-adjusted mortality rates due to Alcohol- and Smoking- Related Pancreatic Cancer stratified by states in the United States, 1999-2023

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