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Long-Term Survivors of Pancreatic Cancer

A California Population-Based Study

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Objectives: Pancreatic cancer continues to carry a poor prognosis with survival rates that have had minimal improvement over the past 4 decades. We report a population-based, comprehensive analysis of long-term survivors of pancreatic adenocarcinoma diagnosed in the diverse population of California.

Methods: Data from the California Cancer Registry were used to evaluate long-term survival. A total of 70,442 patients diagnosed with pancreatic adenocarcinoma between 1988 and 2009 were identified. Logistic regression was used to identify factors associated with achieving 5-year survival.

Results: The overall 5-year survival was 2.5%, with minimal incremental improvements throughout the 3 decades. Age, stage, degree of differentiation, and surgical resection were associated with 5-year survival. Furthermore, younger age and receiving care at a National Cancer Institute–designated cancer center were similarly correlated with 5-year survival regardless of surgical intervention. In addition, we identified stage, differentiation, and adjuvant chemotherapy as significant factors for long-term survival in surgically resected patients. In the unresectable patients, Asian/Pacific islanders and Hispanics were significantly more likely to reach the 5-year milestone than non-Hispanic whites.

Conclusions: Although pancreatic cancer mortality remains high, our study highlights baseline characteristics, treatment, biological factors, and ethnicity that are associated with long-term survival. These findings may serve as a springboard for further investigation.

Key Words: pancreatic adenocarcinoma, long-term survival, surgical resection, chemotherapy, differentiation, race/ethnicity

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Pancreatic cancer is the third leading cause of cancer-related deaths in the United States. More than 53,000 new cases and over 41,000 deaths occur annually.[1] Moreover, it is estimated to become the second-leading cause of cancer death in the United States by 2020.[2] Despite the various advances in multimodality treatment, long-term survival rates continue to range between 8% and 10%.[1,3,4] Surgical resection remains the only potentially curative modality for patients with pancreatic cancer. However, only 15% to 20% of patients qualify for resection, because most tumors are locally advanced or metastatic at the time of diagnosis. Nevertheless, patients who undergo successful resection and adjuvant therapy have 5-year survival rates of approximately 20%, with a median survival time of 25 to 30 months.[2,3,5,6]

Therefore, there is a pressing need to decipher the underlying elements responsible for the long-term survival of patients with pancreatic cancer including genetic, immune and molecular mechanisms, as well as clinical outcome and racial-socioeconomic disparities. To date, there are very few population-based survival studies analyzing long-term survival of patients with pancreatic adenocarcinoma.[7–9] However, these analyses are limited and do not include data from the most recent decade, nor they do investigate racial-socioeconomic disparities. Racial and socioeconomic disparities have been increasingly highlighted recently, due to growing evidence of these inequalities in various aspects of the US health care system.[10,11] Therefore, we report a population-based, comprehensive analysis of long-term survivors of pancreatic adenocarcinoma diagnosed from 1988 to 2009 in the diverse population of California.

MATERIALS AND METHODS

The California Cancer Registry (CCR) is a state-mandated registry that was established in 1985 and routinely abstracts demographic, tumor, and treatment data on all cases diagnosed in the state. The 4 regional registries comprising the CCR are part of the national Surveillance, Epidemiology, and End Results (SEER) program and case ascertainment is estimated to be greater than 95% complete.[12] We obtained data from the CCR on all cases diagnosed with invasive pancreatic cancer between January 1, 1988, and December 31, 2009 (n = 70,442), excluding cases diagnosed on death certificate or autopsy (n = 2067), without valid dates of diagnosis or follow-up (n = 1384), without microscopically confirmed tumors (n = 15,133), with histologies other than

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TABLE 1. Characteristics of Cases With Microscopically Confirmed Pancreatic Adenocarcinoma Diagnosed in California, 1988–2009

		Survived at Least 5 Years	
	All, n = 39,460, n (%)	**No, n = 38,473, n (%)**	**Yes, n = 39,460, n (%)**
Age at diagnosis, y			
0–49	2604 (6.6)	2493 (6.5)	111 (11.2)
50–59	6235 (15.8)	6031 (15.7)	204 (20.7)
60–69	10,965 (27.8)	10,673 (27.7)	292 (29.6)
70–79	12,974 (32.9)	12,679 (33.0)	295 (29.9)
80+	2604 (6.6)	2493 (6.5)	111 (11.2)
Age at diagnosis, median (range), y	69 (19–103)	70 (19–103)	66 (21–90)
Sex			
Male	20,084 (50.9)	19,603 (51.0)	481 (48.7)
Female	19,376 (49.1)	18,870 (49.0)	506 (51.3)
Race/ethnicity			
Non-Hispanic white	27,478 (69.6)	26,820 (69.7)	658 (66.7)
Non-Hispanic black	3127 (7.9)	3070 (8.0)	57 (5.8)
Hispanic	5559 (14.1)	5408 (14.1)	151 (15.3)
Asian/Pacific islander	3296 (8.4)	3175 (8.3)	121 (12.3)
Quintile of neighborhood SES			
1	5720 (14.5)	5602 (14.6)	118 (12.0)
2	7402 (18.8)	7259 (18.9)	143 (14.5)
3	8371 (21.2)	8178 (21.3)	193 (19.6)
4	8732 (22.1)	8495 (22.1)	237 (24.0)
5	9235 (23.4)	8939 (23.2)	296 (30.0)
Anatomic location			
Head of pancreas	21,574 (54.7)	20,872 (54.3)	702 (71.1)
Body of pancreas	3822 (9.7)	3762 (9.8)	60 (6.1)
Tail of pancreas	3902 (9.9)	3834 (10.0)	68 (6.9)
Other, NOS	6871 (17.4)	6755 (17.6)	116 (11.8)
Overlapping lesion	3291 (8.3)	3250 (8.4)	41 (4.2)
Differentiation			
Well-differentiated	2714 (6.9)	2531 (6.6)	183 (18.5)
Moderately well-differentiated	8340 (21.1)	7939 (20.6)	401 (40.6)
Poorly differentiated, undifferentiated/anaplastic	9177 (23.3)	8973 (23.3)	204 (20.7)
Unknown	19,229 (48.7)	19,030 (49.5)	199 (20.2)
SEER summary stage			
Localized	2842 (7.2)	2592 (6.7)	250 (25.3)
Regional	13,768 (34.9)	13,190 (34.3)	578 (58.6)
Distant	19,884 (50.4)	19,774 (51.4)	110 (11.1)
Unknown	2966 (7.5)	2917 (7.6)	49 (5.0)
Summary treatment			
Surgery + chemo/radiation	3312 (8.4)	2856 (7.4)	456 (46.2)
Surgery only	3112 (7.9)	2826 (7.3)	286 (29.0)
Chemo/radiation only	14,120 (35.8)	13,994 (36.4)	126 (12.8)
None	18,916 (47.9)	18,797 (48.9)	119 (12.1)
Surgical resection			
No	33,036 (83.7)	32,791 (85.2)	245 (24.8)
Yes	6424 (16.3)	5682 (14.8)	742 (75.2)
Radiation			
No	32,520 (82.4)	31,880 (82.9)	640 (64.8)
Yes	6940 (17.6)	6593 (17.1)	347 (35.2)
Chemotherapy			
No	23,226 (58.9)	22,784 (59.2)	442 (44.8)
Yes	16,234 (41.1)	15,689 (40.8)	545 (55.2)

(Continued on next page)

TABLE 1. *(Continued)*

	All, n = 39,460, n (%)	Survived at Least 5 Years	
		No, n = 38,473, n (%)	Yes, n = 39,460, n (%)
NCI-designated cancer center			
No	33,552 (85.0)	32,854 (85.4)	698 (70.7)
Yes	5908 (15.0)	5619 (14.6)	289 (29.3)
Year of diagnosis			
1988–1995	12,133 (30.7)	11,927 (31.0)	206 (20.9)
1996–2003	13,626 (34.5)	13,311 (34.6)	315 (31.9)
2004–2009	13,701 (34.7)	13,235 (34.4)	466 (47.2)

NOS indicates not otherwise specified.

adenocarcinoma (n = 11,839), and who were not identified as non-Hispanic white, non-Hispanic black, Hispanic, or Asian/Pacific islander (n = 213).

The CCR routinely performs follow-up on patient vital status through hospital follow-up as well as regular linkages to other national and state databases, including state and national vital statistics, Social Security Administration, credit agencies, and the Department of Motor Vehicles. Vital status follow-up was complete through December 31, 2014. We calculated survival time in months from date of diagnosis to date of last contact or date of death, if deceased. Cases with less than 60 months survival time who were alive at the time of last follow-up, but whose vital status had not been confirmed as of December 31, 2014 (n = 257) were excluded as being lost to follow-up. Median follow-up for cases that were not deceased was 8.5 years (102.0 months; range, 60.1–315.5 months). The final cohort consisted of 39,460 patients.

For each patient, CCR abstracts age, sex, race/ethnicity, anatomic site of tumor, histology, extent of disease at diagnosis, first course of cancer-directed therapy (chemotherapy, radiation, and surgery), reporting hospital, and census-block group of residence at time of diagnosis. Anatomic subsite and histology were defined by specific *ICD-O-3* topography and morphology codes, respectively. Adenocarcinomas were identified based on the following *ICD-O-3* codes: 8140–8144, 8190, 8211, 8261–8263, 8290, 8310, 8440, 8500, 8503, 8560, 8570. Stage at diagnosis was defined using SEER summary stage (localized, regional, distant, unknown). SEER localized stage represents tumor confined to the pancreas, regional stage represents tumor with direct extension to adjacent organs or structures or spread to regional lymph nodes, and distant stage represents involvement of distant sites or lymph nodes. Because cancer registries generally do not collect individual-level information on patient socioeconomic status (SES), we determined the patient's neighborhood SES using a previously described index[13,14] that incorporates census measures of education, income, occupation, and cost of living. Each patient was assigned a quintile of neighborhood SES based on the neighborhood distribution of residents in California. Patients with a missing block group were randomly assigned to a block group within their county of residence.

The CCR identifies patients who have been diagnosed and/or treated at one of California's National Cancer Institute (NCI)–designated cancer centers. National Cancer Institute cancer center designation can be viewed as a proxy for facilities with greater availability of specialized care and higher patient and procedure volumes.

We compared demographic and tumor characteristics between 5-year survivors and those surviving less than 5 years, using χ^2 and *t*-tests, as appropriate. Kaplan-Meier curves of overall mortality were compared using log rank test. Logistic regression analysis was used to identify factors associated with the binary outcome of achieving the 5-year survival milestone. In this exploratory analysis, we modeled the effects with both univariate and multivariate regression of the following variables on the outcome: race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific islander), sex, age (continuous), SES quintile, anatomic tumor location (head, body, tail, overlapping/not otherwise specified), SEER summary stage (localized, regional, distant, unknown), receipt of care at an NCI-designated cancer center (yes/no), surgical resection with curative intent (yes/no), receipt of radiation (yes/no), receipt of chemotherapy (yes/no), and year of diagnosis (1988–1995, before any chemotherapy approval, 1996–2003, post approval of gemcitabine in 1996, and 2004–2009, post the final result of ESPAC-1 trial). We repeated the analysis stratified on surgical resection. All analyses were performed using SAS 9.4 (SAS Institute, Cary, Ind).

RESULTS

We identified 70,442 patients who were diagnosed with pancreatic adenocarcinoma between 1988 and 2009 in the CCR. Of those patients, 39,460 meet our inclusion criteria, and 987 (2.5%) survived at least 5 years (Table 1). For all patients, the median age at diagnosis was 69 years, with a similar distribution by sex. The majority of patients were non-Hispanic white (70%), followed by Hispanics (14.1%), Asian/Pacific islanders (8.4%), and non-Hispanic black (7.9%). Approximately half of the cases (48.7%) did not have pathological differentiation documented; of the documented cases, 23.3% were poorly differentiated or anaplastic tumors and 21.1% were moderately differentiated. As defined by SEER data, 7.2% of patients had localized disease, 34.9% had regional disease, and 50.4% of patients had distant disease, the remainder 7.5% had unknown SEER stage. Sixteen percent of all cases underwent surgical resection, 18% had radiation, and 41% received chemotherapy. Most patients (85%) did not receive care at an NCI designated cancer center. Yearly analysis of treatment modalities from 1988 to 2009 stratified by stage demonstrated interesting trends. The percentage of patients with regional disease who received surgery and systemic therapy increased since 1988, and the proportion of untreated patients decreased. Furthermore, the percentage of patients with distant disease who received chemotherapy and/or radiation treatment increased after the year 1996, whereas the percentage of nontreated patients decreased (Supplemental Fig. 1, http://links.lww.com/MPA/A664).

Long-term survivors (defined as alive after 5 years) were significantly younger at diagnosis, median age of 66 years, as compared with those who died before 5 years (median age of

70 years), and a greater proportion were of an Asian/Pacific islander or a Hispanic ethnic background. Furthermore, tumors of long-term survivors were more likely to be well or moderately differentiated, and the majority were located at the head of the pancreas. As expected, a greater proportion of long-term survivors had localized disease at diagnosis. Interestingly though, distant disease did not preclude long-term survival, as approximately 11% of long-term survivors presented with distant disease.

The majority of long-term survivors (75.2%) underwent surgical resection or resection combined with chemotherapy

TABLE 2. Associations of Patient, Tumor, and Facility Characteristics With 5-Year Survival

	Univariate Model OR (95% CI)	Multivariate Model OR (95% CI)	Multivariate Model *P*
Age (per 10 years)	**0.76 (0.72–0.80)**	**0.84 (0.79–0.90)**	**<0.0001**
Sex			0.0641
Male	Reference	Reference	
Female	1.09 (0.96–1.24)	1.14 (0.99–1.30)	
Race/ethnicity			**0.0002**
Non-Hispanic white	Reference	Reference	
Asian/Pacific islander	**1.55 (1.28–1.89)**	**1.52 (1.23–1.88)**	
Hispanic	1.14 (0.95–1.36)	**1.24 (1.01–1.51)**	
Non-Hispanic black	**0.76 (0.58–0.99)**	0.88 (0.65–1.18)	
Differentiation			**<0.0001**
Poorly differentiated/anaplastic	Reference	Reference	
Moderately differentiated	**2.22 (1.87–2.64)**	**1.51 (1.26–1.80)**	
Well-differentiated	**3.18 (2.59–3.90)**	**3.09 (2.48–3.86)**	
Unknown	**0.46 (0.38–0.56)**	**1.48 (1.18–1.86)**	
Anatomic location			0.7555
Head of pancreas	Reference	Reference	
Body of pancreas	**0.47 (0.36–0.62)**	0.89 (0.67–1.18)	
Overlapping, other, NOS	**0.47 (0.39–0.56)**	1.06 (0.87–1.28)	
Tail of pancreas	**0.53 (0.41–0.68)**	1.01 (0.77–1.33)	
SEER summary stage			**<0.0001**
Distant	Reference	Reference	
Localized	**17.34 (13.80–21.78)**	**6.41 (4.95–8.30)**	
Regional	**7.88 (6.42–9.67)**	**2.40 (1.90–3.04)**	
Unknown	**3.02 (2.15–4.24)**	**4.37 (3.07–6.22)**	
Surgery			**<0.0001**
No	Reference	Reference	
Yes	**17.48 (15.09–20.25)**	**10.72 (8.83–13.01)**	
Radiation			0.3854
No	Reference	Reference	
Yes	**2.62 (2.29–3.00)**	1.08 (0.91–1.28)	
Chemotherapy			**0.0010**
No	Reference	Reference	
Yes	**1.79 (1.58–2.03)**	**1.33 (1.12–1.57)**	
Quintile of neighborhood SES			**0.0049**
1 (lowest)	Reference	Reference	
2	0.94 (0.73–1.20)	0.94 (0.72–1.21)	
3	1.12 (0.89–1.41)	1.02 (0.79–1.30)	
4	**1.32 (1.06–1.66)**	1.19 (0.93–1.52)	
5 (highest)	**1.57 (1.27–1.95)**	**1.34 (1.06–1.71)**	
Care at NCI-designated Cancer Center			**<0.0001**
No	Reference	Reference	
Yes	**2.42 (2.10–2.78)**	**1.41 (1.21–1.65)**	
Year of diagnosis			**<0.0001**
1988–1995	Reference	Reference	
1996–2003	**1.37 (1.15–1.64)**	**1.23 (1.02–1.49)**	
2004–2009	**2.04 (1.73–2.41)**	**1.67 (1.38–2.01)**	

Values in bold signify statistically significant association at $P < 0.05$.

NOS indicates not otherwise specified.

and radiation, as compared with those patients who did not survive 5 years (15%). Long-term survivors were twice as likely to have had radiation as a combined modality with chemotherapy with or without surgery (35% vs 17%) and were more likely to have received chemotherapy (55% vs 41%). In addition, long-term survivors were roughly twice as likely to have been seen at an NCI-designated cancer center (29% vs 15%) and have been diagnosed in recent years. Approximately half of patients who died within 5 years received no cancer-directed therapy. This may reflect the era of treatment as no treatment was available before 1996 when gemcitabine was the first chemotherapy to be approved (Supplemental Table 1, http://links.lww.com/MPA/A665).

On further analysis using univariate logistic regression models, localized disease and surgical intervention were the most significant predictors of long-term survival (Table 2). Despite a reduction in effect size after adjustment for other covariates in the multivariate model, both stage and surgery remained the strongest predictors of long-term survival. Surgically resected patients were over 10 times more likely to reach the 5-year milestone than unresected patients (odds ratio [OR], 10.7; 95% confidence interval [CI], 8.83–13.01), although the effect of localized disease (OR, 6.41; 95% CI, 4.95–8.30) was smaller than that of surgery after the adjustment. Median survival of our cohort stratified by surgical resection was 13.7 months (95% CI, 13.1–14.0), compared with a mere 3.7 months (95% CI, 3.7–3.8) for unresectable patients (Fig. 1). Furthermore, chemotherapy and radiation were also associated with 5-year survival in a univariate analysis. However, after adjustment for other tumor and sociodemographic factors in a multivariate analysis, only chemotherapy maintained a significant association (OR, 1.33; 95% CI, 1.12–1.57) with long-term survival.

Well-differentiated tumors were also highly associated with long-term survival (OR, 3.09; 95% CI, 2.48–3.86); however, anatomic location of the tumor was not significantly associated with long-term survival after adjusting for stage. Later year of diagnosis was associated with long-term survival (OR, 1.23; 95% CI, 1.02–1.49 for diagnoses in 1996–2003 vs 1988–1995 and OR, 1.67; 95% CI, 1.38–2.01 for patients diagnosed in 2004–2009 vs those diagnosed in 1988–1995), as was receipt of care at an NCI-designated cancer center (OR, 1.41; 95% CI, 1.21–1.65).

Asian/Pacific islanders and Hispanics were more likely than non-Hispanic whites to achieve long-term survival (OR, 1.52; 95% CI, 1.23–1.88; OR, 1.24; 95% CI, 1.01–1.51, respectively). Older age was correlated with a decreased likelihood of reaching 5-year survival (OR, 0.84 per 10 years; 95% CI, 0.79–0.90), but there was no significant effect of sex. Although the effect was slightly attenuated after adjustment for other factors, higher neighborhood SES was associated with a greater likelihood of being a 5-year survivor (highest vs lowest neighborhood SES, OR, 1.34; 95% CI, 1.06–1.71).

Given that surgery is one of the strongest predictors of survival, and the fact that patients with resectable disease differ clinically from those of unresectable disease, having significantly higher median survival (Fig. 1), we performed a stratified logistic regression analysis, revealing some interesting differences in the associations with long-term survival between the surgical and nonsurgical groups (Table 3). One of the most significant associations noted was for stage, which was over 3 times as large for localized resectable patients (OR, 12.19; 95% CI, 7.68–19.36) than localized unresectable patients (OR, 3.73; 95% CI, 2.39–5.80). Similarly, but to a lesser extent, differentiation was also associated with long-term survival. The effect of well versus poorly differentiated tumors was larger in resected versus unresected cases (OR, 3.29; 95% CI, 2.56–4.25 in resected patients and OR, 2.53; 95% CI, 1.62–3.95 in unresected patients). Chemotherapy was also associated with 5-year survival, but only in the adjuvant setting (OR, 1.46; 95% CI, 1.19–1.80); however, radiation was not associated with long-term survival in resected patients (OR, 1.04; 95% CI, 0.85–1.28).

Similarly, the later year of diagnosis (OR, 1.36; 95% CI, 1.08–1.72 for 1996–2003 vs 1998–1995 and OR, 1.96; 95% CI, 1.55–2.48 for 2004–2009 vs 1988–1995), neighborhood SES (OR, 1.63; 95% CI, 1.21–2.21 for highest vs lowest quintile), and female sex (OR, 1.22; 95% CI, 1.04–1.44) were only associated with long-term survival in surgically resected cases.

Although race/ethnicity was not associated with 5-year survival in surgically resected cases, it proved to be one of the most significant factors associated with 5-year survival in unresectable disease. Asian/Pacific islanders with unresectable disease were more than 3 times (OR, 3.45; 95% CI, 2.49–4.79) as likely as non-Hispanic whites to survive over 5 years after diagnosis, and Hispanics were almost twice (OR, 1.81; 95% CI, 1.27–2.59) as likely. The magnitude of the effect of Asian race/ethnicity was on par with that of localized stage. Lastly, receiving care at an NCI-designated cancer center (OR, 1.34; 95% CI, 1.12–1.61 resected and OR, 1.63; 95% CI, 1.18–2.25 unresected) and younger age (OR per 10 years, 0.89; 95% CI, 0.83–0.96 resected and OR, 0.76; 95% CI, 0.68–0.85 unresected) were similarly associated with greater likelihood of 5-year survival for both groups.

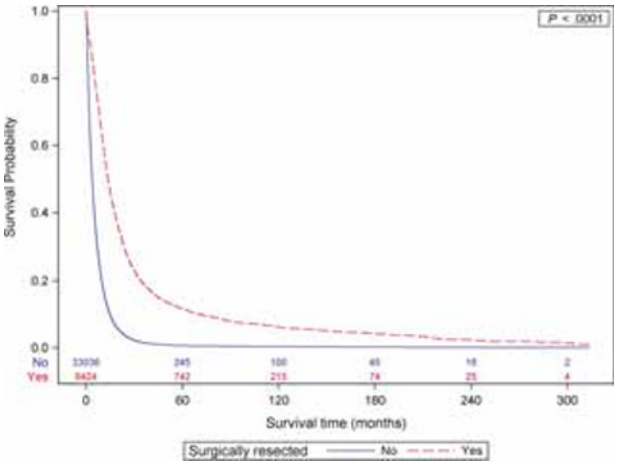

FIGURE 1. Overall survival by surgical resection.

DISCUSSION

In our study, the crude overall long-term survival, defined as 5 years or longer, of patients diagnosed with pancreatic adenocarcinoma in California between 1988–2009 was 2.5%. This is similar to the percentage reported by Lambe et al[15] using population-based data from a Swedish registry and Zijlstra et al[16] from the Netherlands cancer registry; however, lower than the 6% to 10% noted in other SEER and European databases.[3,17] These differences may be explained by differences in methodology between the studies. Although we, Lambe et al, and Zijstra et al measured long-term survival as the proportion of patients confirmed to be alive 5 years after diagnosis, Bouvier et al and Sirri et al reported 5-year relative survival, which is a theoretical measure that estimates the probability of survival at 5 years in the absence of other causes of death. Regardless of the actual percentage of 5-year survival, the fact remains that in the general population, long-term

TABLE 3. Associations of Patient, Tumor, and Facility Characteristics With 5-Year Survival, Stratified by Surgical Resection

	Unresected, Total n = 33,036			Surgically Resected, Total n = 6424		
	5-year Survivors/Nonsurvivors	OR (95% CI)	*P**	5-year Survivors/Nonsurvivors	OR (95% CI)	*P**
Age at diagnosis per 10 years, mean, y	65.4/68.9	**0.76 (0.68–0.85)**	**<0.0001**	64.3/65.5	**0.89 (0.83–0.96)**	**0.0028**
Sex						
Male	128/16,684	Reference	0.8083	353/2919	Reference	**0.0131**
Female	117/16,107	0.97 (0.75–1.25)		389/2763	**1.22 (1.04–1.44)**	
Race/ethnicity						
Non-Hispanic white	126/22,790	Reference	**<0.0001**	532/4030	Reference	0.6424
Asian/Pacific islander	54/2688	**3.45 (2.49–4.79)**		67/487	0.95 (0.72–1.27)	
Hispanic	49/4631	**1.81 (1.27–2.59)**		102/777	1.08 (0.84–1.38)	
Non-Hispanic black	16/2682	1.01 (0.59–1.73)		41/388	0.84 (0.59–1.19)	
Quintile of neighborhood SES						
1 (lowest)	47/4848	Reference	0.1652	71/754	Reference	**0.0073**
2	36/6225	**0.62 (0.40–0.97)**		107/1034	1.17 (0.84–1.62)	
3	46/7022	0.74 (0.49–1.13)		147/1156	1.24 (0.90–1.69)	
4	56/7191	0.91 (0.60–1.36)		181/1304	**1.43 (1.05–1.94)**	
5 (highest)	60/7505	0.96 (0.64–1.46)		236/1434	**1.63 (1.21–2.21)**	
Anatomic site						
Head of pancreas	141/16,572	Reference	0.7693	561/4300	Reference	0.8552
Body	22/3484	0.84 (0.53–1.33)		38/278	0.91 (0.63–1.32)	
Tail	16/3403	0.82 (0.48–1.39)		52/431	1.11 (0.80–1.53)	
Overlapping, other, NOS	66/9332	1.02 (0.75–1.38)		91/673	1.05 (0.82–1.34)	
Differentiation						
Poorly differentiated/anaplastic	44/6914	Reference	**<0.0001**	160/2059	Reference	**<0.0001**
Moderately differentiated	33/5301	0.87 (0.55–1.37)		368/2638	**1.68 (1.38–2.05)**	
Well-differentiated	38/1980	**2.53 (1.62–3.95)**		145/551	**3.29 (2.56–4.25)**	
Unknown	130/18,596	1.00 (0.70–1.42)		69/434	**2.10 (1.52–2.89)**	
SEER summary stage						
Distant	88/19,043	Reference	**<0.0001**	22/731	Reference	**<0.0001**
Localized	30/1906	**3.73 (2.39–5.80)**		220/686	**12.19 (7.68–19.36)**	
Regional	88/8983	**1.92 (1.39–2.65)**		490/4207	**4.14 (2.66–6.46)**	
Unknown	39/2859	**3.53 (2.36–5.26)**		10/58	**6.95 (3.06–15.76)**	
Radiation						
No	188/28,000	Reference	0.2733	452/3880	Reference	0.6811
Yes	57/4791	1.21 (0.86–1.71)		290/1802	1.04 (0.85–1.28)	

(Continued on next page)

TABLE 3. *(Continued)*

	Unresected, Total n = 33,036			Surgically Resected, Total n = 6424		
	5-year Survivors/Nonsurvivors	OR (95% CI)	*P**	5-year Survivors/Nonsurvivors	OR (95% CI)	*P**
Chemotherapy						
No	130/19,753	Reference	0.7001	312/3031	Reference	**0.0003**
Yes	115/13,038	1.06 (0.79–1.42)		430/2651	**1.46 (1.19–1.80)**	
Cancer center						
No	189/28,451	Reference	**0.0029**	509/4403	Reference	**0.0013**
Yes	56/4340	**1.63 (1.18–2.25)**		233/1279	**1.34 (1.12–1.61)**	
Year of diagnosis						
1988–1995	75/10,559	Reference	0.5962	131/1574	Reference	**<0.0001**
1996–2003	81/11,444	1.07 (0.78–1.49)		234/2182	**1.36 (1.08–1.72)**	
2004–2009	89/11,033	1.19 (0.85–1.67)		377/2668	**1.96 (1.55–2.48)**	

Values in bold signify statistically significant association at $P < 0.05$.
*Wald χ^2 P value.
NOS indicates not otherwise specified.

survival of pancreatic adenocarcinoma has remained discouragingly low. Therefore, understanding the characteristics these individuals share may help lead to improved outcomes in the population.

Similar to previous results from the United States and international population-based cancer registries,[1,3,18,19] we found that age, stage, degree of differentiation, and surgical resection were associated with 5-year survival. Surgery is regarded as the only potentially curative option for pancreatic adenocarcinoma, and in our analysis, it was the factor most strongly associated with long-term survival. However, we also identified a subset of long-term survivors that did not undergo resection with curative intent. Because the clear majority of pancreatic cancer patients do not undergo surgery, we were particularly interested in uncovering unique associations with survivorship in this rare and understudied group of patients.

Using stratified analysis, we found that specific factors such as younger age and receiving care at an NCI-designated cancer center were similarly associated with 5-year survival regardless of surgical intervention, whereas the effect of other prognostic factors differed between the 2 groups. In contrast to the findings in the surgically resected cohort, where clinicopathologic and treatment-related factors were more strongly associated with long-term survival, in unresected patients, race/ethnicity was almost as strongly associated with 5-year survival as stage. In the unresected cohort, Asian/Pacific islanders and Hispanics were significantly more likely to reach the 5-year milestone than non-Hispanic whites.

The improved overall survival associated with Asian race has inconsistently been reported in the literature. Using CCR data, Zell et al[20] found that after adjusting for treatment and SES, non-Chinese Asian race was associated with a decreased hazard of death. Gong et al[21] reported that Asian/Pacific islander race and receiving any active treatment at the time of diagnosis as independent factors for longer survival in SEER identified residents of San Francisco Bay Area counties. However, other SEER population-based studies have reported comparable overall survival between Asians and whites.[22–24] This inconsistency may relate to the lack of adjustment for SES or treatment in the latter studies. In addition, the Asian populations of California and those of other geographic areas within the US may differ in the proportion of foreign-born individuals or in the representation of the various Asian ethnic groups, which may also contribute to the inconsistent associations reported by different studies.

In contrast to Asians, previous studies have reported similar[20] or worse[25] survival outcomes for pancreatic adenocarcinoma in Hispanics compared with non-Hispanic whites. To our knowledge, we are the first to report an association between Hispanic ethnicity and improved 5-year survival outcomes. This novel finding should be confirmed by future studies.

Both the Asian and Hispanic communities in California have large immigrant populations, and it has been suggested that the survival benefit seen in these populations may be artifactual, the result of loss to follow-up due to return migration of terminally ill patients. To minimize this potential bias, we required confirmation of vital status at 5 years for all nondeceased cases. Therefore, it is unlikely that return migration could explain the improved survival we observed.

It is noteworthy that neither we nor others[9,26] found an association with race/ethnicity after controlling for SES in surgically resected patients. Although differences in long-term survival might be attributed to differential access and utilization of care among racial/ethnic groups, it appears unlikely that compared with non-Hispanic whites, Asian, and Hispanic minority patients would have improved access to care, resulting in a survival

advantage. Instead, it may reflect biological differences that exist among races, which only become apparent in situations where the disease is unchecked by surgical intervention.

Dong et al[27] previously reported differences in K-*ras* point mutations and p53 expression between Asian and Western populations with pancreatic carcinomas. It is possible that our finding of a positive association of long-term survival with race, but not SES, in patients with unresectable disease reflects racial differences in biological or immunological factors or genetic-immune-environment interactions that influence the disease's aggressiveness or progression. Such differences may offer clues to the biology of the disease and warrant further investigation.

The need for a better understanding of the biology of this disease is highlighted by the finding that almost 12% of long-term survivors in our study were diagnosed with distant disease. We acknowledge that because of the limited diagnostic workup performed in some cases, especially those that did not undergo surgical resection, some of these patients may have been inaccurately staged, misdiagnosed, or had a more favorable diagnosis such as ampullary, periampullary, or even neuroendocrine tumors. Our inability to conduct histopathologic review is one of the study's major limitations. To reduce the possibility of biasing our results by including other types of tumors or benign pancreatic masses, we required that all cases have microscopic confirmation of their pancreatic cancer diagnosis.

Although stage and tumor characteristics showed the expected associations with survival in regression analysis, we recognize that the lack of histopathologic review likely resulted in some degree of misclassification, which could have potentially inflated our survival estimates. Nevertheless, it is important to note that the finding of long-term survival in the face of adverse prognostic features is not unique to our study. It is well documented that Asian/Pacific islanders carry the lowest overall cancer incidence and death rates.[1] And it has previously been described by several other investigators in surgical case series, including those with pathologic review of specimens,[28–30] underscoring the fact that even within the group of long-term survivors there is significant heterogeneity in tumor biology that we do not understand.

Our study has some additional limitations. The registry records limited personal and clinical information, and we could not assess the effects of other potential confounders such as comorbidity, tobacco and alcohol use, family history, performance status, perioperative factors, or tumor molecular characteristics. Further, this study includes only residents of California, who may not be representative of patients in other regions.

Despite these limitations, our study has several key strengths. Ours is the largest cohort of 5-year survivors of pancreatic adenocarcinoma reported to date and is the first to address long-term survival in a surgically unresected population. It is based on cancer registry data that is subject to rigorous follow-up and quality control standards. Most importantly, the population-based nature of our analysis makes our findings generalizable to a much larger population than any prior studies.

Although better patient selection, surgical techniques, and postoperative treatments have benefitted patients with resectable pancreatic adenocarcinoma, it has not translated into a meaningful improvement in outcomes at the population level because too few patients present with disease amenable to resection. Until we develop strategies that lead to earlier diagnosis or therapies that are effective enough to convert the unresectable to resectable, we are unlikely to improve cure rates. The promise of targeting molecular vulnerabilities has been unfulfilled with the exception of rare patients with deficient mismatch repair (~1%–2%) treated with PD-1 blockade[31,32] and *BRCA* mutations (~4%–5%) treated with platinum agents and experimental PARP inhibitors.[33,34] Nevertheless, the impressive responses in these small subgroups offer proof of concept that there remain subgroups susceptible to targeted therapy and that the immune system is potent enough to be effective if there are neoantigens to recognize. The key to these developments is achieving a better understanding of the biology and immunology of the disease, and studying this unique cohort of long-term survivors may bring us a step closer to achieving this goal.

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