RESEARCH ARTICLE

Racial and Social Economic Factors Impact on the Cause Specific Survival of Pancreatic Cancer: A SEER Survey

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Abstract

Background: This study used Surveillance, Epidemiology and End Results (SEER) pancreatic cancer data to identify predictive models and potential socio-economic disparities in pancreatic cancer outcome. Materials and Methods: For risk modeling, Kaplan Meier method was used for cause specific survival analysis. The Kolmogorov-Smirnov's test was used to compare survival curves. The Cox proportional hazard method was applied for multivariate analysis. The area under the ROC curve was computed for predictors of absolute risk of death, optimized to improve efficiency. Results: This study included 58,747 patients. The mean follow up time (S.D.) was 7.6 (10.6) months. SEER stage and grade were strongly predictive univariates. Sex, race, and three socio-economic factors (county level family income, rural-urban residence status, and county level education attainment) were independent multivariate predictors. Racial and socio-economic factors were associated with about 2% difference in absolute cause specific survival. Conclusions: This study s found significant effects of socio-economic factors on pancreas cancer outcome. These data may generate hypotheses for trials to eliminate these outcome disparities.

Keywords: Pancreatic cancer - radiotherapy - SEER - socio-economic disparity - cause specific survival

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Introduction

Pancreatic cancer is an aggressive disease with an actuarial mortality rate is about 90% (Strimpakos et al., 2012). For operable pancreatic cancers, the patients are usually treated with adjuvant chemoradiotherapy (Regine et al., 2008) in the United States and with chemotherapy (Neoptolemos et al., 2012) in Europe. Systematic therapy is the mainstay for metastatic pancreatic cancer (Tokh et al., 2012). The results for current managements are disappointing, active investigations are under way to improve the outcome of pancreatic cancer (Strimpakos et al., 2012). There are scant data on the effects of socio-economic factors on the pancreatic cancer survival (van Loon et al., 1995; Gill and Martin, 2002). This study is a part of a larger effort to survey the Surveillance, Epidemiology and End Results (SEER) for socio-economic disparities in cancer treatment outcomes. In particular, this study investigated racial and socio-economic factors on the cause specific survival of pancreas cancer.

Materials and Methods

SEER registers public use data. These data can be used for analysis with no internal review board approval needed. For risk modeling, Kaplan Meier method was used for cause specific survival analysis. Kolmogorov-Smirnov's test was used to compare survival curves. Cox proportional hazard method was used for multivariate analysis. The variables were coded as below. SEER stage: 0=local/regional, 1=metastatic/un-staged; Grade: 0=grade 1-2, 1=grade 3-4, ungraded; Sex: 0=female, 1=male; Race: 0=non African American, 1=African American; Rural Urban residence status: 0=urban, 1= rural; County level % college graduate: 0>25%, 1≤25%; County level family income: 0=more than $50k/year, 1=less or equal to $50k/years. SEER Clinical Outcome Prediction Expert (SCOPE) (Cheung, 2012) was used to mine SEER data and construct accurate and efficient prediction models. The data were obtained from SEER 18 database. SEER*Stat (http://seer.cancer.gov/seerstat/) was used for listing the cases. The filter used was: Site and Morphology. ICD-O-3 Hist/behav, malignant='8003/3: Malignant tumor, pancreatic type'. Patients diagnosed from 2004-2009 were included. The areas under the receiver operating characteristic (ROC) curve were computed for absolute cause specific deaths. These ROC models were optimized to improve efficiency. All of the statistics and programming of this study were performed in Matlab (www.mathworks.com). The variable 'SEER cause-specific death classification' was used as the outcome variable.

Results

This study included 58747 patients (Table 1-2, Figure 1). The mean (S.D.) age was 70.2 (12.9) years. The mean

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Table 1. The Risk Models Include the Socio-demographic, Tumor and Treatment Factors for Pancreatic Cancer

Initial univariate risk models		Number	%	ROC Area	S.D.
Study population		58747			
Age of diagnosis:	Mean/S.D.	70/13			
	<20 years	32	0.054	0.5	0
	≥20 years old	58715	99.950		
Follow up (months):	Mean/S.D.	8/11			
Sex:	Female	29590	50.370	0.51	0
	Male	29157	49.630		
SEER historic stage A:	Distant, level III*	29764	50.660	0.6	0.01
	Regional, level II**	15813	26.920		
	Localized, level I***	5345	9.098	0.59	0
	Unstaged, level IV	7825	13.320		
Grade:	Poorly differentiated; Grade III	7612	12.960	0.56	0
	Moderately differentiated; Grade II	7359	12.530		
	Unknown	40629	69.160		
	Well differentiated; Grade I	2594	4.416		
	Undifferentiated; anaplastic; Grade IV	553	0.941		
Rural-Urban Continuum	Counties in metropolitan areas ge 1 million pop	35380	60.220	0.5	0
Code 2003	Counties in metropolitan areas of 250,000-1 million pop	11082	18.860		
	Urban pop of ge 20,000 adjacent to a metropolitan area	1807	3.076		
	Unknown/missing/no match	8	0.014		
	Urban pop of ge 20,000 not adjacent to a metropolitan area	884	1.505		
	Counties in metropolitan areas of lt 250 thousand pop	4919	8.373		
	Urban pop of 2,500-19,999, adjacent to a metro area	2310	3.932		
	Urban pop of 2,500-19,999, not adjacent to a metro area	1470	2.502		
	Comp rural lt 2,500 urban pop, adjacent to a metro area	440	0.749		
	Comp rural lt 2,500 urban pop, not adjacent to metro area	383	0.652		
	Unknown/missing/no match (Alaska - Entire State)	64	0.109		
County Family Income:	≥$50000	32540	55.390	0.51	0.01
	<$50000	26207	44.610		
County % college graduate:	≥25%	27224	46.340	0.52	0
	<25%	31523	53.660		
Race:	White/others	51839	88.240	0.5	0
	Black	6908	11.760		
Radiation treatment given:	None	46993	79.990	0.52	0
	Refused	640	1.089		
	Recommended, unknown if administered	326	0.555		
	Unknown	2339	3.981		
	Beam radiation	8219	13.990		
	Radiation, NOS method or source not specified	187	0.318		
	Radioisotopes	22	0.037		
	Combination of beam with implants or isotopes	8	0.014		
	Radioactive implants	13	0.022		
Reason no cancer-directed:	Not recommended	39818	67.780	0.58	0
Surgery:	Surgery performed	9500	16.170		
	Recommended but not performed, unknown reason	2592	4.412		
	Recommended but not performed, patient refused	977	1.663		
	Unknown; death certificate or autopsy only case	2472	4.208		
	Not recommended, contraindicated due to other conditions	2944	5.011		
	Not performed, patient died prior to recommended surgery	175	0.298		
	Recommended, unknown if performed	269	0.458		
SEER cause-specific death	N/A not first tumor	10542	17.940		
classification	Dead	37737	64.240		
	Alive or dead of other cause	10468	17.820		
Derived AJCC Stage Group,	IA, level I	845	1.438	0.57	0.01
6th ed (2004+)	IB, level II	2820	4.800		
	IIA, level III	5234	8.909		
	IIB, level IV	6256	10.650		
	IINOS, level V	450	0.766		
	III, level VI	4330	7.371		
	IV, level VII	27147	46.210		
	UNK Stage, level VIII	10965	18.660		
	NA, level IX	700	1.192		

*Model: I,II,III,IV; **Model: optimized; ***Model: (I,II),III,IV

Table 2. Absolute Cause Specific Mortality (%) Associated with Different Models

Variables: Risk models		No. at risk	expected risk of death
Age of diagnosis:			
	<20 years	32	0.16
	≥20 years old	58715	0.64
Sex:	Female	29590	0.65
	Male	29157	0.63
Grade:	Well differentiated; Grade I	2594	0.42
	Moderately differentiated; Grade II	7359	0.54
	Poorly differentiated; Grade III	7612	0.63
	Undifferentiated; anaplastic; Grade IV	553	0.62
	Unknown	40629	0.68
Rural-Urban Continuum Code 2003:			
	Counties in metropolitan areas ge 1 million pop/ Counties in metropolitan areas of 250,000-1 million pop/ Urban pop of ge 20,000 adjacent to a metropolitan area versus	48269	0.64
	Others	10478	0.66
County Family Income:			
	≥$50000	32540	0.63
	<$50000	26207	0.66
County % college graduate:			
	≥25	27224	0.63
	<25	31523	0.65
Race:	White/others	51839	0.64
	Black	6908	0.65
Radiation treatment given:			
	Beam Radiation	8219	0.58
	Others	50528	0.65
Reason no cancer-directed surgery:			
	Surgery performed	9500	0.41
	Others	49247	0.69
SEER Staging:			
	Localized	5345	0.45
	Regional	15813	0.55
	Distant	29764	0.71
	Un-staged/others	7825	0.71
Derived AJCC Stage Group, 6th ed (2004+):			
	IA	845	0.32
	IB	2820	0.46
	IIA	5234	0.54
	IIB	6256	0.52
	IINOS	450	0.63
	III	4330	0.64
	IV	27147	0.71
	UNK Stage	10965	0.69
	NA	700	0.25

follow up time (S.D.) was 7.6 (10.6) months. SEER stage (Figure 2a) and grade (Figure 2b) were strongly predictive univariates. Sex, race, and three socio-economic factors (SEER county level family income, rural-urban residence status, and county level education attainment) were independent multivariate predictors (Table 3). Racial and socio-economic factors were associated with about 2% difference in absolute cause specific survival (Table 2). The absolute risk of death from pancreatic cancer was 64.2% for the entire study population. Only 32 SEER patents younger than 20 years old were diagnosed with pancreatic cancer from 2004-2009. They had a 15.6% risk of cause specific death compared with 64.3% for the older patients (Table 2). There was slightly higher risk of cause specific death for female and male patients (Table 2). Pancreatic adenocarcinomas accounted for about 1/3 of all cases. Pancreatic adenocarcinomas had a similar risk of cause specific death compared with other histological types (Table 2). The risk of cause specific death was 42% for grade I, 54% for grade II, 63% for grade III and 62% for grade IV. Being un-graded had a 68% risk of cause specific death.

SEER staging was more accurate in terms of measured ROC areas (Table 1). Using SEER stage, there was a 45% and 55% risk of death respectively for localized and regional disease respectively. This risk increased to more than 71% for distant metastasis. When the staging was not complete, it was associated with 71% risk of death (Table 2) that is same as that of the metastatic disease. The three socio-economic factors, lower county family income, rural residence, and lower county education attainment were associated with about 2% disadvantage in cause specific survival. Radiotherapy had a 7.6% cause specific survival advantage. Surgery was associated with 40.9% risk of pancreatic cancer death while 68.7% risk of death was associated with no surgery performed. For the SEER stage model, the staging was defined as localized, regional, distant or incompletely staged/others. The stage status was highly predictive of cause specific survival (ROC area or 0.60). This 4-tiered staging model was optimized to a 3-tiered model consisted of localized/regional versus distant versus un-staged/others with a ROC area of 0.59

Table 3. Univariate Kolmogorov-Smirnov's 2-sample Tests and Multivariate Cox Proportional Hazard Models

		Kolmogorov-Smirnov 2-sample test			Cox proportional hazard model		
		l	p	k	beta	s.e.	p
SEER stage	0=local/regional 1=metastatic/unstaged	1	1.32E-17	0.7619	0.7741	0.0118	0
Grade	0=grade 1-2 1=grade 3-4, ungraded	1	4.97E-16	0.7231	0.5541	0.0156	0
Sex	0=female 1=male	0	0.1692	0.1896	-0.0391	0.0105	0.0001
Race	0=non African American 1=African American	0	1	0.0565	0.0811	0.016	0
Rural Urban residence	0=urban 1=rural	0	0.9503	0.0908	0.0543	0.0143	0.0001
County level %college graduate	0>25% 1≤25%	0	0.3948	0.1538	0.0311	0.0144	0.0311
County level family income	0≥$50k/year 1≤$50k/year	0	0.2026	0.1818	0.0614	0.0148	0

*The l is equal to 1 for positive pair-wise comparison of the survival curves as measured by statistics k. Cox proportional hazard coefficients and their standard errors are respectively beta and s.e

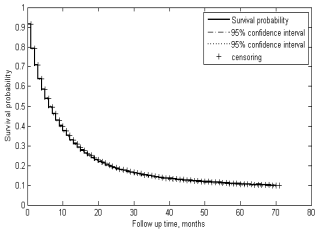

Figure 1. Kaplan-Meier Plot of Pancreatic Cancer Cause Specific Survival of SEER Patients. The 95% confidence intervals and censoring markers '+' were shown but were very close to each others

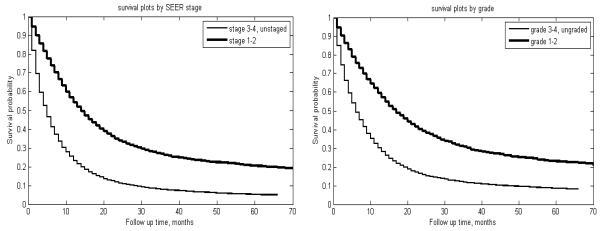

Figure 2. The Kaplan-Meier Survival Plots by Risk Stratification Based on a) SEER Stage and b) Grade. The results of their respective 2-sample Kolmogorov-Smirnov's tests were shown in Table 3

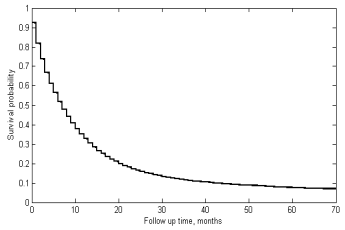

Figure 3. The Cox Proportional Hazard Fit Based on the Parameters

(Table 1).

Figure 2 shows the survival curves separated by univariates including a) SEER stage and b) grade. Table 3 shows the results of the univariate analysis. SEER stage and grade were very strong predictors and were very statistically significant. Sex, race and socio-economic predictors were not significant in univariate analysis (Table 3). When all the pretreatment and socio-economic factors were analyzed in a multivariate analysis, all of the predictors became statistically significant (Table 3). Female sex was shown to have a higher cause specific mortality (Table 2) and under Cox multivariate analysis (Table 3). The Cox proportional hazard fit for the model is shown in Figure 3.

Discussion

The effects of socio-economic factors on the treatment outcome of pancreas cancer have been controversial. Some studies have linked low socio-economic status with poor pancreas outcome (Brown et al., 1998). This link has been attributed to an increased distance to major medical centers (Gill and Martin, 2002), and a lack of specialization (van Oost et al., 2006). Other studies have shown a lack of effects from socio-economic factors on pancreas cancer treatment outcome (Kuhn et al., 2010). The Surveillance Epidemiology and End Results (SEER) cancer registry data have been to build prognostic models for pancreatic cancer (Baine et al., 2011; Singal et al., 2012). SEER data have been a particularly important source for identifying disparities in cancer treatment. However, the nature of the socio-economic barriers in good outcome for pancreatic cancer has not been well characterized. This study also examined socioeconomic factors that were predictors of treatment outcome. Receiver operating characteristic (ROC) curve was used to construct and measure the accuracy of models from (Cheung, 2012) SEER outcome data. In addition to constructing the best predictors of absolute cause specific survival for pancreas cancer (Figure 1 and Table 1-2), this study also aimed to identify barriers to good treatment outcome that might be discernable only from a large national database.

In order to be consistent over decades, SEER historical stage abstracts the staging into simple but important stages for cancer progression: localized, regional and distant. SEER stage was highly predictive of patient outcome (Table 1, 2). The model has a ROC area of 0.60. Thus complete staging is important in this disease since it will aid patient selection and council. Regional pancreatic cancer was an aggressive disease; there was a 55% risk of cause specific (Table 2). These are patients most likely to benefit from radiotherapy (Franko et al., 2012; Worni et al., 2012). Thus radiation oncologist should be more attentive in recommending RT for these patients. After optimization the 4-tiered stage model was reduced to a 3-tiered model based on ROC area calculations (Table 1) with essentially the same ROC area but with the improved simplicity.

An important and thought provoking recent 10-15 years long term study has shown that moving patients from low income neighborhoods to high income ones improve their obesity and diabetes (Ludwig et al., 2011). It is conceivable that similar effects may be observed for cancer patients including pancreatic cancer patients. In this study, SEER stage (Figure 2a) and grade (Figure 2b) were significant predictors of actuarial cause specific survival of pancreas cancer (Table 3). The socio-economic factors were not significant as univariate predictors, this were probably due the masking effects of the very strong SEER stage and grade predictors. When these factors were accounted for in a multivariate Cox (Figure 3) analysis, rural residence, living in low income and low education attainment neighborhoods decreased cause specific survival of pancreatic cancer (Table 3).

In conclusion, this study has found significant effects of socio-economic factors on pancreas cancer outcome. These data may generate hypotheses for trials to eliminate these outcome disparities.

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