

Rising trends in pancreatic cancer incidence and mortality in 2000–2014

Wenrui Wu^{1,2,*}
 Xingkang He^{3,4,*}
 Liya Yang^{1,2}
 Qing Wang^{1,2}
 Xiaoyuan Bian^{1,2}
 Jianzhong Ye^{1,2}
 Yating Li^{1,2}
 Lanjuan Li^{1,2}

¹State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China; ²Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou, China; ³Department of Gastroenterology, Sir Run Run Shaw Hospital, Zhejiang University Medical School, Hangzhou, China; ⁴Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, Stockholm, Sweden

*These authors contributed equally to this work

Background: The morbidity and mortality of pancreatic cancer vary considerably around the world. The aim of this study was to characterize and evaluate recent changes in incidence and incidence-based mortality in the USA.

Methods: Incidence and incidence-based mortality data were based on the 18 Surveillance, Epidemiology, and End Results (SEER) registries through SEER*Stat software. We adopted joinpoint regression to analyze the temporal trends stratified by age, gender, ethnicity, stage, tumor site, and size.

Results: Based on 18 SEER data sets, the age-adjusted incidence of pancreatic cancer increased from 11.85/100,000 in 2000 to 14.70/100,000 in 2014, increasing by an average annual percentage change (AAPC) of 1.6 (95% CI 1.5–1.8, $p < 0.05$). The incidence-based mortality also increased, from 9.96/100,000 in 2001 to 12.96/100,000 in 2014, increasing by an AAPC of 1.9 (95% CI 1.3–2.5, $p < 0.05$). However, we observed a deceleration in mortality since 2005, with the annual percentage change decreasing from 4.1 (2001–2005) to 1.0 (2005–2014). These increasing trends in pancreatic cancer were observed in most subgroups (stratified by age, gender, ethnicity, stage, tumor site, and size).

Conclusion: The incidence and mortality rates of pancreatic cancer in the USA have increased significantly since 2000, highlighting the need for increased preventive, screening, and surveillance efforts.

Keywords: epidemiology, pancreatic cancer, incidence, mortality, trend, SEER

Introduction

Pancreatic cancer is considered one of the most lethal malignancies, with dismal prognosis. According to Cancer Statistics, 2017,¹ an estimated 53,670 new patients will be diagnosed with pancreatic cancer and 43,090 deaths will be caused by this disease per year in the USA. The 5 year survival rate of pancreatic cancer remains as low as 8.2% in the USA.² The close parallel between the incidence of and mortality from pancreatic cancer reflects the fatal nature of this disease. To date, several risk factors, including smoking, alcohol, obesity, and type 2 diabetes, have been identified for pancreatic cancer.^{3–5}

Because of the low rates of early detection and poor prognosis, pancreatic cancer remains a tremendous public health burden around the world, especially in developed countries. It has been reported that North America and Western Europe have the highest incidence rates.⁶ Therefore, there is an urgent need for a comprehensive understanding of recent trends regarding pancreatic cancer in the USA. To our knowledge, recent changes in pancreatic cancer remain largely unknown. Most previous studies evaluated

Correspondence: Lanjuan Li
 State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, NO. 79, Qingchun Road, Hangzhou City 310003, Zhejiang Province, China
 Tel +86 571 8723 6458
 Fax +86 571 8723 6459
 Email ljlj@zju.edu.cn

the trends in pancreatic cancer from 1970 to 2002 and indicated a declining trend since 1980. These results may not be representative of the trends for pancreatic cancer in the past decade. To bridge this gap, therefore, we conducted this study based on the Surveillance, Epidemiology, and End Results (SEER) data set, which represents epidemiological trends only in the USA. We aimed to investigate and characterize the recent temporal trends in the USA during 2000–2014.

Method

Data source

Incidence data for pancreatic cancer were obtained by SEER*Stat version 8.3.4 from the database of incidence–SEER 18 registries research data.⁷ Mortality data were obtained from incidence-based mortality–SEER 18 registries research data.⁸ In incidence-based mortality analysis, we excluded the first year (2000) to ensure that most of the deaths occurred in patients who were diagnosed with pancreatic cancer after 2000. Cases of pancreatic cancer were included in the present study based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). Only microscopically confirmed pancreatic cancer and the first matching record were selected. Microscopically confirmed criteria included positive histology, positive cytology, and positive microscopic confirmation, with method unspecified.⁹ The age of the population was limited to between 20 and ≥ 85 years. Primary sites coded as head of pancreas (C25.0), body of pancreas (C25.1), tail of pancreas (C25.2), pancreatic duct (C25.3), other specified parts of pancreas (C25.7), overlapping lesion of pancreas (C25.8), and pancreas, not otherwise specified (C25.9) were included. Cases identified only from autopsy records or death certificates were excluded. As the SEER database holds deidentified data and is publicly available, no approval was required by an institutional review board, and approval from the ethics board was not required.

Statistics

The incidence and incidence-based mortality rates were calculated by SEER*Stat version 8.3.4 and age-adjusted rates were calculated by adjustment to the 2000 US standard population. The National Cancer Institute's Joinpoint regression analysis program, version 4.5.0.1,^{10,11} was used to calculate the annual percentage change (APC) and average annual percentage change (AAPC) to quantify changes in incidence and mortality, and by demographic and tumor characteristics. The program also selected the best-fitting log-linear regression model to identify calendar years (i.e. the

joinpoints) when APCs changed significantly. All statistical analysis was two sided and significance was taken as $p < 0.05$.

Results

In total, 119,412 patients with pancreatic cancer were identified in 18 SEER registries during 2000–2014, and 94,856 cases died between 2001 and 2014. Detailed characteristics are summarized in Table 1. The age-adjusted incidence and incidence-based mortality rates were 13.4 (95% CI 13.3–13.5) and 12.0 (95% CI 11.9–12.1), respectively. Notably, we observed that the mortality rate of cancer was comparable to its incidence, suggesting the highly lethal property of this malignancy. Compared with females, males had higher incidence and mortality rates. For young patients (aged < 50 years), both incidence and mortality rates were relatively low. Most pancreatic cancer cases and deaths occurred in elderly patients (> 60 years). Black patients had higher morbidity and mortality rates than other ethnic groups. In addition, advanced stage, tumors in the head of the pancreas, and median tumor size (2–4 cm) carried greater morbidity and mortality rates of pancreatic cancer.

During the study period, the age-adjusted incidence gradually increased from 11.85/100,000 person-years in 2000 to 14.70/100,000 person-years in 2014, at an AAPC of 1.6 (95% CI 1.5–1.8) (Figure 1 and Table 2). No significant cut-point was identified by joinpoint regression, indicating that the increasing trend in incidence remained steady. For incidence-based mortality, it increased from 9.96/100,000 person-years in 2001 to 12.96/100,000 person-years in 2014, at an AAPC of 1.9 (95% CI 1.3–2.5). A significant cut-point was noted in the mid-2000s (2005) and there were two distinct trends, from 2001 to 2005 and from 2005 to 2014 (Figure 2 and Table 3). The mortality rate initially increased at an APC of 4.1 (95% CI 2.1–6.0) from 2001 to 2005 and then slowed at an APC of 1.0 (95% CI 0.5–1.5) (Figure 2 and Table 3), indicating that the survival rate rose after 2005.

Changes in incidence and mortality stratified by demographic and tumor characteristics are presented in detail in Tables 2 and 3. When age-specific trends were analyzed, trends towards an increase were observed in all age subgroups, and increases were especially pronounced for the population aged 20–29 years and ≥ 80 years. The incidence rate among patients aged 70–79 years leveled off during 2009–2014 (Figure 3). With regard to mortality, in general, the more recent mortality rates increased more slowly or remained steady (Figure 4). When gender-specific trends were explored, incidence and mortality rates increased regardless of gender. The AAPC in incidence rate was higher

Table 1 Pancreatic cancer incidence (2000–2014) and incidence-based mortality (2001–2014)^a

Variable	Incidence			Incidence-based mortality				
	Cases		Rate (%)	95% CI	Deaths		Rate (%)	95% CI
	n	(%)			n	(%)		
Overall	119,412		13.4	(13.3, 13.5)	94,856	12.0	(11.9, 12.1)	
Gender								
Male	61,754	51.7	15.5	(15.3, 15.6)	49,252	51.9	14.0	(13.9, 14.1)
Female	57,658	48.3	11.7	(11.6, 11.8)	45,604	48.1	10.4	(10.3, 10.5)
Age (years)								
20–29	247	0.2	0.1	(0.1, 0.2)	72	0.1	0.0	(0.0, 0.1)
30–39	1,344	1.1	0.8	(0.7, 0.8)	607	0.6	0.4	(0.4, 0.4)
40–49	6,835	5.7	3.6	(3.5, 3.7)	4,328	4.6	2.6	(2.4, 2.7)
50–59	20,835	17.4	13.0	(12.8, 13.1)	14,562	15.4	10.1	(9.9, 10.2)
60–69	33,021	27.7	32.5	(32.2, 32.9)	25,501	26.9	28.0	(27.7, 28.4)
70–79	35,235	29.5	55.4	(54.9, 56.0)	28,981	30.6	51.6	(51.1, 52.2)
≥80	21,895	18.3	53.4	(52.7, 54.1)	20,805	21.9	56.5	(55.8, 57.3)
Ethnicity								
White	96,119	80.5	13.3	(13.2, 13.4)	77,189	81.4	11.9	(11.9, 12.0)
Black	14,300	12.0	16.9	(16.6, 17.2)	10,498	11.1	15.7	(15.4, 16.0)
Other	8,993	7.5	10.7	(10.5, 11.0)	7,169	7.6	9.3	(9.1, 9.51)
SEER stage								
Localized	10,738	9.0	1.2	(1.2, 1.2)	6,486	6.8	0.8	(0.8, 0.9)
Regional	37,239	31.2	4.2	(4.1, 4.2)	28,594	30.1	3.6	(3.6, 3.7)
Distant	64,824	54.3	7.2	(7.2, 7.3)	54,511	57.5	6.9	(6.8, 6.9)
Unknown	6,611	5.5	0.7	(0.7, 0.8)	5,265	5.6	0.7	(0.7, 0.7)
Site								
Head	59,012	49.4	6.6	(6.6, 6.7)	46,723	49.3	5.9	(5.9, 6.0)
Body	13,687	11.5	1.5	(1.5, 1.6)	10,772	11.7	1.4	(1.3, 1.4)
Tail	15,938	13.3	1.8	(1.8, 1.8)	12,006	12.7	1.5	(1.5, 1.5)
Other^b	30,775	25.8	3.5	(3.4, 3.5)	25,355	26.7	3.2	(3.2, 3.3)
Tumor size (cm)								
≤2	9,872	8.3	1.1	(1.1, 1.1)	6,555	6.9	0.8	(0.8, 0.8)
2–4	41,725	34.9	4.7	(4.6, 4.7)	32,751	34.5	4.2	(4.1, 4.2)
>4	35,157	29.4	3.9	(3.9, 4.0)	28,187	29.7	3.5	(3.5, 3.6)
Unknown	32,658	27.3	3.7	(3.6, 3.7)	27,363	28.8	3.5	(3.4, 3.5)

Note: ^aRate is per 100,000 person-years and age-adjusted to the 2000 US standard population. ^bOther sites include: C25.9, pancreas, not otherwise specified; C25.8, overlapping lesion of pancreas; C25.7, other specified parts of pancreas; C25.3, pancreatic duct; C25.4, islets of Langerhans.

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

in females (1.7%) than in males (1.4%) between 2000 and 2014. It increased at a lower rate in males during 2008–2014 (APC=1.1, 95% CI 0.7–1.5) and remained unchanged in females during the same period (APC=1.7, 95% CI 1.5–1.9) (Table 2 and Figure S1). In terms of mortality, the AAPC in mortality rate was similar in females and males (Table 3 and Figure S2). When ethnicity-specific trends were analyzed, the incidence rate was higher in white than in non-white patients. Among white people, it initially increased at an APC of 1.2% and accelerated at an APC of 2.4% between 2003 and 2008. Thereafter, it slowed to an annual increase of 1.2% in 2008–2014 (Table 2 and Figure S3). With regard to mortality trends, the largest increases occurred between 2001 and 2005 in white patients (Table 3 and Figure S4).

When stage-specific trends were analyzed, the incidence trend was particularly noteworthy for localized tumors compared with pancreatic cancer in regional and distant stages (Table 2, Figure S5). Mortality stabilized or increased slightly in recent years, indicating improved survival rates (Figure S6). When site-specific trends were analyzed, there were overall increasing trends in the incidence and mortality of cancers of the head, body, and tail of the pancreas, but not in other parts of the pancreas (Figures S7 and S8). When size-specific trends were analyzed, the annual rates of increase in incidence and mortality decreased for large tumors (>2 cm). For small tumors (≤2 cm), mortality remained steady since 2006, although the incidence increased by 5.7% on average (Figures S9 and S10).

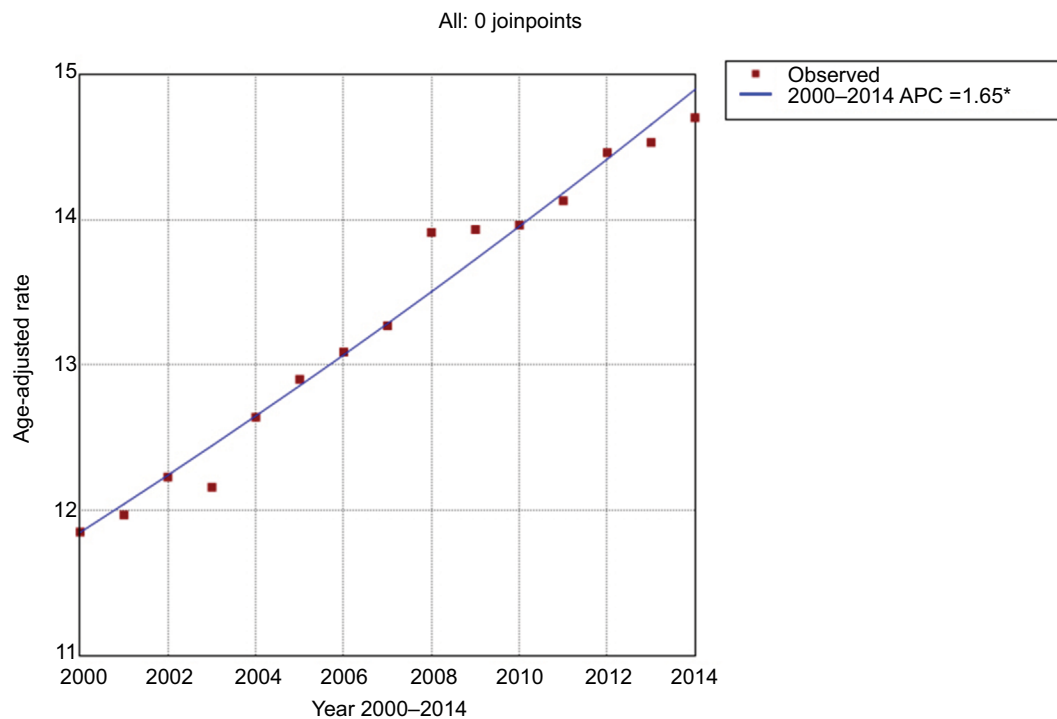


Figure 1 Trends in pancreatic cancer incidence during 2000–2014. Rates were age-adjusted to the 2000 US standard population.

Note: *The annual percentage change (APC) is significantly different from zero at the $\alpha=0.05$ level. Final selected model: 0 joinpoints.

Discussion

It is well acknowledged that the incidence and mortality of pancreatic cancer vary greatly across regions and populations worldwide. In general, high incidences and mortality rates are reported in developed countries and elderly populations.^{12–14} In the current study, an upward trend in pancreatic cancer incidence was noted throughout the study period, regardless of age, gender, ethnicity, and tumor stage, site, and size. The trend in mortality initially increased sharply and then slowed down after 2005. The detailed reasons for the more slowly increasing trends were unclear and we supposed that improvements in therapy for pancreatic cancer may be part of the explanation.¹⁵ The mortality rate remained steady or slightly increased. The overall increased trends in incidence and mortality were not influenced by other variables.

Those findings were slightly different from other registry-based data, where the trend remained relatively stable or even decreased gradually. In Europe, Wood et al¹⁶ examined the incidence, survival, and mortality trends of pancreatic cancer in England and Wales during 1975–2000. For both males and females, the incidence rate declined from peak levels during the 1970s and 1980s, and then fluctuated or leveled off. A similar trend in mortality was also observed

during this period. Another study¹⁷ from 22 European countries also documented a leveling-off trend in mortality in Europe during the 1990s. In the USA, Weiss and Benarde¹⁸ assessed the temporal trends in mortality during 1920–1978. For males, mortality initially increased steeply to a peak in 1970, and thereafter declined gradually. For females, the increase was continuous but slower during this period. In 1995, Zheng et al¹⁹ analyzed the incidence of pancreatic cancer in Connecticut, USA, during 1935–1990. From the early 1970s, there were no signs of an increasing trend in incidence in Connecticut. For males, the incidence increased during 1935–1964 and leveled off thereafter. For females, the incidence increased during 1935–1974 and then remained relatively stable. Another study²⁰ based on nine SEER registries also revealed a decreased incidence trend for pancreatic cancer between 1973 and 2002. In terms of mortality, Ma et al²¹ reported that white and black people experienced opposite trends. In white males, mortality decreased during 1970–1995 and then increased to 2009. In white females, mortality slightly increased during 1970–1984, leveled off until the late 1990s, and increased again thereafter. However, in black patients mortality initially increased and decreased thereafter. We did not observe different trends in black and

Table 2 Trends in incidence for pancreatic cancer, 2000–2014^a

Variable	Overall trend (2000–2014)		Joinpoint analysis								
			Trend 1			Trend 2			Trend 3		
	AAPC (%)	95% CI	Year	APC (%)	95% CI	Year	APC (%)	95% CI	Year	APC (%)	95% CI
Overall	1.6*	(1.5, 1.8)									
Gender											
Male	1.4*	(1.1, 1.8)	2000–2003	0.7	(−0.7, 2.1)	2003–2008	2.3*	(1.5, 3.1)	2008–2014	1.1*	(0.7, 1.5)
Female	1.7*	(1.5, 1.9)									
Age (years)											
20–29	5.3*	(3.2, 7.5)									
30–39	2.1*	(0.6, 3.7)									
40–49	0.8*	(0.2, 1.4)									
50–59	1.4*	(1.0, 1.7)									
60–69	1.3*	(1.0, 1.6)									
70–79	1.5*	(1.2, 1.8)	2000–2009	2.1*	(1.7, 2.4)	2009–2014	0.4	(−0.4, 1.3)			
≥80	2.8*	(2.3, 3.2)									
Ethnicity											
White	1.8*	(1.6, 1.9)	2000–2003	1.2*	(0.4, 2.0)	2003–2008	2.4*	(1.9, 2.9)	2008–2014	1.2*	(1.0, 1.5)
Black	1.2*	(0.7, 1.6)									
Other	1.6*	(1.1, 2.0)									
SEER stage											
Localized	5.4*	(4.6, 6.1)									
Regional	2.0*	(1.5, 2.6)	2000–2003	1.2	(−1.6, 4.2)	2003–2008	4.2*	(2.5, 6.0)	2008–2014	0.1	(−0.7, 0.9)
Distant	1.5*	(1.3, 1.6)									
Site											
Head	1.1*	(0.9, 1.3)									
Body	5.1*	(4.5, 5.7)									
Tail	4.2*	(3.7, 4.7)									
Other^b	−0.1	(−0.4, 0.2)									
Tumor size (cm)											
≤2	5.7*	(5.0, 6.5)									
2–4	5.5*	(4.8, 6.2)	2000–2008	7.4*	(6.3, 8.6)	2008–2014	3.0*	(1.7, 4.2)			
>4	4.4*	(3.9, 4.9)	2000–2008	5.9*	(5.1, 6.7)	2008–2014	2.4*	(1.5, 3.4)			

Note: ^aRates are per 100,000 person-years and age-adjusted to the 2000 US standard population. ^bOther sites include: C25.9, pancreas, not otherwise specified; C25.8, overlapping lesion of pancreas; C25.7, other specified parts of pancreas; C25.3, pancreatic duct; C25.4, islets of Langerhans. *The APC or AAPC is significantly different from zero ($p < 0.05$).

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; AAPC, average annual percentage change; APC, annual percentage change.

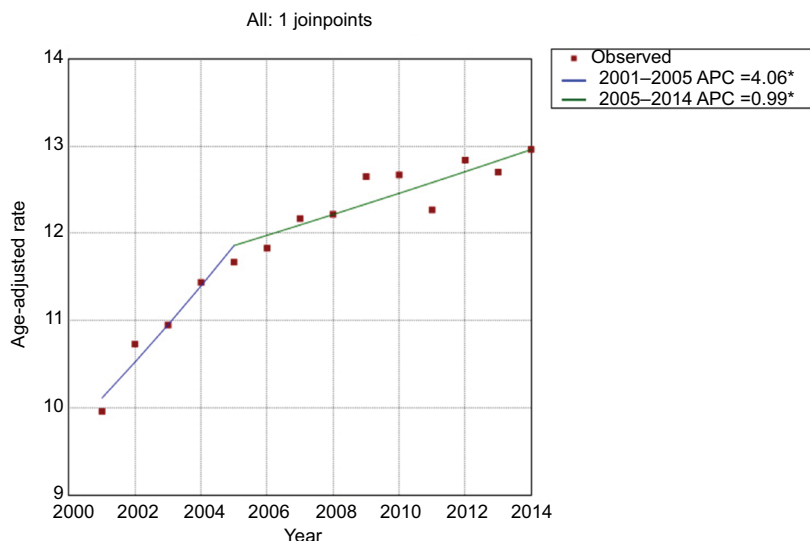


Figure 2 Trends in pancreatic cancer mortality during 2000–2014. Rates were age-adjusted to the 2000 US standard population.

Note: *The annual percentage change (APC) is significantly different from zero at the $\alpha = 0.05$ level. Final selected model: 1 joinpoint.

Table 3 Trends in mortality for pancreatic cancer, 2001-2014^a

Variable	Overall trend (2000–2014)		Joinpoint analysis								
			Trend 1			Trend 2			Trend 3		
	AAPC (%)	95% CI (%)	Year	APC (%)	95% CI (%)	Year	APC (%)	95% CI	Year	APC (%)	95% CI
Overall	1.9*	(1.3, 2.5)	2001–2005	4.1*	(2.1, 6.0)	2005–2014	1.0*	(0.5, 1.5)			
Gender											
Male	1.6*	(1.2, 2.1)	2001–2005	4.5*	(2.3, 6.8)	2005–2014	0.9*	(0.4, 1.4)			
Female	1.6*	(1.1, 2.0)	2001–2009	2.4*	(1.6, 3.2)	2009–2014	0.3	(–1.2, 1.7)			
Age (years)											
20–29	1.6	(–4.1, 7.6)									
30–39	–0.2	(–2.1, 1.8)									
40–49	–0.0	(–1.3, 1.3)									
50–59	0.6*	(0.0, 1.2)	2001–2007	2.2*	(0.6, 3.8)	2007–2014	–0.5	(–1.6, 0.6)			
60–69	1.1*	(0.5, 1.8)	2001–2005	4.4*	(0.5, 8.4)	2005–2014	0.3	(–0.6, 1.2)			
70–79	1.6*	(1.1, 2.0)	2001–2003	6.9	(–0.4, 14.8)	2003–2014	1.2*	(0.7, 1.6)			
≥80	3.4*	(2.9, 3.9)									
Ethnicity											
White	1.8*	(1.4, 2.2)	2001–2005	4.2*	(2.5, 5.8)	2005–2014	1.2*	(0.8, 1.6)			
Black	0.9*	(0.2, 1.6)									
Other	1.2*	(0.5, 1.9)									
SEER stage											
Localized	4.8*	(3.9, 5.8)	2001–2004	12.4*	(3.2, 22.4)	2004–2014	3.9*	(2.9, 4.9)			
Regional	2.6*	(1.7, 3.5)	2001–2003	10.3	(–0.8, 22.5)	2003–2009	3.6*	(1.5, 5.6)	2009–2014	0.0	(–1.8, 1.8)
Distant	1.3*	(1.0, 1.6)	2001–2006	2.5*	(1.0, 3.9)	2006–2014	0.8*	(0.2, 1.4)			
Site											
Head	1.4*	(0.9, 2.0)	2001–2004	5.9*	(1.4, 10.6)	2004–2014	0.8*	(0.2, 1.4)			
Body	4.7*	(3.7, 5.7)	2001–2008	7.3*	(5.6, 8.9)	2008–2014	2.2*	(0.6, 3.8)			
Tail	3.6*	(2.9, 4.3)									
Other^b	–0.1	(–0.5, 0.3)									
Tumor size (cm)											
≤2	5.8*	(3.7, 8.0)	2001–2006	12.6*	(6.9, 18.7)	2006–2014	1.8	(–0.1, 3.7)			
2–4	6.0*	(4.7, 7.4)	2001–2005	10.5*	(7.2, 13.9)	2005–2009	5.6*	(1.6, 9.8)	2009–2014	2.9*	(1.4, 4.5)
>4	4.9*	(4.4, 5.4)	2001–2007	7.5*	(6.4, 8.6)	2007–2014	2.7*	(2.0, 3.3)			

Note: ^aRates are per 100,000 person-years and age-adjusted to the 2000 US standard population. ^bOther sites include: C25.9, pancreas, not otherwise specified; C25.8, overlapping lesion of pancreas; C25.7, other specified parts of pancreas; C25.3, pancreatic duct; C25.4, islets of Langerhans. *The APC or AAPC is significantly different from zero ($p < 0.05$).

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; AAPC, average annual percentage change; APC, annual percentage change.

white patients in the current study. Different population origins may partly account for the different trends. Indeed, two studies from Europe published in 2017 showed an increasing incidence trend in pancreatic cancer, and the study from France²³ also described diverging trends in pancreatic cancer incidence and mortality.^{22,23} The incidence in both males and females increased during the past three decades, while mortality remained similar in men and slightly increased in women.²³ Several commentaries considered that these trends might be artificial.^{24,25} The incidence and mortality rates in China also increased gradually, as reported by Chen et al.²⁶ Owing to the lack of early diagnosis and effective therapies, the burden of pancreatic cancer remains huge.

Regarding increased trends in incidence, advances in high-resolution imaging and the widespread adoption of

endoscopic ultrasound may have contributed to more cases of pancreatic cancer being diagnosed in the early stages. Sharp increases in the incidence of localized and small tumors (<2 cm) in the current study also support this explanation (Figures S5 and S9). Early stage and small size are two important prognostic factors for pancreatic cancer.²⁷ The early diagnosis of pancreatic cancer may have partly decreased the mortality rate after 2006. Besides, recent advances in therapies for pancreatic cancer have partly improved the survival outcomes of pancreatic cancer.^{15,28} Rising mortality rates in early stages and small-size pancreatic cancer also slowed down in recent years in the current study (Figures S6 and S10). The potential mechanisms underlying the increased trends in incidence and mortality warrant investigation in further studies.

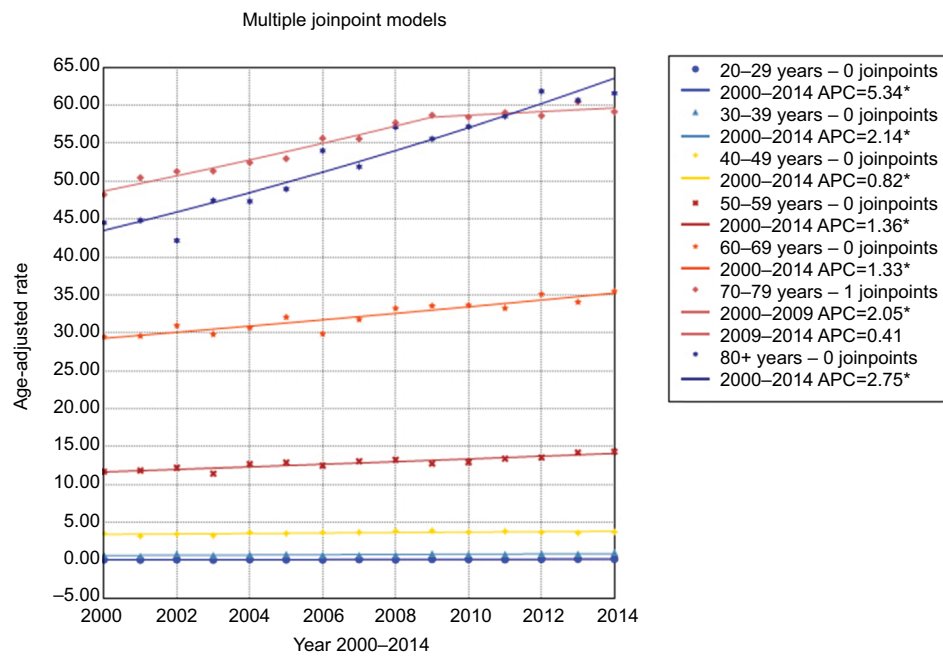


Figure 3 Trends in pancreatic cancer incidence during 2000–2014 stratified by age subgroups. Rates were age-adjusted to the 2000 US standard population. **Note:** * $p < 0.05$.

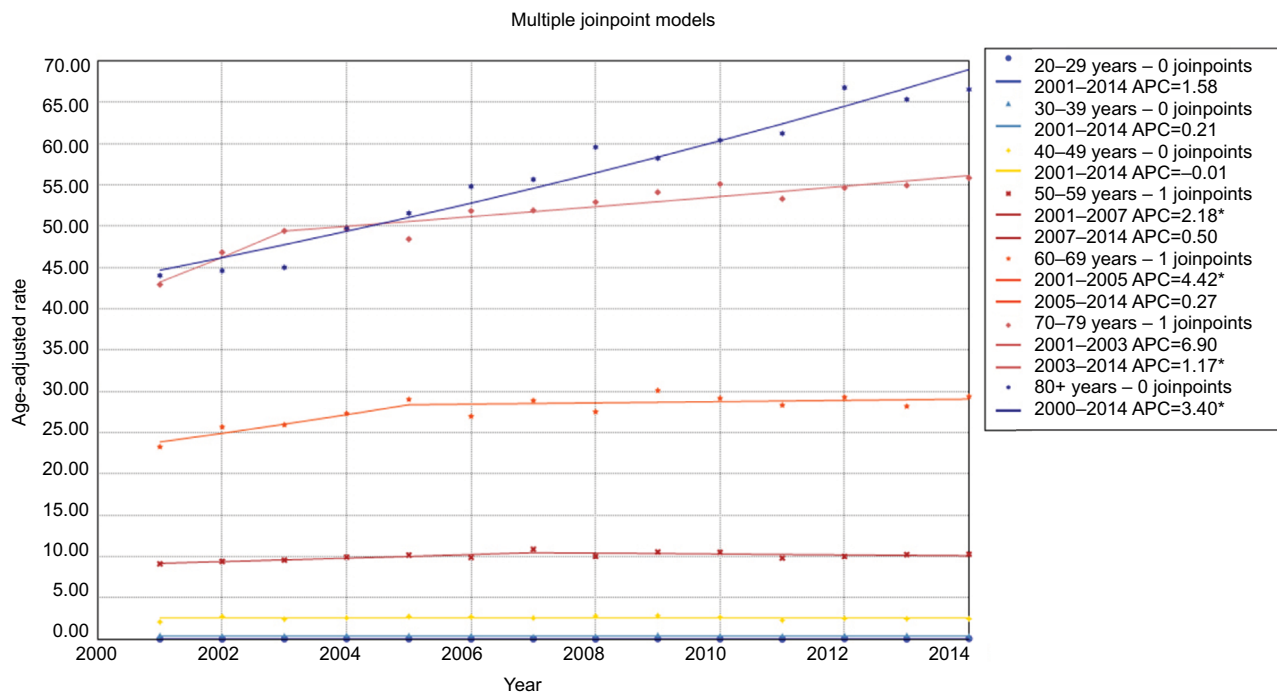


Figure 4 Trends in pancreatic cancer mortality during 2000–2014 stratified by age subgroups. Rates were age-adjusted to the 2000 US standard population. **Note:** * $p < 0.05$.

One strength of our study is that the results are based on 18 SEER registries, comprising the largest data set and covering approximately 30% of the overall US population. The high-quality data source indirectly supports the reliability of the overall results. However, there are also some

limitations to our study. The results may be restricted to the US population and may not be generalizable to other populations in the world. In addition, we were unable to compare long-term trends based on the 18 SEER registries. Furthermore, several factors such as tobacco consumption,

obesity, and chronic pancreatitis^{29–31} could not be examined in the current study.

Taken together, our findings reveal that there were increasing trends in incidence and mortality rates of pancreatic cancer, and fill a critical knowledge gap concerning recent trends in pancreatic cancer. Further studies are needed to determine the potential mechanisms underlying the increased trends in pancreatic cancer in the USA.

Abbreviations

SEER: Surveillance, Epidemiology, and End Results

ICD-O-3: International Classification of Diseases for Oncology, Third Edition

APC: annual percentage change

AAPC: average annual percentage change

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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