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Trends in Cancer and Pulmonary Embolism-related mortality in the adult U.S. population: A CDC WONDER database analysis from 1999 to 2020

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ABSTRACT

Introduction. Cancer and pulmonary embolism (PE) remain significant global health challenges, with approximately 20 million new cancer cases diagnosed worldwide, resulting in 9.7 million deaths. We aimed to assess trends in PE-associated mortality among U.S. cancer patients (1999–2020).

Material and methods. CDC WONDER death certificate data identified 179,044 PE-associated deaths in cancer patients (age ≥25). Age-adjusted mortality rates (AAMRs) per 100,000 were obtained, stratified by year, sex, race/ethnicity, region, and cancer type, with 95% confidence intervals. Joinpoint regression identified trends.

Results. A total of 179,044 PE-associated deaths in U.S. adults with cancer were recorded from 1999 to 2020, with AAMRs rising during this period. Overall, men had higher AAMRs than women (4.2, 95% CI: 4.0–4.3 vs 3.4, 95% CI: 3.3–3.5). AAMRs were highest among NH Black/African Americans (5.7, 95% CI: 5.7–5.8); the largest absolute number of deaths occurred in Whites, and the fewest in American Indians/Alaska Natives. Most deaths (64%) occurred in medical facilities. Among cancer types, lung cancer showed the highest mortality (AAMR 1.0, 95% CI: 0.97–1.05), whereas prostate cancer had the lowest (AAMR 0.20, 95% CI: 0.20–0.21).

Conclusions. PE-associated mortality in cancer patients rose from 1999 to 2020, disproportionately affecting men, NH Black/African Americans, Midwest residents, and lung cancer patients.

Introduction

Cancer and pulmonary embolism (PE) remain among the major public health problems worldwide. According to the Global Cancer Statistics (GLOBOCAN) 2022 estimates, approximately 20 million new cases were diagnosed with cancer, and 9.7 million died because of it [1]. The latest AHA report showed that about 400,000 patients were hospitalised solely for PE in the U.S. in 2020. [2]. In 2024, it is estimated that the number of deaths due to cancer in the U.S. will be over 600,000, of which around 125,070 will be attributed to lung cancer [2]. Furthermore, a recent analysis of the World Health Organisation mortality database revealed a total of 18,726,382 deaths that were due to venous thromboembolism (VTE), of which 86,930 (0.46%) were presumed secondary to PE [3]. However, the current data on these two diseases are still incomplete; therefore, there is a need for more extensive investigations to better understand their burden at both national and international levels.

In the last few decades, multiple radical changes have been noted in the diagnosis and management of cancer patients. The early detection of neoplastic lesions has never been more possible with the implementation of existing cancer diagnostic techniques, such as positron emission tomography, X-ray computed tomography, and magnetic resonance spectroscopy, as well as molecular diagnostic methods [4], alongside the expansion of effective screening programs [5,6]. In contrast, advances in understanding cancer biology have also led to the continuous development of more sophisticated anti-neoplastic agents such as targeted drug therapies, immunotherapies, and personalised medicines [7]. Subsequently, the cases of cancer have witnessed a remarkable increase, while the mortality has declined [8].

An improvement in PE treatment options has also been marked over the last few decades, with the widespread adoption of percutaneous revascularisation and the refinement of medical management [9]. Yet, the number of hospitalised patients with PE continues to rise, with indications of lower mortality and better survival [10,11]. In this context, evaluating epidemiological trends in cancer and PE populations is essential, especially when data are available in robust databases. In this study, we used the CDC WONDER registry to assess the mortality outcomes among the U.S. population diagnosed with cancer and PE from 1999 to 2020.

Methodology.

Study setting and population

We analysed data from the CDC WONDER database from January 1st, 1999, to December 31st, 2020, [12] using the death certificates from the Multiple Cause-of-Death Public Use records of participants with malignant neoplasms and pulmonary embolisms. These deaths were determined by identifying cases where both neoplasms or pulmonary embolisms were reported as contributing or underlying causes of death on the certificates. The specific codes used for identification are C00-C97 for malignant neoplasms and I26.0 and I26.9 for pulmonary embolisms, according to the International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10). Additionally, a sensitivity analysis was conducted for deaths due to pulmonary embolism and cancer, where malignant neoplasms (C00-C97) were listed as the underlying cause of death,

with pulmonary embolism as the contributing cause. Data for deaths due to cancer and Pulmonary embolisms were accumulated for ages 25 and above. Furthermore, we performed an analysis stratifying by age into three categories: young adults (25–44 years), middle-aged (45–64 years), and older adults (≥ 65 years) **(see Table 1)**. This study was exempt from local institutional review board approval because it used a deidentified government-issued public-use dataset.

Data abstraction

Data regarding deaths in people with pulmonary embolism and cancer, population sizes, years, demographics, and regions were abstracted. Race was reported on death certificates according to standards from the U.S. Office of Management and Budget. Different races were classified as non-Hispanic (NH) White, NH Black or African American, Hispanic or Latino, NH American Indian or Alaskan Native, and NH Asian[12]. Regions were classified into Northeast, Midwest, South, and West according to the U.S. Census Bureau definition [13].

Statistical analysis

Crude and age-adjusted mortality rates (AAMRs) per 100,000 population were obtained from CDC WONDER and stratified by year, sex, race, state, region, and cancer type, with 95% confidence intervals. AAMRs were standardised to the 2000 U.S. standard population [14]. Trends were analysed using the Joinpoint Regression Program (version 4.9.0.0, National Cancer Institute) [15], permitting a maximum of three joinpoints per model. Final models were selected using Bayesian Information Criterion (BIC) and permutation testing (10,000 permutations, α=0.05). For the overall analysis, males and females, one significant joinpoint was identified at 2016 (segments: 1999–2016; 2016–2020). Race-stratified models identified 1–3 joinpoints per group (e.g., Whites: 2016; Blacks: 2012, 2015). Cancer type models showed varying joinpoints (e.g., lung: 2004;

Table 1. Frequency and age-adjusted mortality rates per 100,000 in people with pulmonary embolism and cancer concomitantly.

Demographics	Deaths	Population	Overall age-adjusted mortality rate per 100,000 (95% CI)
Entire cohort	179,044	4,473,854,489	3.7 (3.7–3.8)
Sex			
Male	89,013	2,154,556,911	4.2 (4.2–4.2)
Female	90,031	2,319,297,578	3.4 (3.4–3.4)
Race			
Asian or Pacific Islander	3,195	237,142,712	1.6 (1.6–1.7)
Black or African American	26425	518937524	5.7 (5.7–5.8)
White	139328	3095342890	3.7 (3.7- 3.8)
American Indian or Alaska Native	779	33081153	2.8 (2.6- 3.0)
Hispanic or Latino	8951	589350210	2.2 (2.2–2.3)
Census Region			
Northeast	34,845	827,193,779	3.8 (3.7–3.8)
Midwest	42,858	969,567,311	4 (4.0–4.0)
South	62,315	1,652,256,217	3.5 (3.5–3.5)
West	39,026	1,024,837,182	3.7 (3.7–3.8)
Location of death			
Medical Facility	111,780	*	*
Hospice Facility	9,256	*	*
Nursing home / long term care	15,262	*	*
Home	37,288	*	*
Age groups			
Young Adults (25-44 years)	6,235	1,851,376,757	0.4 (0.4–0.4)
Middle age (45-64 years)	54,622	1,694,001,067	3.1 (3.0–3.1)
Older age (65+ years)	118,187	928,476,665	12.9(12.8–13.0)

CI – confidence interval. * The relevant data was not available on the CDC WONDER website.

gastrointestinal: 2016; prostate, haematological, and breast cancers: 2018). Annual per cent changes (APCs) were calculated for each segment and considered significant if slopes differed from zero (two-tailed t-test, $p \leq 0.05$).

Results

A total of 179,044 deaths in U.S. adults occurred from pulmonary embolism in cancer patients from 1999 to 2020. Overall, men had higher AAMRs than women (AAMR = 4.2, 95% CI: 4.0, 4.3 versus 3.4, 95% CI: 3.3, 3.5, respectively). When stratified by race, AAMRs were highest among Black or African America (AAMR = 5.7, 95% CI: 5.7, 5.8), followed by Whites (AAMR = 3.7, 95% CI: 3.7, 3.8), American Indian or Alaska Native (AAMR = 2.8, 95% CI: 2.6, 3.0), Hispanics or Latinos (AAMR = 2.2, 95% CI: 2.2, 2.3), and lastly Asian or Pacific Islander (AAMR = 1.6, 95% CI: 1.6, 1.7). Notably, the most significant number of deaths was recorded in Whites, and the lowest number of fatalities occurred in American Indians or Alaska Natives. Data on the location of death were available for 173,586 (96.95%) of these patients. Of these, 64.39% occurred within medical facilities, 21.48% at home, 8.79% in nursing homes/long-term care facilities, and 5.33% in hospice facilities (see **Table 1**).

Annual trends for pulmonary embolism and cancer-related AAMR

The overall AAMR increased from 1999 to 2020. A slight significant rise was observed from 1999 until 2016 (APC = 0.74, 95% CI: 0.49, 0.99; **Figures 1, 2**), after which a more remarkable rise until 2020 was observed (APC = 5.1, 95% CI: 2.75, 7.51; **Figures 1, 2**).

Pulmonary embolism and cancer-related AAMR stratified by sex

In 1999, the AAMR for men was 2.5 (95% CI: 2.4, 2.6; **Figure 2**), which was followed by a steady increase in AAMR to 2.7(95% CI: 2.6 – 2.8; **Figure 2**) in 2016 (APC: 0.25, 95% CI: -0.21, 0.56; **Figure 3**). A noticeable increase in AAMR was observed from 2016 to 2020 (AAMR = 3.3, 95% CI: 3.2, 3.4; APC = 4.88, 95% CI: 2.49, 10.04; **Figure 2**, **Figure 3**).

The AAMR for women was 1.9 (95% CI: 1.8, 1.9; **Figure 2**), which significantly increased to 2.3 (95% CI: 2.2, 2.3; **Figure 2**) in 2016 (APC: 1.10, 95% CI: 0.63, 1.41; **Figure 3**). Similarly, a more significant AAMR increase was observed from 2016 to 2020 (AAMR = 2.9, 95% CI: 2.8, 2.9; APC = 5.27, 95% CI: 2.49, 10.04; **Figures 2, 3**).

Pulmonary embolism and cancer-related AAMR stratified by race

AAMRs rose steadily for American Indian/Alaska Natives (APC = 2.19, 95% CI: 0.81–3.59) and

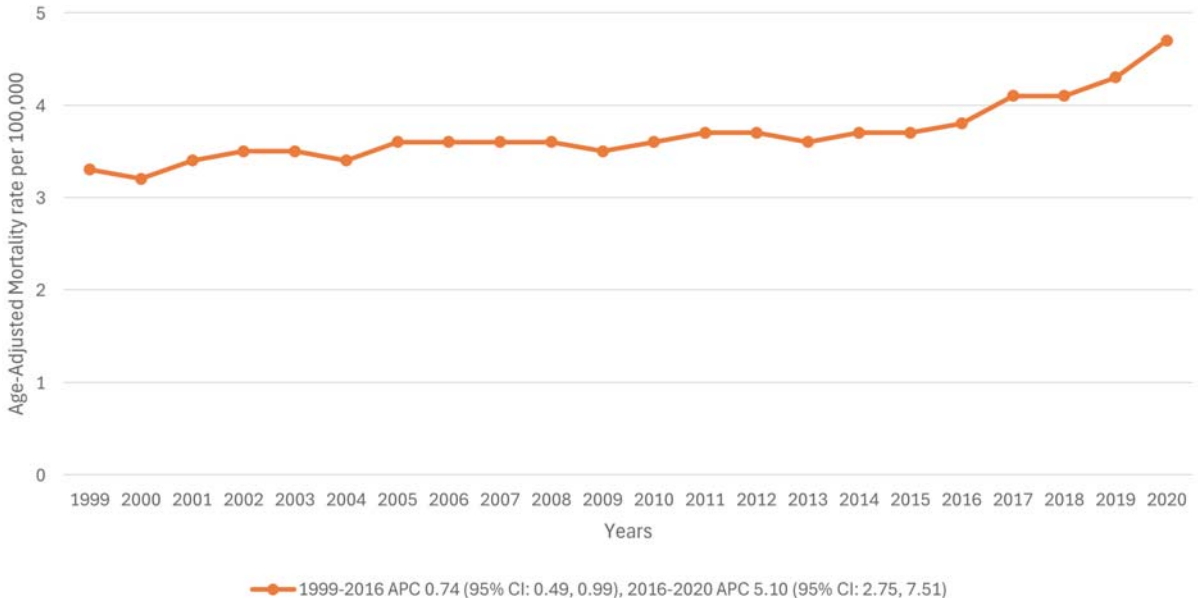

Figure 1. AAMRs per 100,000 adults with cancer-pulmonary embolism from 1999 to 2020.

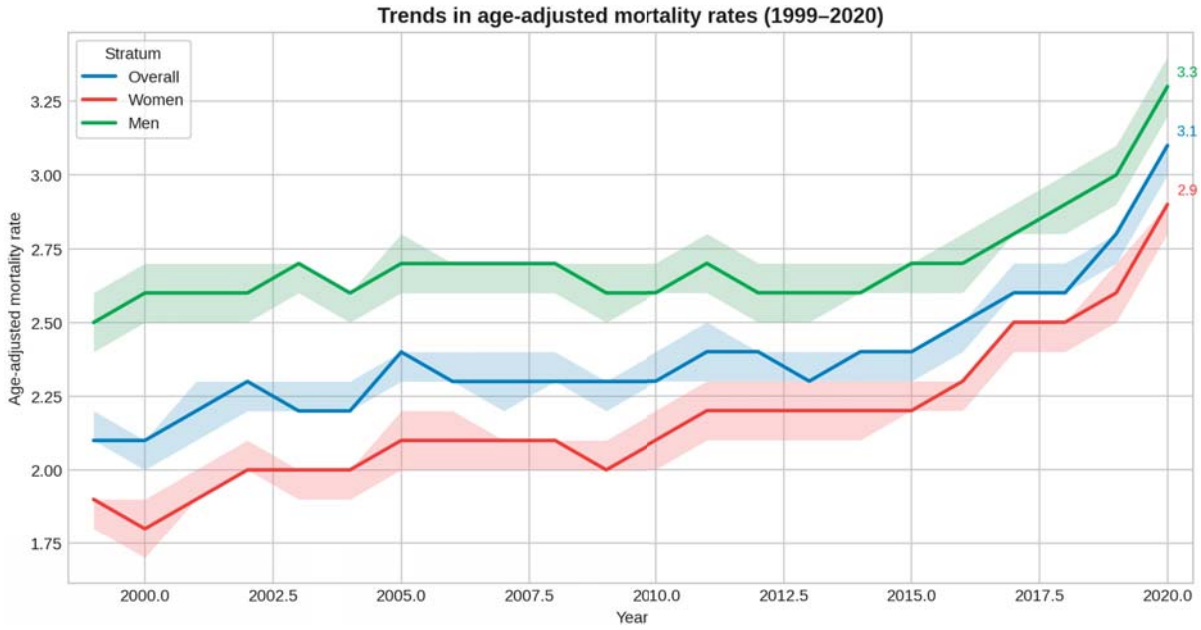

Figure 2. Trends in overall and sex-stratified age-adjusted mortality rates from 1999 to 2020.

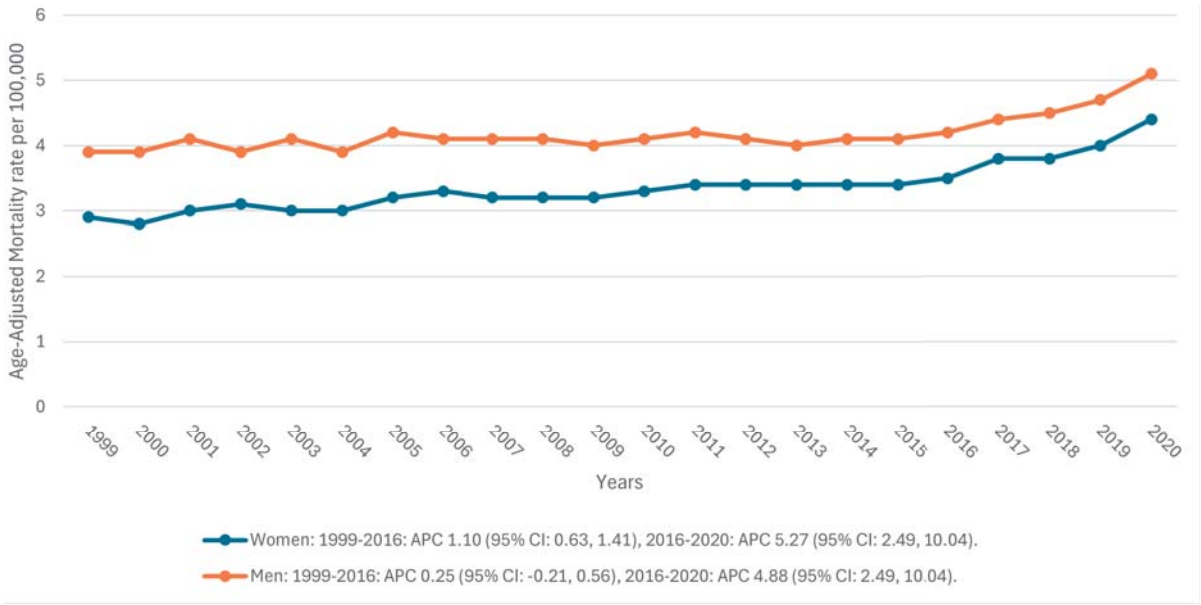

Figure 3. Sex-stratified cancer and pulmonary embolism-related AAMRs per 100,000 in adults from 1999 to 2020.

Hispanics or Latinos (APC = 1.58, 95% CI: 1.08–2.08) from 1999 to 2020. Among Asian or Pacific Islanders, AAMR increased from 1.1 in 1999 to 1.8 in 2011 (APC = 4.02, 95% CI: 2.25–5.82), then declined slightly until 2015 (APC = -5.34, 95% CI: -18.15–9.47), followed by a sharp rise through 2020 (APC = 7.77, 95% CI: 0.98–15.01). In Black or African Americans, AAMR climbed from 5.3 in 1999 to 5.8 in 2012 (APC = 0.66, 95% CI: 0.22–1.10), dipped until 2015 (APC = -2.76, 95% CI: -10.54–5.68), then increased sharply through 2020 (APC = 5.89, 95% CI: 3.93–7.88). Whites rose from 3.2 in 1999 to 3.9 in 2016 (APC = 0.91, 95% CI: 0.67–1.14), followed by a more pronounced increase to 4.8 by 2020 (APC = 5.34, 95% CI: 3.13–7.61). Full results are shown in **Table 2** and **Figure 4.**

Table 2. Cancer and pulmonary embolism–related age-adjusted mortality rates per 100,000 stratified by race in adults in the United States from 1999 to 2020. Abbreviations: NH, Non-Hispanic; AAMR, age-adjusted mortality rates; CI, confidence interval.

Year	Age Adjusted mortality rates (95% CI)				
	NH White (AAMR, 95% CI)	NH Blacks/African American (AAMR, 95% CI)	NH Asian/Pacific Islander (AAMR, 95% CI)	NH American Indian/ Alaska Native (AAMR, 95% CI)	Hispanic or Latino (AAMR, 95% CI)
1999	3.2 (3.2–3.3)	5.3 (5–5.7)	1.1 (0.8–1.4)	2.4 (1.4–3.8)	1.3 (1.1–1.5)
2000	3.2 (3.1–3.3)	5.2 (4.9–5.6)	1.3 (1–1.7)	Unreliable (1–3)	1.1 (0.9–1.3)
2001	3.4 (3.3–3.5)	5.3 (5–5.7)	1.2 (0.9–1.5)	2.4 (1.4–3.6)	1.3 (1.1–1.5)
2002	3.4 (3.4–3.5)	5.4 (5–5.7)	1 (0.7–1.3)	Unreliable (1–3)	1.5 (1.3–1.7)
2003	3.5 (3.4–3.6)	5.4 (5.1–5.8)	1.2 (0.9–1.5)	Unreliable (0.9–2.7)	1.2 (1.0–1.4)
2004	3.4 (3.3–3.5)	5.7 (5.3–6)	1.5 (1.2–1.8)	2.2 (1.4–3.4)	1.3 (1.1–1.4)
2005	3.6 (3.5–3.7)	5.8 (5.5–6.2)	1.6 (1.3–1.9)	2 (1.2–3.2)	1.3 (1.1–1.4)
2006	3.6 (3.5–3.7)	5.5 (5.2–5.9)	1.5 (1.2–1.8)	2.4 (1.5–3.7)	1.3 (1.1–1.4)
2007	3.6 (3.5–3.7)	5.5 (5.1–5.8)	1.6 (1.3–1.9)	2 (1.2–3.1)	1.2 (1.0–1.3)
2008	3.6 (3.5–3.7)	5.4 (5.1–5.8)	1.5 (1.2–1.8)	3.5 (2.4–4.8)	1.3 (1.2–1.5)
2009	3.5 (3.4–3.6)	5.7 (5.3–6)	1.5 (1.3–1.8)	3.2 (2.2–4.6)	1.3 (1.1–1.4)
2010	3.6 (3.5–3.7)	5.8 (5.4–6.1)	1.7 (1.4–2)	3 (2.1–4.2)	1.3 (1.2–1.5)
2011	3.7 (3.6–3.8)	5.6 (5.3–5.9)	1.8 (1.5–2)	2.9 (2–4.1)	1.4 (1.3–1.6)
2012	3.6 (3.5–3.7)	5.8 (5.5–6.2)	1.8 (1.6–2.1)	3.2 (2.2–4.3)	1.4 (1.3–1.6)
2013	3.7 (3.6–3.8)	5.6 (5.2–5.9)	1.5 (1.3–1.7)	2.4 (1.6–3.4)	1.5 (1.3–1.6)
2014	3.7 (3.6–3.8)	5.4 (5.1–5.7)	1.6 (1.4–1.8)	2.6 (1.8–3.6)	1.4 (1.3–1.5)
2015	3.8 (3.7–3.9)	5.4 (5.1–5.7)	1.4 (1.2–1.7)	2.9 (2.1–3.9)	1.5 (1.3–1.6)
2016	3.9 (3.8–3.9)	5.6 (5.3–5.9)	1.6 (1.4–1.8)	2.5 (1.8–3.5)	1.5 (1.4–1.7)
2017	4.1 (4.0–4.2)	6 (5.7–6.3)	1.6 (1.4–1.8)	3.9 (2.9–5)	1.6 (1.5–1.7)
2018	4.2 (4.1–4.3)	6.1 (5.8–6.4)	1.7 (1.5–2)	2.8 (2–3.7)	1.6 (1.5–1.7)
2019	4.4 (4.3–4.4)	6.5 (6.2–6.8)	2 (1.7–2.2)	3.9 (3–4.9)	1.7 (1.6–1.8)
2020	4.8 (4.7–4.9)	7.3 (7–7.6)	2.1 (1.9–2.4)	3.7 (2.9–4.8)	1.9 (1.8–2.0)

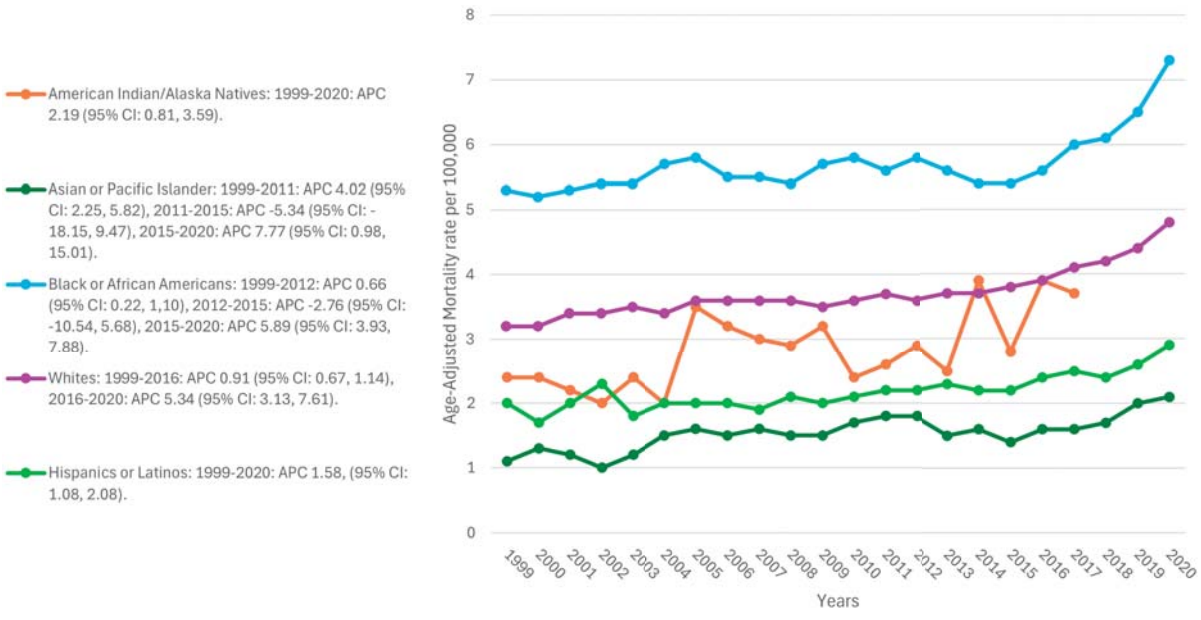

Figure 4. AAMR per 100,000 in cancer and pulmonary embolism adults from 1999 to 2020 stratified by race.

Pulmonary embolism and cancer-related AAMR stratified by geographic regions

Differences in AAMRs ranged from 2.6 (95% CI: 2.4–2.8) in Hawaii to 6.8 (95% CI: 6.2–7.3) in the District of Columbia (see **Supplementary Table 1)**. States in the 90th percentile of mortality included Vermont, Nebraska, Colorado, Maryland, New Hampshire, Washington, Rhode Island, Minnesota, and Ohio. In contrast, Arizona, Nevada, New Mexico, Utah, New York, Arkansas, Louisiana, Georgia, Florida, and Alabama fell in the lower 10th percentile. Regionally, the Midwest showed the highest mortality (AAMR: 4.0, 95% CI: 4.0–4.0), followed by the Northeast (3.8), West (3.7), and South (3.5) **(see Table 1, Figure 5)**. Race--region analysis indicated that NH Blacks/African Americans and NH Whites consistently had the highest AAMRs (see **Supplementary Table 2, Supplementary Figure 1)**.

AAMRs stratified by pulmonary embolism and types of cancer

Among different types of cancer, the highest mortality rates were observed with lung cancer (AAMR = 1, 95% CI: 0.97, 1.05), followed closely by gastrointestinal cancer (AAMR = 0.88, 95% CI: 0.85, 0.93). The AAMRs for breast and haematological cancers were almost similar (AAMR = 0.31, 95% CI: 0.3, 0.33; AAMR = 0.3, 95% CI: 0.27, 0.31, respectively). The lowest AAMRs were observed with prostate cancer (AAMR = 0.20, 95% CI: 0.20, 0.21; **Supplementary Table 3**; **Supplementary Figure 2**).

We observed that the AAMRs for lung cancer significantly increased from 1999 to 2004 (APC = 4.36, 95% CI: 1.19, 7.63), after which a lower rise was observed till 2020 (APC = 0.78, 95% CI: 0.25, 1.31). Regarding the AAMRs for gastrointestinal cancers, non-significant changes were observed from 1999 to 2020 (APC = 0.43, 95% CI: -0.16, 1.03), after which a significant rise was seen till 2020 (APC = 6.40, 95% CI: 2.78, 10.14). In contrast, the AAMRs for prostate, breast, and haematological cancers remained constant from 1999 to 2020, after which a slight rise was observed (see **Supplementary Figure 2**).

Primary cause of death in patients with pulmonary embolism and cancer

We assessed the top 15 primary causes of death in patients with pulmonary embolism and cancer. We observed that malignant neoplasms were the

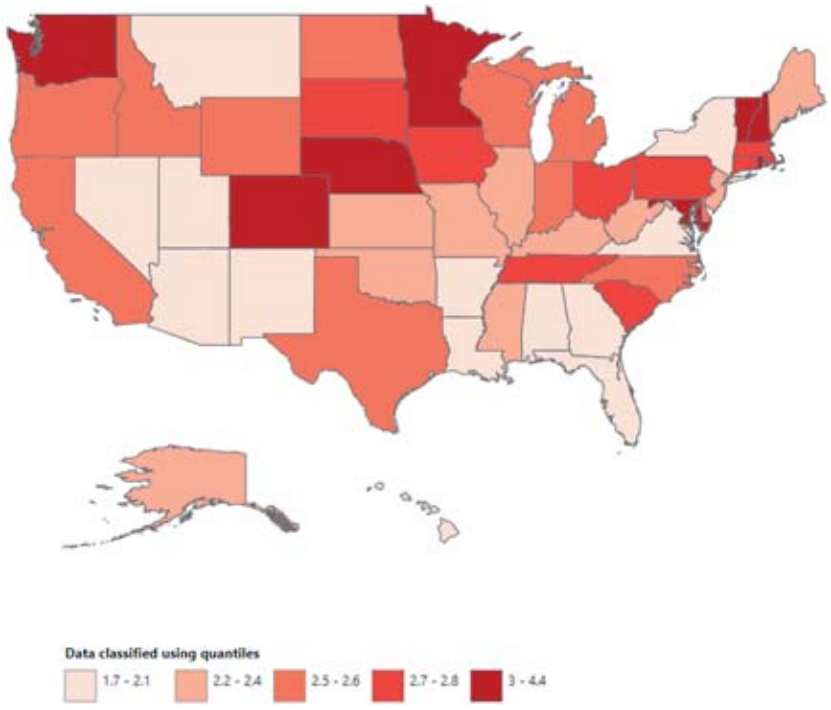

Figure 5. Cancer- pulmonary embolism-related mortality in adults in the U.S. stratified by states, 1999–2020.

primary leading cause of death in patients with pulmonary embolism and cancer (AAMR = 3.3, 95% CI: 3.3, 3.3), followed by diseases of the heart (AAMR = 0.2, 95% CI: 0.2, 0.2) (see **Supplementary Table 4**).

Sensitivity analysis

Sensitivity analysis yielded 6–32% lower AAMRs across groups, with the largest reduction among American Indians/Alaska Natives (-32.1%), but identical rank order preservation in all demographics, racial, and geographic comparisons (NH Black > Male > Midwest > NH White; see **Supplementary Table 5**). All observed disparities remained robust to this more restrictive case definition.

Discussion

We found that overall mortality rates increased over time, with the highest AAMRs observed among men and NH Black/African American populations and the lowest among women, NH Asian/Pacific Islanders, and Hispanics/Latinos. Geographically, the Midwest exhibited the highest rates. Lung cancer was associated with the highest mortality across cancer types.

The overall mortality rate of cancer patients with PE steadily increased from 1999 to 2020, rising gradually until 2016 and more sharply thereafter. These findings align with a retrospective cohort study by Janus et al. [16], which showed a 43% increase in PE-related AAMR among 13,917,133 deceased cancer patients between 1999 and 2000, despite a concurrent decline in overall cardiovascular AAMR. A Canadian retrospective cohort study similarly demonstrated worse short- and long-term survival among cancer patients with PE, and a Norwegian study reported a 13-fold higher mortality hazard ratio compared to the general population [17,18]. The growing mortality rate may reflect the increased longevity of cancer patients, adverse effects of anti-cancer therapies, improved PE detection (including incidental findings), and underlying pathophysiology consistent with Virchow's triad (hypercoagulability, blood flow stasis, and endothelial damage), which is often present in cancer patients. Previous studies have shown that surgery, systemic chemotherapy, targeted agents, immunotherapy, and supportive treatments all contribute to an increased risk of venous and arterial thromboembolism in cancer populations, supporting our interpretation that anti-cancer therapies may partially underlie the observed mortality patterns in this cohort [19–22].

Cancer can cause an imbalance in the coagulation system by producing and secreting various pro-inflammatory cytokines and pro-coagulation factors that activate both the intrinsic and extrinsic coagulation pathways, leading to a hypercoagulable state [23]. Additionally, cancer can cause endothelial damage by directly invading nearby blood vessels, whereas cancer-related fatigue and disabilities can result in prolonged immobilisation, leading to stasis in the cardiovascular circulation [23,24]. In the past few decades, significant advances in cancer treatment have led to improved survival rates and extended life expectancy for cancer patients, even those with advanced disease and distant metastasis [4,5,7]. However, despite the incredible merits of current anti-cancer therapies, we can hypothesise that they might also increase the risk of cancer patients acquiring a thromboembolism disorder. The literature demonstrates that different anticancer regimens, including chemotherapy, immunotherapy, targeted therapy, and surgery, are associated with impairment of coagulation pathways, increased platelet activation, and endothelial injury, thereby promoting the formation of blood clots [19,25]. In addition, improved survival rates in cancer patients treated with anticancer therapeutics have led to increased longevity [26]. This extended life expectancy paradoxically increases the cumulative risk of acquiring PE in these patients, as the longer they live, the more they are exposed to PE-associated risk factors present in the cancer pathophysiology and anti-cancer regimen side effects.

The diagnosis of PE remains challenging, but advances in imaging techniques have substantially improved detection rates over the past two decades, including a marked increase in incidental PE discovered during contrast-enhanced CT for oncologic staging [27–29]. While our data show rising PE-related mortality in cancer patients across demographic and cancer-type strata, improved detection is one potential contributor to this trend alongside evolving treatment

practices and cancer survivorship. However, our ecological design precludes causal attribution [30]. Incidental PE in cancer patients correlates with advanced disease and poor prognosis, but studies indicate that mortality is primarily driven by progressive malignancy and cancer treatments rather than PE itself [31–33].

Our analysis reported that the overall AAMR mortality rate in men was significantly higher than in women. This result is consistent with other findings in the literature. This could be explained by differences in biological and hormonal composition between men and women, as well as the higher prevalence of comorbidities, which are considered risk factors for PE in men compared to women [34,35].

We also reported significant differences in the AAMR across races. Our findings showed that Black or African Americans had the highest mortality rate compared to other races. In contrast, NH Asian or Pacific Islanders and Hispanics or Latinos had the lowest mortality rate. Racial differences in PE-associated mortality have been established in the literature [16,34,36]. Higher rates among African Americans compared to Whites may reflect a combination of socioeconomic status, structural racism, genetic predisposition (e.g., thrombomodulin/*THBD* variants rs2144940, rs2567617, rs1998081, more prevalent in African ancestry, explaining about 7% of excess VTE risk via lower thrombomodulin expression [37]), and higher prevalence of comorbidities (e.g., diabetes, obesity, hypertension, CKD, all VTE risk amplifiers [36,38].

Additionally, our findings align with other studies showing lower mortality in Hispanics or Latinos than in Whites, suggesting a possible biological component [34]. We also observed fluctuating trends in the American Indian or Alaska Native subgroup from 1999 to 2020, likely due to a smaller sample size and variations in healthcare access, socioeconomic factors, and biological risks. Geographically, the Midwest had the highest mortality rate, while the South had the lowest. Across regions, Black or African Americans and NH Whites had the highest mortality rates. These differences may be driven by variations in cancer screening practices, insurance coverage, health education, guidelines implementation, and access to specialised oncology centres [39,40].

Regarding cancer types, lung cancer had the highest mortality rate, whereas prostate cancer had the lowest – consistent with evidence that PE is implicated in about 10% of lung cancer deaths [41,42]. Lung cancer is also more prevalent among men, which may help explain our finding of higher mortality in men [43]. Our age-stratified mortality analysis showed that adults aged 65+ years, despite being the smallest subgroup, had the highest number of deaths, while those aged 25–44 years, the largest subgroup, had the fewest. These findings align with previous studies linking advanced age with higher mortality in VTE or cancer, potentially due to increased comorbidities and age-related physiological changes exacerbating these conditions [44,45].

Limitations.

Our analysis of 179,044 PE-associated deaths in cancer patients fills an important literature gap but has limitations. Reliance on death certificate data (CDC WONDER) may introduce misclassification bias in cause-of-death coding. The database lacks patient-level data (socioeconomic status, cancer stage, treatment regimens, comorbidities, PE characteristics), precluding refined risk-factor analysis. Changes in diagnostic/reporting practices over two decades (e.g., increased CT use) may have influenced observed mortality trends. Sensitivity analysis confirmed the robustness of disparities despite AAMRs being 6–32% lower, though it cannot fully exclude the possibility of coding changes. Finally, as a descriptive study of aggregated data, we could not perform formal between-group APC comparisons or multivariable adjustment; Joinpoint pairwise testing and Poisson regression using 2021–2026 data with restricted-access vital statistics should be considered in future studies.

Conclusions

From 1999 to 2020, PE-associated mortality in cancer patients increased, with the highest rates among men, NH Black/African Americans, the Midwest region, and lung cancer patients. These disparities highlight the need for targeted VTE prevention strategies in high-risk cancer populations.

Statements and declarations

Author contributions
O.A. and A.N.: conceptualisation and methodology. O.A. and B.A.: investigation and data curation. A.N., B.A. and M.A.: formal analysis. A.N., B.A., A.G., Y.K.: Writing – Original Draft. O.A. and M.T.: Supervision. O.A., M.T. and M.A.: Project administration. O.A., M.A., H.A.: Writing – Review & Editing. All authors read and approved the final content.

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The data is available at reasonable request from the corresponding author.

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Supplementary materials

Supplementary Table 1. Cancer pulmonary embolism–related age-adjusted mortality rates per 100,000, stratified by states in adults in the United States from 1999 to 2020.

State	Age-Adjusted Mortality Rate (95%CI)	State	Age-Adjusted Mortality Rate (95%CI)
Alabama	3 (2.9–3.1)	Montana	3.3 (3–3.6)
Alaska	3.7 (3.2–4.1)	Nebraska	5.3 (5.1–5.6)
Arizona	2.7 (2.6–2.8)	Nevada	2.8 (2.6–2.9)
Arkansas	3.2 (3–3.3)	New Hampshire	4.8 (4.5–5.1)
California	3.8 (3.7–3.8)	New Jersey	3.4 (3.3–3.5)
Colorado	4.9 (4.7–5.1)	New Mexico	2.8 (2.6–3)
Connecticut	4.3 (4.1–4.4)	New York	3.2 (3.1–3.2)
Delaware	4.1 (3.7–4.4)	North Carolina	4 (3.9–4.1)
District of Columbia	6.8 (6.2–7.3)	North Dakota	4 (3.6–4.4)
Florida	2.7 (2.6–2.7)	Ohio	4.4 (4.3–4.5)
Georgia	3 (2.9–3.1)	Oklahoma	3.4 (3.2–3.5)
Hawaii	2.6 (2.4–2.8)	Oregon	4.1 (3.9–4.2)
Idaho	3.9 (3.6–4.2)	Pennsylvania	4.2 (4.1–4.3)
Illinois	3.7 (3.6–3.7)	Rhode Island	4.8 (4.5–5.2)
Indiana	4 (3.8–4.1)	South Carolina	4.3 (4.1–4.4)
Iowa	4.1 (4–4.3)	South Dakota	4.2 (3.9–4.6)
Kansas	3.4 (3.2–3.5)	Tennessee	4.2 (4.1–4.3)
Kentucky	3.7 (3.6–3.9)	Texas	4 (3.9–4.1)
Louisiana	2.7 (2.5–2.8)	Utah	3.2 (3–3.4)
Maine	3.5 (3.2–3.7)	Vermont	5.7 (5.3–6.2)
Maryland	4.9 (4.8–5.1)	Virginia	3.3 (3.2–3.4)
Massachusetts	4.2 (4–4.3)	Washington	4.8 (4.7–4.9)
Michigan	3.8 (3.7–3.9)	West Virginia	3.7 (3.5–3.9)
Minnesota	4.7 (4.5–4.8)	Wisconsin	3.9 (3.8–4.1)
Mississippi	3.5 (3.3–3.6)	Wyoming	3.8 (3.4–4.2)
Missouri	3.5 (3.4–3.6)		

CI – confidence interval.

Supplementary Table 2. Age-adjusted death rate per 100,000 according to race in different regions of the United States.

Race	Northeast (AAMR, 95% CI)	Midwest (AAMR, 95% CI)	South (AAMR, 95% CI)	West (AAMR, 95% CI)
Asian or Pacific Islander	1.2 (1.1–1.3)	1.3 (1.1–1.4)	1.4 (1.2–1.5)	1.9 (1.8–2.0)
Black or African American	5.7 (5.5–5.8)	6.2 (6.0–6.4)	5.4 (5.3–5.5)	6.9 (6.6–7.2)
White	3.8 (3.7–3.8)	3.9 (3.9–4.0)	3.3 (3.3–3.4)	4.1 (4.1–4.2)
American Indian or Alaska Native	2.0 (1.4–2.8)	3.0 (2.5–3.6)	2.7 (2.4–3.1)	2.8 (2.5–3.2)
Hispanic	2.0 (1.8–2.1)	1.8 (1.7–2.0)	2.2 (2.2–2.3)	2.4 (2.3–2.5)

CI – confidence interval; AAMR – age-adjusted mortality rate.

Supplementary Table 3. Age-adjusted death rate per 100,000 population stratified by types of cancer in the United States.

Year	Lung cancer (AAMR, 95% CI)	Gastrointestinal cancer (AAMR, 95% CI)	Prostate cancer (AAMR, 95% CI)	Hematological cancer (AAMR, 95% CI)	Breast cancer (AAMR, 95% CI)
1999	0.8 (0.8–0.8)	0.8 (0.8–0.9)	0.2 (0.2–0.3)	0.3 (0.3–0.3)	0.3 (0.3–0.3)
2000	0.8 (0.8–0.9)	0.8 (0.7–0.8)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.3)
2001	0.9 (0.9–1.0)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.3)
2002	0.9 (0.9–1.0)	0.8 (0.8–0.8)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.4)
2003	0.9 (0.9–0.9)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.4)	0.3 (0.3–0.3)
2004	1.0 (0.9–1.0)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.2–0.3)	0.3 (0.3–0.3)
2005	1.0 (1.0–1.0)	0.9 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.4)
2006	1.0 (1.0–1.0)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.3)
2007	1.0 (1.0–1.0)	0.9 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.2–0.3)	0.3 (0.3–0.3)
2008	1.0 (1.0–1.1)	0.9 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.2–0.3)	0.3 (0.3–0.3)
2009	1.0 (1.0–1.1)	0.8 (0.8–0.8)	0.2 (0.2–0.2)	0.3 (0.2–0.3)	0.3 (0.2–0.3)
2010	1.1 (1.0–1.1)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.3)
2011	1.1 (1.0–1.1)	0.9 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.3)
2012	1.0 (1.0–1.1)	0.9 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.2–0.3)	0.3 (0.3–0.4)
2013	1.1 (1.0–1.1)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.3)
2014	1.0 (1.0–1.1)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.3)
2015	1.0 (1.0–1.1)	0.9 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.2–0.3)	0.3 (0.3–0.3)
2016	1.0 (1.0–1.1)	0.9 (0.9–1.0)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.3)
2017	1.1 (1.1–1.2)	1.0 (1.0–1.0)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.3)
2018	1.1 (1.0–1.1)	1.0 (1.0–1.1)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.4)
2019	1.1 (1.0–1.1)	1.1 (1.0–1.1)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.4 (0.3–0.4)
2020	1.2 (1.1–1.2)	1.2 (1.2–1.2)	0.3 (0.2–0.3)	0.4 (0.3–0.4)	0.4 (0.4–0.4)

CI – confidence interval; AAMR – age-adjusted mortality rate.

Supplementary Table 4. Top 15 leading causes of death for people with pulmonary embolism and cancer.

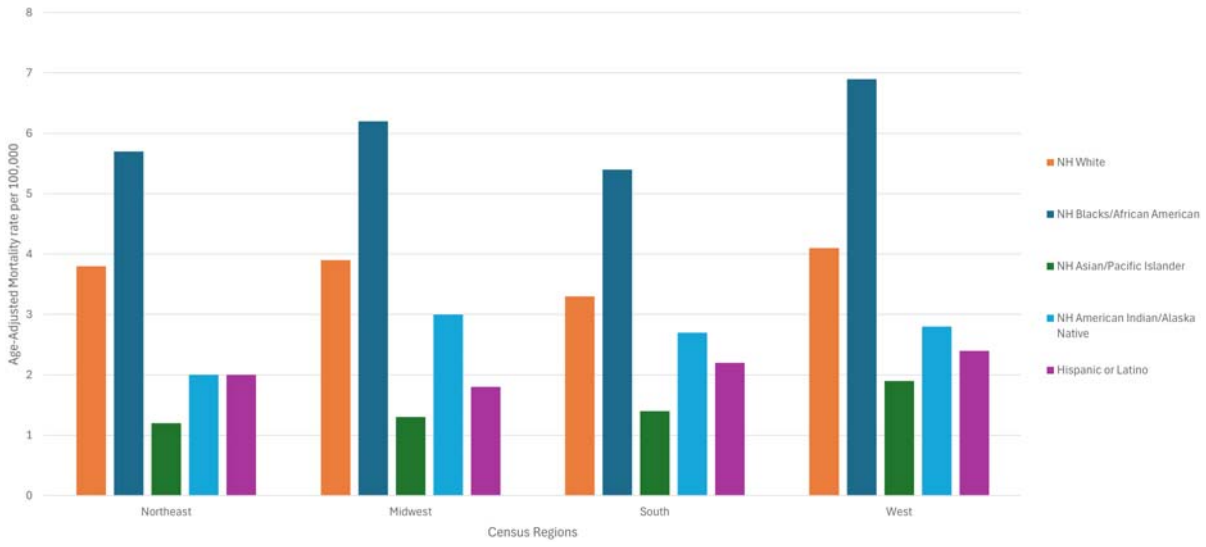
15 leading causes of death	Number of deaths (n)	Age adjusted mortality rate per 100,000 (95% CI)
Malignant neoplasms (C00-C97)	158180	3.3 (3.3–3.3)
Diseases of heart (I00-I09,I11,I13,I20-I51)	8251	0.2 (0.2–0.2)
Chronic lower respiratory diseases (J40-J47)	1902	0.0 (0.0–0.0)
Cerebrovascular diseases (I60-I69)	1201	0.0 (0.0–0.0)
Accidents (unintentional injuries) (V01-X59,Y85-Y86)	975	0.0 (0.0–0.0)
Septicemia (A40-A41)	598	0.0 (0.0–0.0)
Diabetes mellitus (E10-E14)	417	0.0 (0.0–0.0)
COVID-19 (U07.1)	341	0.0 (0.0–0.0)
Essential hypertension and hypertensive renal disease (I10,I12,I15)	274	0.0 (0.0–0.0)
In situ neoplasms, benign neoplasms and neoplasms of uncertain or unknown behavior (D00-D48)	253	0.0 (0.0–0.0)
Alzheimer disease (G30)	237	0.0 (0.0–0.0)
Pneumonitis due to solids and liquids (J69)	206	0.0 (0.0–0.0)
Nephritis, nephrotic syndrome and nephrosis (N00-N07,N17-N19,N25-N27)	155	0.0 (0.0–0.0)
Complications of medical and surgical care (Y40-Y84,Y88)	130	0.0 (0.0–0.0)
Influenza and pneumonia (J09-J18)	121	0.0 (0.0–0.0)

CI – confidence interval.

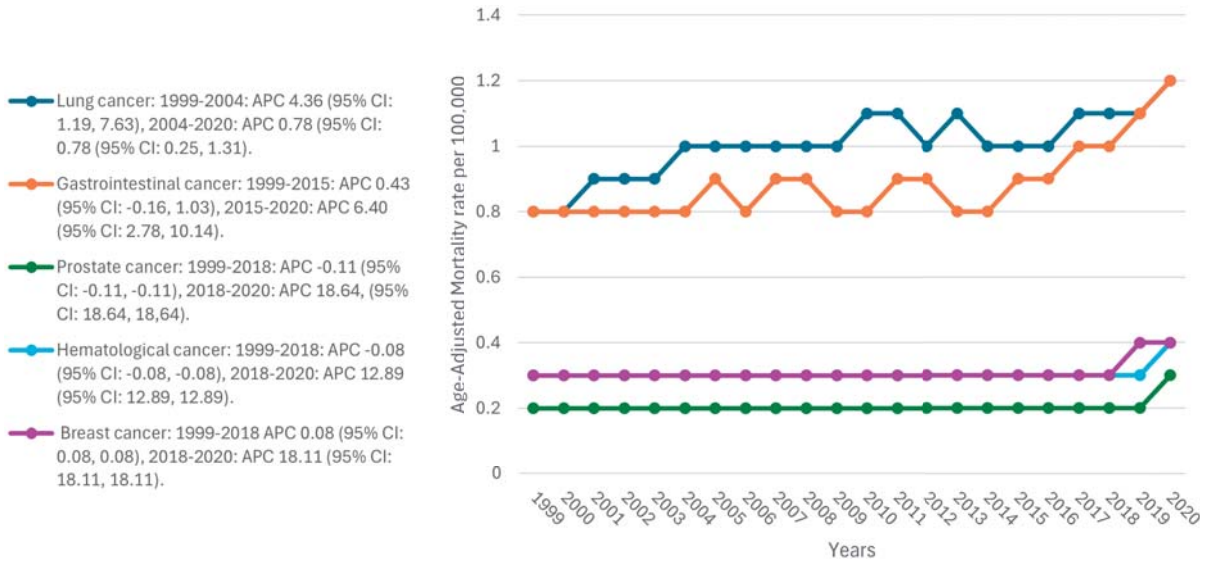
Supplementary Table 5. Sensitivity Analysis: Age-Adjusted Mortality Rates (AAMR) per 100,000 population (95% CI) by case definition.

	Primary Definition (Multiple cause: Cancer + PE)	Sensitivity Definition (Cancer underlying + PE contributing)	% Difference
Overall	3.7 (3.7–3.8)	3.3 (3.3–3.3)	10.8
Female	3.4 (3.4–3.4)	3.0 (3.0–3.0)	11.8
Male	4.2 (4.2–4.2)	3.6 (3.6–3.7)	14.3
Race			
Asian or Pacific Islander	1.6 (1.6–1.7)	1.5 (1.4–1.5)	6.3
Black or African American	5.7 (5.7–5.8)	5.0 (4.9–5.0)	12.3
White	3.7 (3.7- 3.8)	3.2 (3.2–3.2)	13.5
American Indian or Alaska Native	2.8 (2.6- 3.0)	1.9 (1.8–2.1)	32.1
Hispanic	2.2 (2.2–2.3)	2.0 (2.0–2.1)	9.1
Census Region			
Northeast	3.8 (3.7–3.8)	3.3 (3.3–3.4)	13.2
Midwest	4 (4.0–4.0)	3.5 (3.5–3.6)	12.5
South	3.5 (3.5–3.5)	3.1 (3.1–3.1)	11.4
West	3.7 (3.7–3.8)	3.3 (3.3–3.3)	10.8
Location of death*			
Medical Facility	111,780	97,378	12.9
Hospice Facility	9,256	8682	6.2
Nursing home / long-term care	15,262	12920	15.3
Home	37,288	34272	8.1
Other	5,458	4,942	9.5
Total death	179,044	158,194	11.6

* Numbers shown as count of death as Age-Adjusted Mortality Rate per 100,000 (95% CI) are not applicable. Abbreviations: PE – pulmonary embolism



Supplementary Figure 1. Race and Region-wise analysis of AAMR per 100,000 in Cancer-Pulmonary Embolism related Mortality in Adults from 1999-2020.



Supplementary Figure 2. AAMRs per 100,000 adult people with PE stratified by cancer subtypes.