Original Article

Investigating disparities: the effect of social environment on pancreatic cancer survival in metastatic patients

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Background: Pancreatic adenocarcinoma (PCA) incidence is higher in Black compared to White patients. Beyond race, neighborhood socioeconomic status (nSES) may also inform disparities. However, these effects on metastatic pancreatic adenocarcinoma (mPCA) are not well-studied. The aim of this study was to explore whether nSES influences survival in patients with mPCA.

Methods: nSES measures were derived from U.S. census data at the census tract (CT) level. We correlated medical records of mPCA patients (diagnosed 2010-2016; n=370) to nSES measures retrospectively via a geocode derived from patient address. Multivariable cox proportional hazards models were used to identify patient-level (age, sex, race, marital status, treatment (radiation/chemo/surgery), PCA family history, stage, Jewish ancestry, tobacco use, BMI, diabetes, and statin use) and nSES measures (deprivation, racial concentration, stability, transportation access, immigration) associated with mPCA survival; P values <0.05 were significant.

Results: Eighty-two percent of patients were White; less than one-third of patients resided in highly deprived neighborhoods. Three hundred thirty-three mPCA patient deaths occurred, with a survival ranging from 7–9 months (median 8 months). Patient-level factors including younger age, receipt of chemotherapy or initial surgery and statin use, were associated with improved survival, whereas neighborhood stability (i.e., a higher % of residents still living in the same house as 1 year ago) was significantly associated with poor pancreatic survival.

Conclusions: Our findings suggest nSES has limited effect on survival of mPCA patients as compared to clinical variables. This may be due to the aggressive nature of this cancer, however, additional studies with larger, more diverse cohorts are needed to better understand the effect of nSES on survival of patients with mPCA.

Keywords: Pancreatic cancer; survival; social determinants; neighborhood; health disparities

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Introduction

Pancreatic adenocarcinoma (PCA) has a poor prognosis, with an average 5-year survival rate of 8.5% (1) and a median survival after diagnosis of metastatic disease of about 12 months (1). The poor outcomes of PCA can be partially explained by the difficulty of detecting the disease early, leading to an often-advanced clinical presentation. Health disparities may also affect disease outcome, and prognosis.

Incidence rates of PCA are over 50% higher in African-American patients compared to rates in White patients or any other racial group (2). Several studies have demonstrated decreased survival among African American and Hispanic patients with PCA (3-5). Beyond race/ethnicity, other social determinants of health such as socio-economic status (SES) (i.e., low education, employment, income) also have been identified as independent, negative prognostic variables for PCA survival (4-6). Patients with higher SES were found to be more likely to undergo surgery, chemotherapy and radiation treatments, which improve outcomes in PCA (5,6). Further, investigations into the interaction between race and SES have suggested that the observed survival difference between racial groups can be partly accounted for by treatment disparities and variation in a patient's SES (5).

Macro-environmental factors including neighborhood socioeconomic status (nSES) can also contribute to cancer disparities. nSES is often defined by U.S. Census in cancer studies as variables related to SES that describe the economic (e.g., employment, income, poverty), physical (e.g., housing/transportation structure), and social (e.g., education, immigration/migration) characteristics of a person's place of residence (7). There are at least two hypotheses that may explain how nSES can impact cancer outcomes. First, under a chronic stress hypothesis, residents from disadvantaged neighborhoods could experience greater emotional stress and constant "wear and tear" on the body that can affect cancer initiation and progression (8). Second, low nSES may correlate with factors related to health care access, particularly access to quality treatment (9).

In PCA, a recent population-based study showed that nSES remained significantly associated with PCA survival, even when adjusted for patient-level variables, including age, race, insurance and marital status (10,11). However, this study and other similar studies are limited by a lack of information regarding well-known patient clinical comorbidities (i.e., smoking, diabetes), which can have an effect on PCA outcomes (12,13). Further, the majority of prior SES studies in PCA focused primarily on early-stage disease when most patients are diagnosed with advanced disease (4,12,13). Thus, the relationship between nSES and metastatic disease remains uncharacterized. Therefore, the goal of this study was to investigate whether nSES measures are associated with survival in a population of metastatic pancreatic adenocarcinoma (mPCA) patients who were treated at a tertiary cancer center and have both detailed health record and nSES data. Additionally, this study sought to determine whether nSES variables can improve prediction of mPCA survival models, which typically only consider patient-level data. We present the following article in accordance with the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jgo-20-39.

Methods

Study population

Retrospective collection of patient data was approved by Fox Chase Cancer Center IRB (IRB #11-815). A waiver of informed consent was obtained from the IRB due to the study's retrospective design.

With IRB approval, patients diagnosed with mPCA at Fox Chase Cancer Center (Philadelphia, PA), a tertiary care center, between 2010 and 2016 were retrospectively identified using the institution's tumor registry (IRB #11-815). Cases included patients who presented with metastatic disease, as well as patients who presented with earlier stage disease and later recurred. Cases with incomplete medical record data, missing address information, or with a histologic diagnosis other than PCA were excluded, resulting in a total study population of 370 patients. The primary clinical outcome of interest was overall survival from date of diagnosis of metastatic disease. Information regarding date of death was obtained through the tumor registry. Patients who were living as of December 31, 2016 or date of last follow-up were considered censored.

Patient variables

Each patient chart was examined and quality control checked by two independent reviewers to ensure accuracy of the data. Risk factors previously found to be associated with pancreatic cancer risk or survival were included in this analysis: age (1), sex (1), race (1,5), body mass index (BMI) (14), diabetes (15) (yes/no), statin use (16) (yes/no), tobacco use (17) (yes/no), self-identified Jewish

ancestry (18), family history of PCA (18), and marital status (10) (married, not married). Stage at diagnosis was documented, in addition to the received treatment modalities during the disease course (radiation, chemotherapy, and surgical resection prior to diagnosis of metastatic disease). We included chemotherapy administered at or after the time of metastatic diagnosis regardless of regimen or number of drugs used. In addition, radiation therapies were directed at the tumor, rather than palliative treatment for metastases. Age-adjusted Charlson Comorbidity Index (CCI) was calculated for each patient by utilizing the published scoring method (19).

nSES variables

Our study looked at nSES variables that have been found to be associated with outcomes related to cancer and other health conditions (11,20-23). Variables of interest included: (I) deprivation (24), (II) racial concentration (25), (III) transportation access (the % of residents owning a vehicle), (IV) immigration (the % of foreign born residents), and (V) neighborhood stability (the % residents living in the same house as one year prior). Deprivation was measured using a previously validated composite SES measure, created by principal component analysis of seven indicator variables: education (out of individuals age 25 and older, proportion with college, high school and less than high school weighted by 16, 12 and 9 respectively), proportion with a blue collar job, proportion older than age 16 in the workforce without a job, median household income, percent below 200% of the poverty line, median rent, median house value. Deprivation scores for the state of PA ranged from –4.36 (negative scores indicate high deprivation) to 4.99 (positive scores indicate low deprivation). The index is categorized into quintiles based on the census tract values for the overall state with 1 being the highest level of deprivation and 5 being the lowest level of deprivation. Racial concentration (RC) was defined as the degree of isolation/separation of racial/ethnic groups in a neighborhood, with a standard score ranging from –1 [concentration of Non-Hispanic Blacks (NHB)] to 1 [concentration of Non-Hispanic Whites (NHW)]. This measure was categorized into quartiles, based on prior literature (11). Transportation access, immigration, and stability were analyzed as continuous variables.

nSES variables were derived from the U.S. Census American Community Survey (ACS) collected at the census tract level between 2011 and 2015. Census tracts are geographic subdivisions of a county used for the purpose of government population tracking, with an average of 4,000 residents residing in each tract (26). Residential addresses of mPCA patients were geocoded up to the census tract level and assigned a Federal Information Processing Standard (FIPS) geocode (27,28) at the census tract level using Arc GIS software v. 10.6. (ESRI; Redlands, CA). Patient information was then linked to the nSES variables from the U.S. census mentioned above via the FIPS code using Stata v. 11.0 (College Station, TX). Thus, patients residing in the same census tract were assumed to have the same neighborhood characteristics. There were 312 unique census tracts included in this analysis.

Statistical analysis

The relationship between survival, patient-level variables and nSES variables were assessed in multivariable models with and without nSES variables via mixed effect Cox proportional hazards regression models. We accounted for potential clustering effects of individuals within the same CT using random effects (29,30). Hazards ratios and 95% confidence intervals (95% CI) are presented. Variables with P values <0.05 were considered significant. To preliminarily assess the potential clinical relevance of nSES variables, multivariable models with patient-only variables were compared to multivariable models with both patient and nSES variables using likelihood ratio tests (31), time-varying receiver operating characteristic (ROC) curves estimates (32), and the Akaike Information Criteria (AIC) (33).

Results

The study population included 370 patients with mPCA. *Table 1* shows a summary of both patient-level and nSES variables that were considered in the analysis. Patient diagnosis age ranged from 27–89 years (mean 65.6 years), slightly more than half of the patient population was male, and about 80% were NHW. Median survival was 8 months (average follow-up time for all cases =10 months) after metastatic diagnosis with 90% of patients deceased by the end of the study period (December 31, 2016). Most individuals were diagnosed with metastatic (stage IV) disease, and 90% of patients received chemotherapy treatments. About two-thirds of patients had a history of tobacco use, 63% were married, 35% had a history of diabetes, 39% used statins, 14% had a family history of PCA, and 9% had Jewish ancestry.

Table 1 Patient characteristics at diagnosis of metastatic disease

Characteristics	Overall (n=370)
Patient-level factors	
Age (years)	
Mean (SD)	65.6 (10.2)
Median (range)	66.0 (27.0–89.0)
Sex, n (%)	
Male	193 (52.2)
Female	177 (47.8)
Race, n (%)	
Non-Hispanic White (NHW)	304 (82.2)
Non-Hispanic Black (NHB)	52 (14.1)
Other	14 (3.8)
Marital status, n (%)	
Married	232 (62.7)
Not married	138 (37.3)
BMI	
Mean (SD)	25.8 (5.32)
Median (range)	25.2 (14.6–66.2)
Stage at diagnosis, n (%)	
Stage IV	247 (66.8)
Stages I–III	123 (33.2)
Received chemotherapy, n (%)	
No	36 (9.7)
Yes	334 (90.3)
Received radiation, n (%)	
No	259 (70.0)
Yes	111 (30.0)
Received surgery, n (%)	
No	292 (78.9)
Yes	78 (21.1)
History of tobacco use, n (%)	
No	125 (33.8)
Yes	245 (66.2)
History of diabetes, n (%)	
No	242 (65.4)
Yes	128 (34.6)
Family history of pancreatic cancer, n (%)	
No	316 (85.4)
Yes	50 (13.5)
Missing	4 (1.1)
Use of statins, n (%)	
No	225 (60.8)
Yes	145 (39.2)
Jewish ancestry, n (%)	
No	338 (91.4)
Yes	32 (8.6)
Neighborhood-level factors	
Racial concentration, n (%)	
Q1-concentration of NHB	50 (13.5)
Q2	79 (21.4)
Q3	141 (38.1)
Q4-concentration of NHW	100 (27.0)
nSES conditions, n (%)	
Q1-low SES	39 (10.5)
Q2	38 (10.3)
Q3	56 (15.1)
Q4	78 (21.1)
Q5-high SES	149 (40.3)
Missing	10 (2.7)
Stability	
Mean (SD)	0.906 (0.0524)
Median (range)	0.912 (0.554–0.993)
Immigration	
Mean (SD)	0.101 (0.0820)
Median (range)	0.0789 (0.00–0.433)
Transportation access	
Mean (SD)	0.834 (0.122)
Median (range)	0.872 (0.283–0.983)

Sixty-one percent of patients lived in areas with low deprivation. Approximately half of patients in the study lived in neighborhoods which were categorized as high stability, low % immigration, and high transportation access (i.e., neighborhoods were above the median for these variables). For residential concentration, over a quarter of patients lived in neighborhoods with high concentration of NHW and 14% lived in areas with high concentration of NHB.

Referring to *Table 2*, patient-level variables that were found to be significant predictors of survival were consistent across multivariable models. Increasing age was associated with an increased hazard of death [HR =1.24 (95% CI: 1.08–1.42); P<0.001]. The following patient variables demonstrated inverse relationship with risk of death including: chemotherapy treatment [HR =0.13 (95% CI: 0.08–0.21); P<0.001], initial surgical resection [HR =0.54 (95% CI: 0.36–0.81); P=0.003], and statin use [HR =0.76 (95% CI: 0.58–0.99); P=0.025]. In the multivariable model with both patient and nSES measures, only the nSES measure of stability (the % residents living in the same house as one year prior) was statistically significant [HR =1.03 (95% CI: 1.001–1.06); P=0.036]. The remaining nSES variables, which included deprivation index (P=0.784), transportation access (P=0.387), racial concentration (P=0.787) and immigration (P=0.648), were not statistically significant.

To preliminary assess the potential clinical relevance of nSES measures, we compared a multivariable model with patient-level variables only to a multivariable model with both patient and a nSES variable (neighborhood stability). After the addition of neighborhood stability, a decrease in AIC was observed, indicative of improved model fit [AIC patient variable only multivariable model (71.51) *vs.* AIC with nSES (50.03)]. In addition, the likelihood ratio test showed that this improvement was statistically significant (P=0.002). However, referring to *Figure 1*, the area under the ROC curve at 12 months decreased when including the nSES with the significant patient-level variables, indicating that including neighborhood stability does not help to improve prediction of mPCA survival.

Discussion

Health disparities in pancreatic cancer is an understudied area. While studies comparing PCA disease rates by race/ethnicity (2,4) have been conducted, very few also incorporate or study the role of other determinants of disparity such as the effect of nSES. This is the first study to investigate the effect of nSES on pancreatic cancer survival in a group of metastatic patients. Our study found that patients diagnosed with mPCA between 2010–2016 have a median survival of 8 months, which is consistent with the national average of 8–11 months (1,34). We found that while neighborhood stability appeared significantly related to shorter mPCA survival, the addition of this variable did not improve prediction of mPCA survival more than patient variables.

The inverse association between neighborhood stability and PCA survival was not in the expected direction. Previous studies have suggested that neighborhood stability may contribute to stronger social networks and lower perceived stress that can lead to improved health outcomes (35-37). Our results demonstrated an association between high neighborhood stability and decreased survival in mPCA patients. While the direction of this relationship generally does not follow the hypotheses put forth in previous studies (36,37), one study did find an association between residential stability and increased odds of diabetes, a risk factor for pancreatic cancer (23). Thus, while it is possible that this nSES finding could be a spurious association, there still remains a lack of empiric evidence linking neighborhood stability to cancer outcomes specifically. Further, the majority of patients in our study come from high nSES environments and it's likely that the lack of nSES variation in our sample (i.e., limited heterogeneity) would make it insufficient to detect possible associations between nSES and mPCA. Given the finding of a significant association between nSES and mPCA survival in our relatively homogenous sample suggests that future investigations in larger, more socioeconomically diverse study populations are warranted.

Our standard model demonstrated several patient-level variables as significant predictors of survival. These variables included age, receipt of chemotherapy, and initial surgical resection of the primary tumor. Our findings are consistent with the literature, in which the effect on survival by these factors has been well established (5,6,38-41). This result provides validation to the survival model in this study. One relatively novel patient-level finding in this study was the significant effect of statin use on PCA survival. This finding supports available literature which suggests that statins may slow tumor development and progression by disrupting expression and activity of downstream proteins involved in cell signaling and growth (42-44). Epidemiologic studies have also demonstrated an inverse relationship between statin use and pancreatic cancer risk (16,45). Additionally, there is some evidence that statin use after pancreatic cancer diagnosis is

Table 2 Association of patient-only and neighborhood socioeconomic status (nSES) variables with metastatic pancreatic cancer survival

Variables	Patient variables only model			Patient and nSES variables model		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.22	1.06–1.39	<0.001	1.24	1.08–1.42	<0.001
Sex			0.694			0.694
Male	Ref.			Ref.		
Female	0.92	0.71–1.19		0.91	0.71–1.18	
Race			0.784			0.784
White	Ref.			Ref.		
Black	0.96	0.66–1.39		0.99	0.65–1.51	
Other	0.80	0.42–1.53		0.86	0.45–1.64	
Marital status			0.841			0.841
Married	Ref.			Ref.		
Not Married	1.06	0.82–1.38		1.07	0.82–1.40	
BMI	1.02	1.00–1.05	0.154	1.02	0.99–1.05	0.154
Stage			0.702			0.702
High	Ref.			Ref.		
Low	1.57	1.08–2.27		1.65	1.13–2.39	
Received chemotherapy			<0.001			<0.001
No	Ref.			Ref.		
Yes	0.12	0.08–0.20		0.13	0.08–0.21	
Received radiation			0.181			0.181
No	Ref.			Ref.		
Yes	0.83	0.59–1.17		0.78	0.55–1.10	
Received surgery			0.003			0.003
No	Ref.			Ref.		
Yes	0.55	0.37–0.84		0.54	0.36–0.81	
Tobacco use			0.141			0.141
No	Ref.			Ref.		
Yes	1.22	0.93–1.60		1.15	0.88–1.51	
History of diabetes			0.890			0.890
No	Ref.			Ref.		
Yes	1.04	0.80–1.36		1.04	0.80–1.35	
Family history of pancreatic cancer			0.061			0.061
No	Ref.			Ref.		
Yes	0.68	0.46–0.99		0.68	0.47–1.00	
Unknown	1.80	0.58–5.53		1.96	0.63–6.07	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Patient variables only model			Patient and nSES variables model		
	HR	95% CI	P value	HR	95% CI	P value
Use of statins			0.025			0.025
No	Ref.			Ref.		
Yes	0.74	0.57–0.97		0.76	0.58–0.99	
Jewish ancestry			0.724			0.724
No	Ref.			Ref.		
Yes	0.91	0.57–1.44		0.83	0.51–1.36	
Racial concentration*						0.787
Q1	–	–	–	Ref.		
Q2	–	–	–	0.79	0.53–1.17	
Q3	–	–	–	0.82	0.52–1.31	
Q4	–	–	–	0.80	0.48–1.35	
Deprivation index*						0.748
Q1	–	–	–	Ref.		
Q2	–	–	–	1.24	0.69–2.23	
Q3	–	–	–	1.11	0.63–1.98	
Q4	–	–	–	0.92	0.53–1.59	
Q5	–	–	–	0.95	0.56–1.62	
Unknown	–	–	–	1.01	0.41–2.45	
Immigration (% foreign born)	–	–	–	0.58	0.11–3.07	0.648
Stability (% living in the same home as 1 year ago)	–	–	–	1.03	1.00–1.06	0.036
Transportation access (the % of residents owning a vehicle)	–	–	–	1.92	0.44–8.34	0.387

*: Q1, quartile 1 (most deprived), Q2, Q3, Q4, quartile 4 (least deprived).

associated with enhanced survival (46,47). Our results are consistent with the reported protective role of statins that has been described. However, our data does not include the duration and dose of statin therapy or patient adherence to therapy. This limits our ability to interpret this association.

In our study, patient-level factors played a more significant role in mPCA survival, suggesting treatment approaches have a higher impact on survival compared to nSES measures and even well-known patient-level risk factors, including diabetes or obesity (48). This is evidenced by the fact that ROC curve estimates were lower when including nSES variables in the survival model. This suggests there could be a point along the cancer continuum where environmental effects or patient comorbidities may cease to impact cancer outcomes. The majority of studies conducted in nSES and cancer emphasize the impact of nSES on disease development, with less of an emphasis on progression or response to treatments (23,24,49-56). Thus, it's possible that these factors may have less of a role in the setting of advanced cancer or that the short survival of our patient cohort limited the ability to evaluate the effect of these neighborhood variables. That is, under the chronic stress hypothesis, constant exposure to stressful environments could lead to cancer initiation and progression, but once the disease progresses to a certain stage, environmental effects are minimized (57,58).

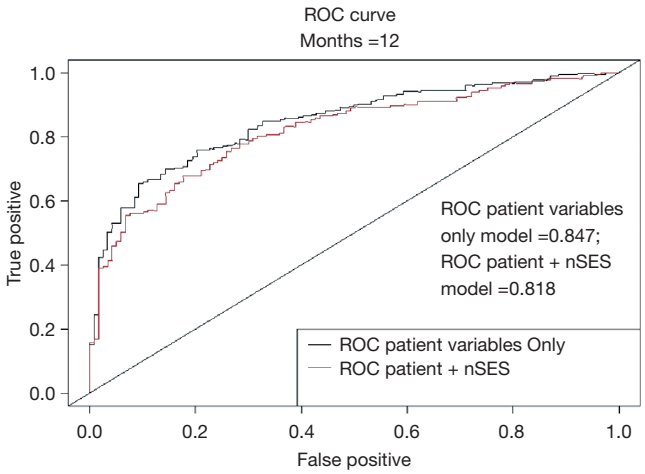

Figure 1 Twelve-month survival receiver operating characteristic (ROC) curves for patient-only and patient + neighborhood socioeconomic variables (nSES) models.

Additional studies would be needed to test this hypothesis in larger more heterogeneous cohorts.

While this study included detailed patient and nSES data, it had a number of limitations. The nSES variables selected in this study are commonly used in cancer studies (11), but there is no agreed upon, standard variable selection process in nSES and cancer research, which can limit the consistency and comparability across studies (59). We were unable to investigate all patient-level variables used in previous mPCA survival studies due to data availability (60,61). However, our study was the first to consider nSES together with patient-level factors and future studies that incorporate addition clinical and nSES variables are warranted. Additionally, the sample size was small and lacked representation by relevant subgroups, including race/ethnicity and stage. Further, this was a single institution study and therefore does not account for regional variations. The majority of patients who present to our center are medically insured, which limited our conclusions and investigations into the effects of health care access on PCA survival. All patients included in this study had metastatic disease while previous literature suggests that nSES effects could differ by stage of disease (62,63). Thus, conducting this analysis in a cohort with more representation from all disease stages, and across race/ethnic and SES gradients may be warranted.

While the results of this study do not fully characterize the relationship between social determinants of health and survival of patients with mPCA, the methodology used represents a novel and potentially clinically useful technique for identifying at risk patient populations. Social determinants of health, like the nSES data used in this study, are rarely, if ever, used by clinicians to guide treatment decisions for their patients. Utilizing information about a patient's economic, physical and social environment can enhance patient care by taking a more holistic approach; one with a more complete understanding of the factors that influence a patient' health. While nSES data is readily available through archives such as the U.S. Census, it's accessibility to clinicians is limited by lack of a strategy to combine this trove of data with more familiar clinical variables. Geocoding can provide a link between clinical data and the social and physical environmental factors. Research that provides insight into the effect of social determinants of health, like neighborhood, on health outcomes would provide clinicians with another resource to help deliver personalized care to patients, particularly to those patients on a disparity-related pathway to disease, who may be at risk for poor outcomes due to socioeconomic circumstances.

Conclusions

In this study, there was suggestion of decreased survival in patients residing in more stable neighborhoods. However, the addition of nSES data to survival models with patient-level variables did not improve prediction accuracy. Consistent with prior data, our results demonstrate that age, receipt of chemotherapy, and initial surgical resection of the primary tumor were significant predictors of survival in this patient population, along with statin use. Further research is warranted to examine nSES effects on mPCA in a larger, more diverse cohort of patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at: http://dx.doi.

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-39). The authors have no conflicts of interest to disclose.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The research was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Retrospective collection of patient data was approved by Fox Chase Cancer Center IRB (IRB #11-815). A waiver of informed consent was obtained from the IRB due to the study's retrospective design.

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