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# Pancreatic Cancer: A Survival Analysis Study in Oklahoma

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#### **Abstract**

**Background**—Pancreatic cancer is among the most deadly cancers. Risk factors associated with the disease include age, race, sex, smoking status, and diabetes status.

**Method**—We conducted a prospective analysis of risk factors and length of survival among pancreatic cancer patients living in Oklahoma between 1997 and 2012 (n=6,291). Kaplan-Meier survival curves were created followed by the log-rank test to compare difference in the survival time. Cox proportional hazard regression models were used to examine the strength of association through the estimated hazard ratios.

**Results**—The median survival time of the cohort was three months. Significant risk factors for reduced survival times included age, stage at diagnosis, and year of diagnosis.

**Conclusion**—Results are in agreement with previous research findings. There have been small but noteworthy improvements in survival times for pancreatic cancer patients in Oklahoma. Length of survival during the study period was significantly associated with known risk factors such as age and stage of diagnosis.

### **BACKGROUND**

Cancer was the second leading cause of death in the United States (US) and Oklahoma in 2013. Pancreatic cancer, in particular, was the fourth most common cause of cancer death

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in the US and Oklahoma from 2008 to 2012.<sup>2</sup> Based on 2012 reports, the US had 43,213 incident cases of pancreatic cancer with an age-adjusted incidence rate (AAIR) of 13.9 per 100,000 and 38,797 pancreatic cancer deaths with an age-adjusted mortality rate (AAMR) of 11.0 per 100,000.<sup>2</sup> In 2000 there were 29,080 incident cases (AAIR 11.1 per 100,000) and 29,331 (AAMR 10.5 per 100,000) deaths from pancreatic cancer. Overall, pancreatic cancer incidence appears to be increasing and mortality appears to be remaining steady. This contrasts with the downward trend in incidence observed in other primary sites such as breast, prostate and even lung cancer.<sup>3,4</sup> Moreover, pancreatic cancer is one of the most lethal cancers with a case fatality rate (ratio) of approximately 0.99%<sup>5</sup> and five-year survival rate of 7.2%<sup>6</sup> that reinforces its serious impact.<sup>7</sup> Some of the proposed reasons to explain the low survival rate experienced by pancreatic cancer patients include the difficulty in diagnosing it early and effectively treating it at any stage.<sup>8</sup>

Substantial research has been conducted to understand pancreatic cancer's molecular influence as well as risk factors associated with its development. Studies have shown that the risk of developing pancreatic cancer is associated with factors such as smoking, age, sex, obesity, alcohol consumption, diabetes, and diet. Age and smoking have been consistently reported to be major risk factors for pancreatic cancer, with smoking contributing to roughly 20% of all pancreatic cancer cases. A case control study conducted by Patrick and colleagues found a high odds ratio (OR) of 15.4 (CI 3.18–74.9) for smoking exposure. The risk of pancreatic cancer was also reported to be higher in males compared to females, though the difference was small. When looking at race, African Americans have higher incidence and mortality rates compared to whites overall.

Important factors that have stimulated a great deal of research in risk for pancreatic cancer are obesity and diabetes. <sup>13</sup> Individuals with a body mass index of 30 or higher and individuals with centralized fat distribution had increased risk of pancreatic cancer, with estimates around 20% higher risk of developing pancreatic cancer compared to those of normal weight. <sup>17–22</sup> One quarter (25%) of pancreatic cancer patients had diabetes at the time of diagnosis and almost 40% were prediabetic. <sup>11,23–25</sup> Compared to non-diabetics, diabetic individuals have a 50% increased risk of pancreatic cancer. <sup>25</sup> While not significant, a population based study of the association between pancreatic cancer and diabetes suggested that approximately 1% of diabetic patients were diagnosed with pancreatic cancer within three years of being diagnosed with diabetes. <sup>11</sup> Another study found a significant association between diabetes and pancreatic cancer, with an OR of 2.16 (CI: 1.60–2.91). <sup>12</sup> The researchers also found that the risk of being diagnosed with pancreatic cancer was highest during the first year of being diagnosed with diabetes (OR: 6.68, CI 3.56–12.6) and decreased over time. <sup>12</sup>

Despite the many studies carried out to assist in understanding some of the risk factors associated with pancreatic cancer, incidence and mortality rates, in particular, remain considerably high. Future research should therefore focus on studies that would help improve quality of life of these patients, which would increase the prevalence and possibly reduce the case fatality rate. One way of achieving this is to examine how certain characteristics could be used to predict the survival time of patients diagnosed with pancreatic cancer.

The first purpose of this study was to provide a description of the distribution of risk factors (age at diagnosis, race, sex, stage at diagnosis, and metro vs. non-metro status) in Oklahoma. Secondly, we aimed to examine factors associated with survival time among pancreatic cancer patients in Oklahoma. Specifically, we evaluated the association between age, sex, race, cancer stage, metro vs. non-metro, and survival time by estimating survival curves using the Kaplan-Meier product limit. Due to limited data, diabetes status and smoking status as covariates were not examined. Finally, we aimed to examine the strength of association (using hazard ratios) between significant factors at diagnosis and survival time using a Cox regression model.

#### **METHODS**

Data were obtained from the Oklahoma Central Cancer Registry (OCCR) at the Oklahoma State Department of Health (OSDH), funded by the National Program of Central Cancer Registries (NPCR), Centers for Disease Control and Prevention (CDC), which maintains a population-based cancer database of all cancer cases diagnosed or treated in Oklahoma since January 1, 1997. The OCCR follows standards developed by the North American Association of Central Cancer Registries (NAACCR). This study was determined to be exempt from IRB review by both the University of Oklahoma Health Sciences Center and the Oklahoma State Department of Health.

For this study, invasive pancreas cancer cases (ICD-O-3 site codes C250.0–C25.9, behavior code 3)<sup>26</sup> diagnosed among residents of Oklahoma from January 1, 1997 to December 31, 2012 were extracted from the OCCR database. Cases that were benign or borderline behavior codes and cases whose histology codes (9050–9055, 9140, and 9590–9989) specified mesotheliomas, Kaposi sarcomas and lymphomas were excluded. Cases identified solely through a death certificate (n=386) or at autopsy (n=4) were excluded from this analysis. All cases with either zero survival time or those with less than zero days survivals were excluded (n=104) for a total of sample size of 6,291. This cohort of pancreatic cancer cases was retrieved from the OCCR for the years 1997 through 2012. This final sample represents all pancreatic cancer cases in Oklahoma diagnosed between 1997 and 2012 and followed through October 2014.

Participants' age, race, date of diagnosis, date of last contact, cancer stage, sex, survival time, metro and non-metro status, and vital status were either extracted from the OCCR or calculated based on the available information. Cancer stage at diagnosis was determined using the SEER Summary Stage 2000 for cases diagnosed from 1997 through 2003, and using the derived SEER Summary Stage 2000 for cases diagnosed in 2004 through 2012. Cancer stage at diagnosis was determined using the standard SEER definitions of in-situ, localized, regional, distant and regional, and un-staged. For this study we grouped in-situ and localized, regional and distant, and unstaged into three groups. An individual's race was determined using the OCCR primary race variable for all racial groups except American Indians/Alaskan Natives (AI/AN), whose race was determined using the Indian Health Service (IHS) link variable and/or primary race. Patient's whose address at diagnosis were in metropolitan counties as defined by the rural/urban continuum 2000 were classified as metro, with others as non-metro.<sup>27</sup> The Rural-Urban Continuum Codes designates

metropolitan (metro) counties by the population size of their metro area, and nonmetropolitan (non-metro) counties by degree of urbanization and adjacency to a metro area or areas.<sup>28</sup> These designations were based on the county of residence at diagnosed.

Survival time was calculated by subtracting date of diagnosis from date of last contact and dividing the outcome by 30 to get survival time in months. For this study their vital status (dead or alive) was followed through November 1, 2014. OCCR does not participate in active follow-up, however, the OCCR periodically conducts passive follow-up of those included in the registry through linkages with the Oklahoma Mortality Data, the Social Security Death Index, and the National Death Index (NDI) to identify those who are deceased.<sup>29</sup> Therefore, the presumed alive assumption for those not listed as dead was used.<sup>30</sup>

We employed an imputation method to reduce overestimation or underestimation of survival due to missing day or month in the date variables.<sup>31</sup> For patients that lacked the day but had the year and month, the 15th day of the month was assigned. For those that had the year but no month and day, the 15th day of the month of January was assigned.

### **ANALYSIS**

Descriptive statistics were calculated for the variables of interest overall and by status (alive vs. deceased). Next, Kaplan-Meier survival curves were created followed by the log rank test<sup>32</sup> to compare differences in the survival time distribution across the following factors: age at diagnosis, sex, cancer stage, metro and non-metro, and race. Cox proportional hazard regression modelling was conducted to examine the strength of association between the covariates and survival time. The proportionality of the covariates was then tested by adding an interaction term between time and the variable of interest.<sup>33</sup> If the interaction term resulted in a p-value less than 0.05, the interaction term was kept in the model to incorporate the non-proportionality. In the final model only variables significant at a p<0.20 were eligible for inclusion and interactions between the covariates were assessed at an alpha of 0.05. Stratification by one of the covariates involved in the interaction or inclusion of the interaction term in the model were used to take the interaction into account. All analyses were conducted using SAS® 9.4.

#### **RESULTS**

Cases of pancreatic cancer were distributed approximately equally by sex (51% male, 49% female). The higher proportion of cases were among whites (85%), those 70 years of age or older (50%), those staged as distant or regional (46%) and those who resided in metro counties at diagnosis (60%; Table 1). The overall median survival time of the cohort was between three and four months (range: 0 to 184 months) (data not shown). The results show increasing median survival for each period 1997–2000 at 3.1 months, 2001–2004 at 3.9 months, 2005–2008 at 4.0 months and 2009–2012 at 4.5 months (Table 2; Figure 1; p=0.0067). Median survival also differed by age at diagnosis: 55 years or less 6.3 months, 56–70 years 4.9 months, and over 70 years 2.8 months (Figure 2; p<0.001). Lastly, median

survival also differed by stage of diagnosis: 7.5 months for in-situ or localized, 2.5 months for distant or regional, and 2.9 months for un-staged.

The hazard ratios (Figure 3; P < .0001) describing the relationship between survival time and each variable separately are reported in Table 3. The proportionality assumptions were not met for years of diagnosis, age at diagnosis, or stage at diagnosis (p < 0.05) so the interaction term between time and each variable was kept in the model to incorporate the non-proportionality into the model. The variables years of diagnosis, age at diagnosis, and stage at diagnosis were significantly associated with survival time. The hazard of death is 2.3 times higher among patients with a distant or regional stage at diagnosis as compared to patients with in-situ or localized stage at diagnosis. Sex (p = 0.88) and metro and non-metro (p = 0.74) were not significantly associated with survival time. The only racial difference associated with survival time were the Asian/Pacific Islanders with a lower hazard ratio (0.70) compared to whites (p = 0.02).

In the final model, years of diagnosis, age at diagnosis, stage at diagnosis, and race were significantly associated with survival time (Table 4). No interactions between covariates were detected. Interaction terms between time and years of diagnosis, age at diagnosis, and stage at diagnosis were included in the final model to take into account the non-proportionality for these variables. Oklahomans diagnosed from 1997–2000 had a hazard of death 1.37 times greater than those diagnosed from 2009–2012 (p<0.0001). Oklahomans age 71 or older hazard of death almost two times (1.89) greater than those diagnosed at age 55 or younger (p<0.0001). Those diagnosed at distant or regional stage had a hazard of death 2.39 times greater than those diagnosed at in-situ or localized (p<0.0001). African Americans in Oklahoma had a hazard of death 1.13 times greater than those who were white (p=0.02).

## **DISCUSSION**

There have been small but noteworthy improvements in survival times for pancreatic cancer patients thus far in Oklahoma. The same observations were made with other covariates in the study. Older age, later stage, and African American race were all associated with a higher hazard of death. These results may be attributed to issues such as inaccessibility to care, social economic status, or even lack of awareness about this specific cancer.

Results obtained from this study are consistent with other studies. For instance, studies have shown that the incidence of the disease is strongly associated with risk factors such as sex, age, and stage of diagnosis, in addition to behavioral factors such as smoking and diabetes status. 8,11–15 The current study also showed significant risk factors including years of diagnosis, age, race and cancer stage. Older individuals and those diagnosed at later stages had a greater risk of dying compared to younger or those diagnosed at earlier stages.

One result that differed from some previous studies was the metro and non-metro. Metro and non-metro was based on county of residence at diagnosis. One other study found a metro and non-metro to be a significant factor in survival from pancreatic cancer, and several other studies have indicated it as a factor for other types of cancer. $^{34-38}$  In the current study, there was no significant difference between metro and non-metro diagnoses (p= 0.74). This may

have been a result of how the counties were categorized into metro and non-metro status. Another explanation for these findings could be that because pancreatic cancer is difficult to diagnose therefore the county of residence at diagnosis would not improve the chance of survival unless in the cancer is diagnosed at a very early stages (which is rare). Additionally, it may be that these metro and non-metro differences are no longer noteworthy or were never significant in Oklahoma.

### STRENGTHS AND LIMITATIONS

This was the first survival analysis study on pancreatic cancer carried out in Oklahoma. The OCCR data set is the only large data set of cancer patients for Oklahoma and it allows for making reasonable estimates that can be generally applicable to the population in Oklahoma.<sup>29</sup> In addition to the study's strengths, there are a number of limitations to note; however, a more complete analysis would have conducted active follow-up, however with the multiple death linkages and using the assumed alive methodology has shown to be accurate.<sup>29,30</sup> Another limitation is that analysis of risk factors such as diabetes and smoking status were not possible due to the data source. Studies have shown that there is an association between tobacco smoking, diabetes and pancreatic cancer.<sup>8,11–15</sup> Future studies should include these additional variables whenever possible. Finally, the data used in our study were limited to Oklahoma, and therefore precluded any inferences beyond the state.

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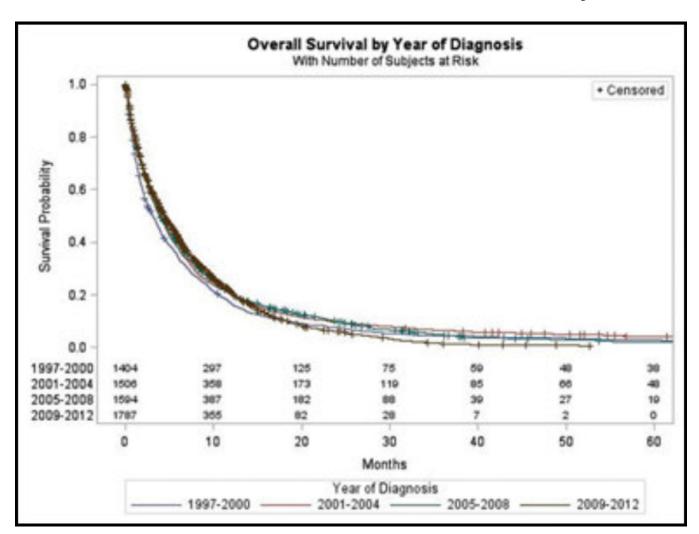
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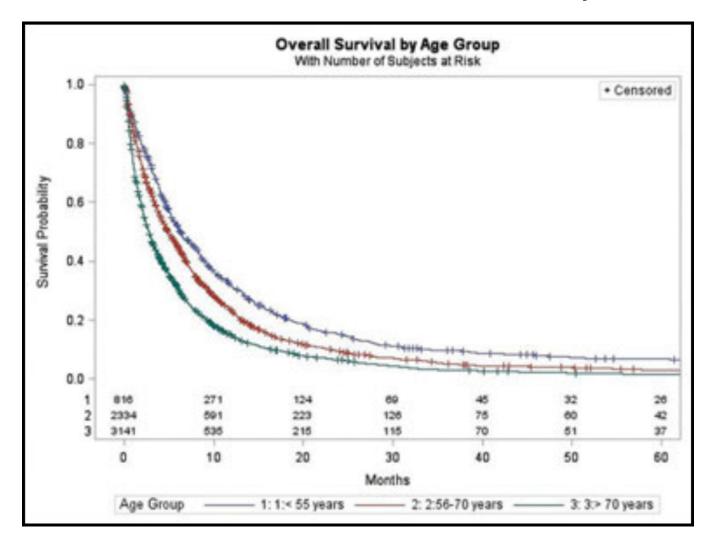
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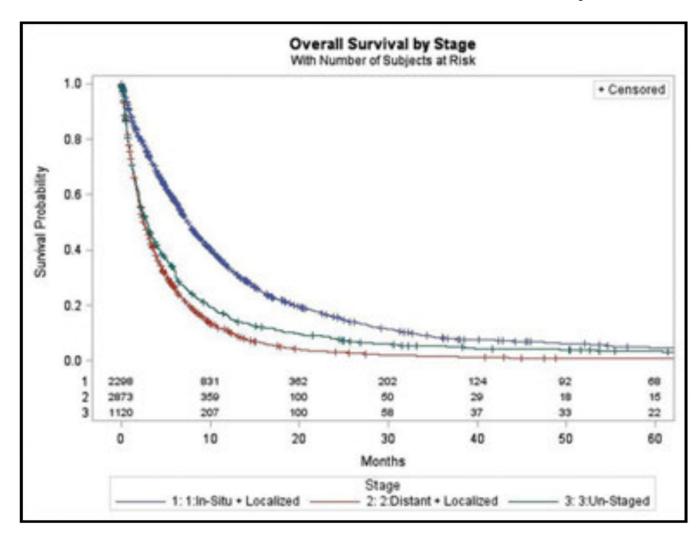
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**Figure 1.**Overall Survival from Pancreatic Cancer by Year of Diagnosis, Oklahoma, 1997–2012



**Figure 2.**Overall Survival from Pancreatic Cancer by Age Group, Oklahoma, 1997–2012



**Figure 3.**Overall Survival from Pancreatic Cancer by Stage at Diagnosis, Oklahoma, 1997–2012

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Table 1

Characteristics of Pancreatic Cancer Patients (n=6,291), Oklahoma, 1997-2012

Variable	% Overall	% Alive	Alive Cases	% Dead	Dead Cases
Overall			425		5,866
Sex <sup>a</sup>					
Male	50.8	51.8	220	8.03	2,978
Female	49.2	48.2	205	49.2	2,887
Race <sup>b</sup>					
African American	7.2	7.4	31	7.2	417
White	85.4	83.2	351	85.5	4,985
American Indians/ Alaskan Native	6.7	7.6	32	9:9	385
Asian/Pacific Islander	8.0	1.9	N/A	2.0	75
Age (years)					
55 or less	13.0	25.4	108	12.1	802
56–70	37.1	46.4	197	36.4	2,137
Older than 70	49.9	28.4	120	51.5	3,021
Stage at diagnosis					
In-situ + Localized	36.5	63.3	569	34.6	2,029
Distant + Regional	45.7	22.8	<i>L</i> 6	47.3	2,776
Un-staged	17.8	13.9	59	18.1	1,061
Rural/Urban Continuum					
Metro	59.7	59.3	173	7.65	2,363
Non-Metropolitan	40.3	40.7	252	40.3	3,503

<sup>&</sup>lt;sup>a</sup>Sex missing (n=1)

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Table 2
Survival Time by Prognostic Factors among Pancreatic Cancer Patients (n=6,291), Oklahoma, 1997–2012

Variable	Median Survival Time (months)	p-value
Overall	3.9	
Years of Diagnosis		
1997–2000	3.1	0.007
2001–2004	3.9	
2005–2008	4.0	
2009–2012	4.5	
Age (years)		< 0.0001
55 or less	6.3	
56–70	4.9	
Older than 70	2.8	
Stage at diagnosis		< 0.0001
In-Situ + Localized	7.5	
Distant + Regional	2.5	
Un-staged	2.9	
Sex		0.88
Male	3.8	
Female	4.0	
Race		0.13
African American	4.1	
White	3.9	
American Indians/Alaskan Native	3.8	
Asian/Pacific Islander	6.1	
Rural/Urban Continuum		0.74
Non-Metro	3.9	
Metro	4.0	

Table 3
Unadjusted Cox Proportional Hazard Models predicting Survival Time (n=6,291), Oklahoma, 1997–2012

Variable	Hazard Ratio	95% CI	p-value
Years of Diagnosis <sup>a</sup>			
1997–2000	1.40	1.28–1.53	< 0.0001
2001–2004	1.13	1.04-1.22	0.003
2005–2008	1.04	0.97-1.12	0.30
2009–2012			Ref
Age (years)			
55 or less			Ref
56–70	1.30	1.18–1.42	< 0.0001
Older than 70	1.80	1.63-1.98	< 0.0001
Stage at diagnosis			
In-Situ + Localized			Ref
Distant + Regional	2.31	2.16–2.47	< 0.0001
Un-staged	2.06	1.88-2.25	< 0.0001
Sex (Female vs Male)	1.00	0.95-1.06	0.88
Race			
African American	0.98	0.88-1.08	0.70
White			Ref
American Indians/Alaskan Native	0.97	0.88-1.08	0.59
Asian/Pacific Islander	0.70	0.52-0.95	0.02
Rural/Urban Continuum (Metro vs Non-Metro)	1.01	0.96–1.06	0.74

 $<sup>^{\</sup>textit{a}} \text{Adjusted for interaction between time and the variable to incorporate the non-proportionality into the model}$ 

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Table 4
Adjusted Cox Proportional Hazard model predicting survival time (n=6,291), Oklahoma, 1997–2012

Variable	Adjusted Hazard Ratio <sup>a</sup>	95% CI	p-value
Years of Diagnosis			
1997–2000	1.37	1.26–1.50	< 0.0001
2001–2004	1.09	1.00-1.18	0.05
2005–2008	1.03	0.96–1.11	0.44
2009–2012	Ref		
Age (years)			
55 or less	Ref		
56–70	1.32	1.21-1.45	< 0.0001
Older than 70	1.89	1.71-2.09	< 0.0001
Stage at diagnosis			
In-Situ + Localized	Ref		
Distant + Regional	2.39	2.24–2.55	< 0.0001
Un-staged	1.89	1.72-2.07	< 0.0001
Sex (Female vs Male)			
Race			
African American	1.13	1.02-1.24	0.02
White	Ref		
American Indians/Alaskan Native	1.09	0.98-1.21	0.10
Asian/Pacific Islander	0.82	0.61-1.12	0.21

<sup>&</sup>lt;sup>a</sup>Adjusted for interaction between time and year of diagnosis, time and age, time and stage (to incorporate the non-proportionality into the model) as well as the other variables in the table