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Associations between Selected Biomarkers and Prognosis in a Population-Based Pancreatic Cancer Tissue Microarray

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Abstract

Pancreatic cancer is the fourth leading cause of cancer death in the United States. Prognostic biomarkers are lacking, and treatment has limited effect on survival. Tissues from Surveillance, Epidemiology, and End Results registries (Iowa, Hawaii, and Los Angeles) were used to build a tissue microarray of 161 pancreatic tumors (113 resections and 48 biopsies). Proportional hazard models adjusted for age, race, sex, stage, time-period of diagnosis, and treatment. Associations were examined between markers (MUC1, MUC2, MUC5AC, synaptophysin, chromogranin, neuron specific enolase, epidermal growth factor receptor, HER2, CD5, CD138, CK5/6, CK19, CK20, and p53) and survival time from diagnosis. After adjusting for covariates, borderline statistically significant associations were seen between expression of each of the three mucins (MUC1, MUC2, and MUC5AC) and shorter survival time. The associations strengthened for 154 (96%) adenocarcinomas, particularly the 120 (75%) well-differentiated to moderately differentiated ductal adenocarcinomas, a tumor type that occurred more often in the cohort among White cases than cases of other racial origin ($P < 0.01$). For differentiated ductal adenocarcinomas, associations with shorter survival time were seen for expression of all three mucins combined versus other mucin expression patterns (adjusted hazard ratio, 1.8; 95% confidence interval, 1.2–2.6) and for MUC2(+) versus MUC2(−) expression (adjusted hazard ratio, 1.6; 95% confidence interval, 1.1–2.4). Mucin gene expression, particularly MUC2 expression, may have prognostic value for differentiated adenocarcinomas. Tumor histologies differed in this and Japanese cohorts. The tissue microarray is

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available to evaluate other biomarkers. Tissue-based surveillance can be used to monitor tumor histology in populations and facilitate applied research.

Introduction

Pancreatic cancer is one of the most lethal cancers worldwide (1). In the United States, the estimated 5-year survival rate for this malignancy is 4.9%, which is the lowest survival rate among the common primary cancer sites.[8] Thus, pancreatic cancer is one of the leading causes of cancer death in the United States (2). The poor prognosis for this cancer stems from the ability of pancreatic tumors to invade locally and metastasize to other organs and lymph nodes during early stages, without clinical signs (3). Although surgery is used with some success, recurrence is common (4). Because the behaviors of pancreatic tumors vary, there is a need to define the tumors that are most responsible for the burden of death. Researchers are therefore working to identify reliable biomarkers to predict pancreatic tumor prognosis (5) and focus clinical and etiologic research on the tumors based on prognosis. The lack of tissues with detailed patient information has been a barrier to this type of research.

Our objective was to develop a cohort for investigating diagnostic and prognostic markers in pancreatic cancer. Toward this goal, we investigated a panel of 14 potential diagnostic and prognostic markers. We assembled invasive tumor tissues from 161 pancreatic cancer cases in three cancer registries that are part of the Surveillance, Epidemiology, and End-Results Program (SEER) of the National Cancer Institute (NCI). Population-based tissue banks have the advantage of providing an unbiased sampling frame for evaluating new molecular classification schemes of cancer that will augment the pathomorphologic approach used presently (6). The resulting tissue microarray (TMA) is among the largest collection of pancreatic carcinomas currently available for study and is available to qualified investigators for additional studies.

Materials and Methods

Case identification and selection

A total of 13,650 pancreatic cancer cases were diagnosed in Hawaii, Iowa, and Los Angeles between 1983 and 2000. These registries, which participate in the NCI's SEER Residual Tissue Repository, retrieve tumor tissue from pathology laboratories that would otherwise be discarded. Only a fraction of cases are available within the discard repository, of which all were obtained and screened for inclusion within the TMA. These tissues are linked to cases from the registries, for which there are additional clinical and demographic data. Thus, cases with tissues in the SEER Residual Discard Repository can be compared with all cases in the population for representativeness and potential biases.

The present report included 113 excised primary pancreatic carcinomas and 48 biopsy specimens. The only selection criteria was epithelial tumor in the pancreas, with sufficient material for construction of the TMA. Residual pancreatic tissue from these cases was assembled and forwarded to the Tissue Array Research Program Laboratory at the NCI for preparation of H&E-stained sections. The 161 cases with sufficient material of epithelial tumors arising in the pancreas ($n = 100$) or consistent with pancreatic origin at metastatic sites ($n = 61$) were included in the TMA. Appropriate ethical and transfer of material approvals were obtained from originating sites, as well as the NCI.

[8] http://seer.cancer.gov/csr/1975_2005/

TMA construction

A TMA of four replicate blocks was built by obtaining targeted tissue core sample of each region as previously described (7), using 1.0-mm needles with a TMArrayer (Pathology Devices). Fifteen cores of normal tissue from the matching pancreatic tumors as well as a selection of 15 adjacent benign tissues at other sites were included in the design. H&E-stained slides were made of every 50th section of the TMA. These slides were reviewed for presence of tumor and histologic assignment.

Histology and immunohistochemistry

The histology of each tumor was blindly reviewed twice by a pathologist (MT & BA) Tissue Array Research Program Laboratory, according to a published classification scheme (8). When different results were obtained from the two pathology reviews, they were reconciled via consultation with a second pathologist (SH). In the analyses presented in this report, the tumors were classified into four histologies:

(*a*) “differentiated ductal adenocarcinomas,” including both well- and moderately differentiated ductal adenocarcinoma; (*b*) “poorly differentiated ductal adenocarcinoma,” (*c*) “specialized adenocarcinoma,” which included cystadenocarcinoma, mucinous and papillary adenocarcinoma, and clear cell carcinomas; and (*d*) “neuroendocrine tumors.”

Immunohistochemical assays were performed according to manufacturer's protocols. Antibodies for mucin markers were purchased from Novocastra Laboratories. Antibodies for the neuron-specific enolase immunohistochemical assay were obtained from Vector Laboratories. Chromogranin, synaptophysin, HER2, EGFR, CD5, CD138, CK5/6, CK19, CK20, and p53 antibodies were obtained from Dako. Immunohistochemistry was performed on a Dako Autostainer following manufacturer's recommendations, with antigen retrieval performed with steam heating in a rice cooker.

Immunohistochemical assessment

The immunohistochemical scoring was performed blindly by pathologists (MT and BA). Signals were considered positive when reaction products localized in the expected cellular component. Markers were categorized by staining intensity and percent of cells stained. Intensity was scored as 0 (no signal), 1 (weak), 2 (moderate), and 3 (marked); and percent stained was scored as 0 (0%), 1 (1–25%), 2 (26–50%), 3 (51–75%), or 4 (76–100%). Mucin expression was recorded as negative, weak, moderate, or marked. Other markers were classified based on the product of staining and intensity scores (range, 0–12), dichotomized as negative to weak (0 or 1) versus moderate to marked signal ($\geq$2).

Statistical models

The association of tumor markers with survival time was evaluated by Cox proportional hazard regression models (PROC PHREG SAS v.9; ref. 9). Survival time was defined as the interval in months from diagnosis to death. Data were censored for seven cases with pancreatic adenocarcinomas that were alive at last follow-up and one case with a neuroendocrine tumor that was lost to follow-up. Beginning with unadjusted and full models, stepwise forward and backward model selection was performed to develop a final model that adjusted for gender, age (<75 versus 75+ y), race (Asian versus non-Asian), stage of disease (local and regional versus distant and unstaged), time period of diagnosis (1983–1991 versus 1992–2000), tumor location (pancreatic versus metastatic site), and ever versus never surgical or radiation treatment for pancreatic cancer. Registry location had negligible effect when combined with these variables and was, therefore, not included in the final model. The covariates used for adjusting were kept constant with single markers added to estimate the adjusted hazard ratio.

χ^2 tests were performed to evaluate the statistical significance of associations between specific tumor histologies and racial subgroups in the TMA (PROC FREQ SAS v.9; ref. 10). Log-Rank Tests were performed to compare Kaplan-Meier survival distribution (11) for tumors by biomarker status (PROC LIFETEST SAS v.9).

Results

Representativeness of the TMA

The TMA (Fig. 1*A*) included tissue from 161 of 13,650 incident pancreatic cancer cases (1.2%) reported by the three registries (Table 1). Nearly half of cases in the TMA were White (48%), followed by Asians and Pacific Islanders (40%), and Blacks (12%). Hispanic ethnicity was reported by 4% of TMA cases. Overall, about half of cases in both the TMA cohort and reference population were male. A higher proportion of TMA cohort than reference cases were younger than age 75 years. The median survival time from diagnosis was longer for TMA cohort than reference cases. The years of diagnosis for TMA cohort cases extended from 1983 to 2000, with the majority of TMA cohort cases diagnosed in the years from 1992 to 1997. A higher proportion of TMA cohort than reference cases were diagnosed at a local or regional stage. In addition, TMA cohort cases were more likely than reference cases to have received surgery or radiation therapy. Differences between TMA cases and the reference population with respect to median survival time from diagnosis, stage of disease at time of diagnosis, and frequency of surgical or radiation treatment were more pronounced for cases from the Hawaii registry than from the Los Angeles or Iowa registries.

Histology

Although the TMA included various tumor type including 120 differentiated ductal adenocarcinomas, 24 poorly differentiated ductal adenocarcinomas, 10 specialized adenocarcinomas, and 7 neurorendocrine tumors, the vast majority of the tumors were adenocarcinomas (96%; Table 1). The 120 differentiated adenocarcinomas (75%) occurred significantly more frequently among White than non-White cases ($P = 0.01$; data not shown).

Survival analyses

For all 161 tumors in the TMA, after adjusting for covariates, borderline statistically significant associations were seen between mucin expression (MUC1, MUC2, and MUC5AC) and shorter survival time (Table 2). No other statistically significant associations between biomarker expression and survival time were observed.

The associations between mucin expression and shorter survival time persisted for all 154 adenocarcinomas combined (96% of TMA tumors; Table 3), and further strengthened for 120 moderate to well-differentiated adenocarcinomas (75% of tumors in the cohort).

For moderate to well-differentiated adenocarcinomas, two noteworthy associations were found. Expression of all three mucins combined was associated with significantly shorter survival time from diagnosis (adjusted hazard ratio, 1.8; 95% confidence interval, 1.2–2.6). Similar results were found for negative and weak MUC2 expression versus moderate to strong MUC2 expression (adjusted hazard ratio, 1.6; 95% confidence interval, 1.1–2.4). The Log-Rank test for the survival distribution of these 2 groups of tumors was statistically significant ($P = 0.02$). Among cases with moderate to well-differentiated pancreatic adenocarcinomas, the association between MUC2 and survival time further strengthened when MUC2 negative tumors were compared with tumors with weak to strong MUC2 expression ($P = 0.006$, Log-Rank test; Table 4; Fig. 2). Adjustment for covariates had limited effect on the association between MUC2 and survival time. Figure 1*B* and *C* show primary and metastatic adenocarcinomas that expressed MUC2.

Mucin expression was not associated with survival times for poorly differentiated ductal adenocarcinomas and there were too few specialized adenocarcinomas to provide informative results. All seven neuroendocrine tumors (Fig. 1*D*) in the TMA were negative for MUC2 expression (data not shown). The three tumors that expressed MUC5AC only were specialized adenocarcinomas occurring among Asian and Pacific Islanders. Two of these cases survived over 40 months from diagnosis (data not shown).

Discussion

Results of this study suggest that mucin gene expression, in particular, MUC2 expression, is a useful complement to histologic classification for predicting prognosis of cases of moderate to well-differentiated ductal adenocarcinoma, which predominated as tumor specimens available for analysis in this study. Among cases with these tumors, expression of all three mucins combined (MUC1, MUC2, and MUC5AC), as well as MUC2 alone, were associated with shorter survival time compared with tumors with other expression patterns. Moderate to well-differentiated ductal adenocarcinomas accounted for 75% of tumors in the cohort and occurred significantly more often among Whites than other races. The common histologies and mucin expression patterns reported in a Japanese study (12) were rare in the present study, occurring in three Asian and Pacific Islanders with specialized adenocarcinomas. Although the representativeness of the cases in the Japanese study compared with the population is unknown, the differences suggest that the distribution of pancreatic tumors may vary across populations.

The failure of the majority of markers to predict prognosis was unexpected. The selection of the biomarkers was based on those markers that we identified as potentially useful at classification of epithelial neoplasms within the pancreas. With the advent of molecular classification, it is common to define a prognostic significance to a marker or panel of markers that define a common group of tumors that cannot be accurately recognized by cytomorphology. For example, synaptophysin and chromogranin performed poorly as diagnostic markers for neuroendocrine tumors. Although synaptophysin and chromagranin did stain the neuroendocrine tumors of the pancreas, in agreement with the pathology literature (13), they also stained a fraction of adenocarcinomas, which reduced their diagnostic specificity. We did note an improvement in overall survival in those patients diagnosed in more recent years than those diagnosed in the early years of patient accrual.

In the present study, one family of markers did show potential prognostic value—the mucins, and particularly MUC2. Because multiple comparisons were performed in this exploratory study, additional analyses are recommended to assess whether these findings can be replicated. Mucins are high molecular weight glycoproteins that are produced by epithelial cells and contribute to protection, renewal, and cell signaling. Various expression patterns of mucins have been reported to predict prognosis for gastric (14), ovarian (15), and pancreatic carcinomas (16). Unlike the present study, in a Japanese study of 47 pancreatic tumors from a hospital-based sample (12), none of the 36 intraductal carcinomas expressed MUC2. Furthermore, patients in the Japanese study with MUC2-negative intraductal carcinomas had worse outcomes than patients with intraductal papillary-mucinous tumors, which generally expressed MUC2. Another Japanese study examined 50 intraductal papillary-mucinous tumors, a rare histology in the current study. In the Japanese study, MUC2 expression was associated with less favorable outcome (17). Because of differences in mucin expression and potential for malignancy, Nakamura and colleagues (17) speculated that prognostic interpretation of biomarkers vary by pancreatic tumors lineages. Differences in histology and expression in this and the Japanese studies also suggest that pancreatic tumor types differ across populations.

This study supports the utility of tissue-based cancer surveillance to test newly developed prognostic markers that may enhance emerging cancer classification systems, and facilitate etiologic research and help to prioritize tumor-specific cancer treatment protocols. For example, if the findings of this study can be replicated through ongoing tissue-based surveillance, moderately to well-differentiated pancreatic ductal adenocarcinomas with the MUC2 (+) phenotype could serve as a case definition for etiologic studies of a dominant pancreatic tumor among White cases that has an unfavorable prognosis. The MUC2 phenotype might also serve as an entry criterion for clinical trials or selection of candidates for surgery that are most likely to have favorable outcomes.

Some limitations of this study were that the TMA did not include enough tissues from Blacks, American Indians and Alaska Natives, and Hispanics to provide robust inferences on the distribution of histologies and prognostic markers of pancreatic tumors for these racial/ethnic groups. In addition, the small numbers of specimens for individual years hindered the ability to ascertain whether tumor patterns were changing over time.

Despite these limitations, the pancreatic cancer TMA assembled for this study is among the largest population-based collections available for evaluating prognostic markers within a well-characterized and racially diverse group of subjects. This resource was developed with the goal that it would be made available to researchers for testing additional biomarkers.[9] It is also our hope that it will continue to be enriched with new case material from these and other registries (6).

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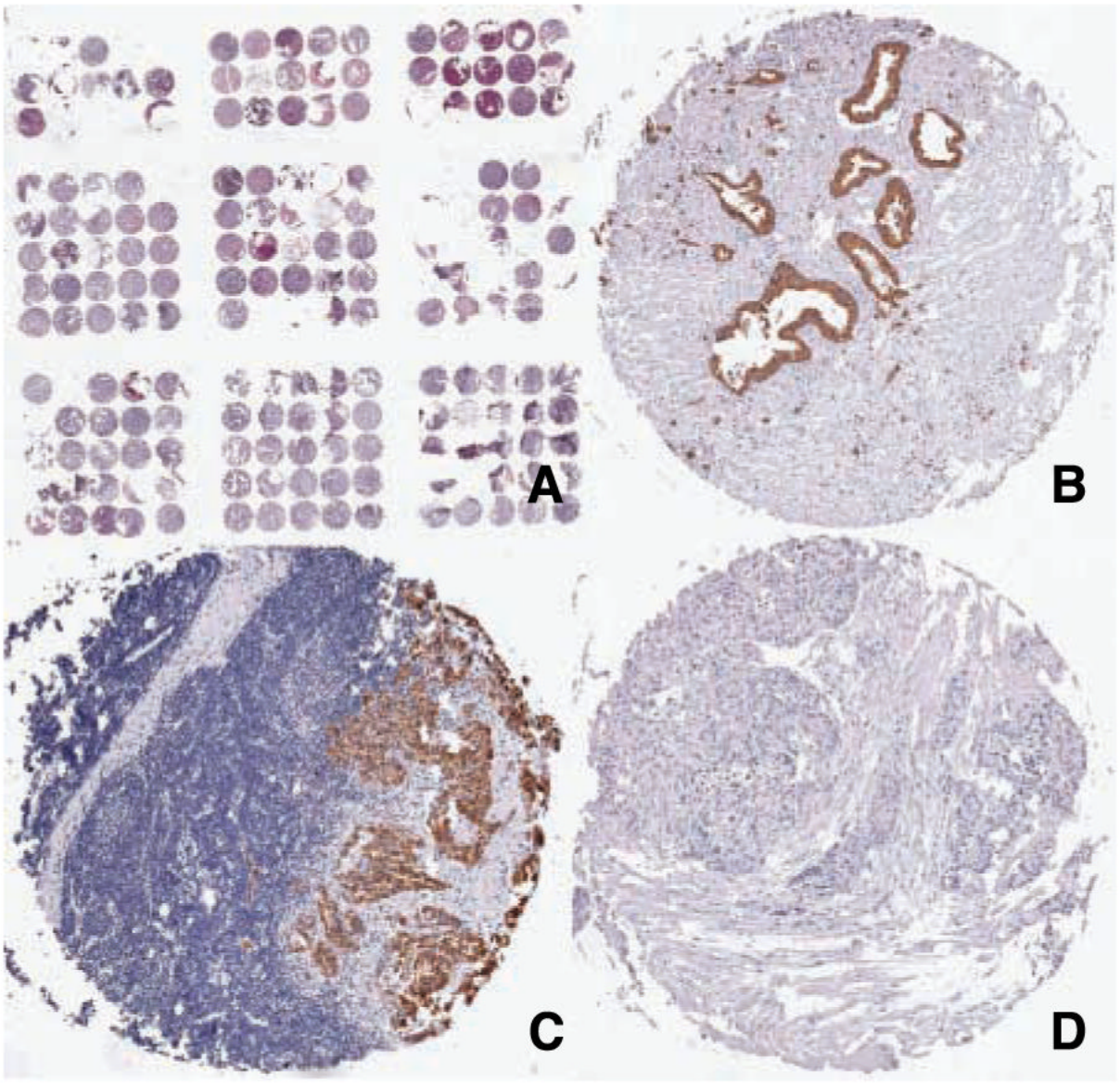

Figure 1.

A, low power H&E image of the pancreatic cancer TMA. *B* to *D*, immunohistochemistry for MUC2. *B*, positive staining for MUC2 pancreatic adencarcinoma; *C*, positive staining for MUC2 in a pancreatic adenocarcinoma metastatic to a lymph node; *D*, a pancreatic neuroendocrine tumor negative for MUC2 expression.

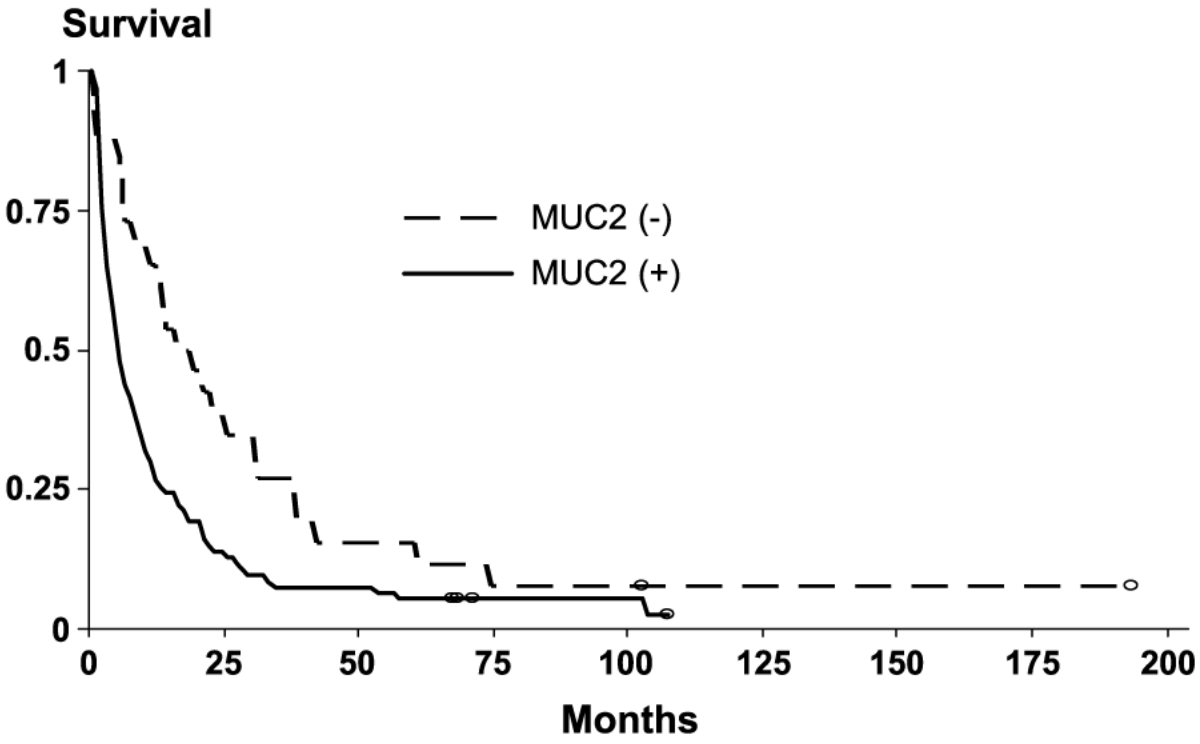

Figure 2.
Kaplan-Meier survival curve, time from diagnosis to death in months for 120 well-differentiated adenocarcinomas (75% of tumors in cohort) by MUC2 expression (negative versus weak, moderate and strong).

Table 1

Attributes of cases in the SEER Residual Tissue Repository pancreatic cancer TMA and all cases in the registries

	Iowa				Hawaii				Los Angeles				Overall			
	TMA	%	Registry	%	TMA	%	Registry	%	TMA	%	Registry	%	TMA	%	Registries	%
Race																
White	35	97%	3389	98%	25	30%	450	25%	18	44%	6574	78%	78	48%	10413	76%
API	0	0%	9	0%	56	67%	1309	74%	8	20%	605	7%	64	40%	1923	14%
Black	1	3%	60	2%	3	4%	8	0%	15	37%	1201	14%	19	12%	1269	9%
AI/AN0		0%	2	0%	0	0%	1	0%	0	0%	5	0%	0	0%	8	0%
Unknown	0	0%	0	0%	0	0%	1	0%	0	0%	36	0%	0	0%	37	0%
Ethnicity																
Hispanic*	0	0%	9	0%	0	0%	8	0%	6	13%	1164	12%	6	4%	1181	9%
Gender																
Male	17	47%	1696	49%	45	54%	960	54%	19	46%	4064	48%	81	50%	6720	49%
Female	19	53%	1764	51%	39	46%	809	46%	22	54%	4357	52%	80	50%	6930	51%
Diagnosis age																
<55	5	14%	312	9%	14	17%	190	11%	8	20%	973	12%	27	17%	1475	11%
55-64	7	19%	518	15%	22	26%	307	17%	13	32%	1509	18%	42	26%	2334	17%
65-74	13	36%	1000	29%	33	39%	583	33%	6	15%	2650	31%	52	32%	4233	31%
75-84	9	25%	1067	31%	14	17%	512	29%	13	32%	2357	28%	36	22%	3936	29%
85+	2	6%	563	16%	1	1%	177	10%	1	2%	932	11%	4	2%	1672	12%
Median Survival (mo)†	5		3		13		4		3		3		6		3	
Diagnosis year																
1983-1985	2	6%	342	10%	3	4%	265	15%	0	0%	0	0%	5	3%	607	4%
1986-1988	3	8%	671	19%	3	4%	94	5%	20	49%	2275	27%	26	16%	3040	22%
1989-1991	0	0%	0	0%	6	7%	342	19%	10	24%	2288	27%	16	10%	2630	19%
1992-1994	14	39%	304	9%	24	29%	376	21%	9	22%	2264	27%	47	29%	2944	22%
1995-1997	14	39%	1085	31%	29	35%	406	23%	1	2%	791	9%	44	27%	2282	17%
1998-2000	3	8%	1058	31%	19	23%	286	16%	1	2%	803	10%	23	14%	2147	16%
Stage at diagnosis																
Local/regional	19	53%	1012	29%	59	70%	623	35%	3	7%	1101	13%	81	50%	2736	20%
Distant	17	47%	1757	51%	24	29%	900	51%	8	20%	1883	22%	49	30%	4540	33%

	Iowa				Hawaii				Los Angeles				Overall			
	TMA	**%**	**Registry**	**%**	**TMA**	**%**	**Registry**	**%**	**TMA**	**%**	**Registry**	**%**	**TMA**	**%**	**Registries**	**%**
Missing	0	0%	691	20%	1	1%	246	14%	30	73%	5437	65%	31	19%	6374	47%
Radiation or surgery																
Ever	16	44%	847	24%	61	73%	550	31%	19	46%	1762	21%	96	60%	3159	23%
Never	20	56%	2613	76%	23	27%	1219	69%	22	54%	6659	79%	65	40%	10491	77%
Histology‡																
AC	35	97%	—	—	79	94%	—	—	40	98%	—	—	154	96%	—	—
Differentiated ductal AC	27	75%	—	—	62	74%	—	—	31	76%	—	—	120	75%	—	—
Poorly differentiated ductal AC	4	11%	—	—	12	14%	—	—	8	20%	—	—	24	15%	—	—
Specialized AC	4	11%	—	—	5	6%	—	—	1	2%	—	—	10	6%	—	—
Neuroendocrine	1	3%	—	—	5	6%	—	—	1	2%	—	—	7	4%	—	—
Total no.cases (% in TMA)	36	of	3460	1.0%	84	of	1769	4.7%	41	of	8421	0.5%	161	of	13650	1.2%

Abbreviations: API, Asians and Pacific Islanders; AI/AN, American Indians and Alaska Natives; AC, adenocarcinoma.

People reporting Hispanic ethnicity could also report white or black race.

Survival time from diagnosis excludes the 8 cases in the TMA and 308 cases in the registries that were alive at last follow up.

Histologic classification performed by NCI Tissue Array Research Program Pathologists (MT, SH), specialized adenocarcinomas: four cystadenocarcinomas, three mucinous adenocarcinomas, two papillary adenocarcinomas, and a clear cell carcinoma.

Table 2

Coxproportional hazard ratio and 95% confidence interval, time from diagnosis to death by biomarker status for all pancreatic tumors in the TMA

Family	Marker	Signal	No*	Median survival†	Unadjusted HR (95% CI)		Adjusted‡ HR (95% CI)	
Mucins	MUC1	Positive	143	6	2.6	(1.5-4.5)	1.7	(1.0-3.1)
		Negative	18	27	1.0	Reference	1.0	Reference
	MUC2	Positive	89	5	1.5	(1.1-2.1)	1.4	(1.0-2.1)
		Negative	72	11	1.0	Reference	1.0	Reference
	MUC5AC	Positive	99	5	1.3	(0.9-1.8)	1.4	(1.0-2.0)
		Negative	62	9.5	1.0	Reference	1.0	Reference
Neuro- endocrine markers	Synaptophysin	Moderate/marked	55	8	0.9	(0.6-1.3)	1.0	(0.7-1.4)
		None/weak	101	6	1.0	Reference	1.0	Reference
	Chromogranin	Moderate/marked	24	13	0.6	(0.4-0.9)	0.9	(0.6-1.5)
		None/weak	130	6	1.0	Reference	1.0	Reference
	Neuron-specific enolase	Moderate/marked	52	5	1.3	(0.9-1.9)	1.1	(0.8-1.7)
		None/weak	99	10	1.0	Reference	1.0	Reference
Growth factor receptors	EGFR	Moderate/marked	40	5	1.2	(0.8-1.8)	1.2	(0.8-1.8)
		None/weak	114	9.5	1.0	Reference	1.0	Reference
	HER2	Moderate/marked	96	6.5	1.2	(0.9-1.7)	0.9	(0.6-1.3)
		None/weak	57	8	1.0	Reference	1.0	Reference
T cell marker	CD5	Moderate/marked	25	9	0.9	(0.6-1.4)	0.9	(0.5-1.3)
		None/weak	131	7	1.0	Reference	1.0	Reference
	CD138	Moderate/marked	109	6	1.1	(0.8-1.6)	1.1	(0.7-1.5)
		None/weak	47	10	1.0	Reference	1.0	Reference
Cytokeratins	CK20	Moderate/marked	70	6.5	1.0	(0.7-1.5)	1.1	(0.8-1.6)
		None/weak	76	9.5	1.0	Reference	1.0	Reference
	CK5/6	Moderate/marked	74	9	0.8	(0.5-1.0)	0.9	(0.6-1.2)
		None/weak	80	6	1.0	Reference	1.0	Reference
	CK19	Moderate/marked	139	6	1.2	(0.8-2.0)	1.3	(0.8-2.1)
		None/weak	22	8.5	1.0	Reference	1.0	Reference
Tumor protein	p53	Moderate/strong	119	6	1.2	(0.8-1.8)	1.0	(0.6-1.5)
		Negative/weak	31	8	1.0	Reference	1.0	Reference

Abbreviation: HR, hazard ratio, CI, confidence interval; NSE, Neuron-specific enolase.

* Number of cases with data available varied by marker.

† Survival time in months from diagnosis to death.

‡ Adjusted for gender, age (<75 versus 75+ y), race (Asian versus non-Asian), stage of disease (local and regional versus distant and unstaged), pancreatic origin versus metastatic site, and ever versus never surgical or radiation treatment for pancreatic cancer.

Table 3

Cox proportional hazard ratios and 95% confidence intervals for time from diagnosis to death, all adenocarcinomas and moderately to well-differentiated adenocarcinoma, SEER Residual Tissue Repository TMA, by mucin expression status

Histology	Mucin	No	Expression status	Median survival*	Unadjusted model HR (95% CI)		Adjusted model† HR (95% CI)	
All ACs	All three mucins combined	81	Positive	5.0	1.6	(1.2-2.3)	1.5	(1.1-2.2)
		73	Negative	11.0	1.0	Reference	1.0	Reference
(96% of tumors in the TMA)	MUC1	139	Positive	20.0	2.4	(1.3-4.4)	1.6	(0.9-3.0)
		15	Negative	6.0	1.0	Reference	1.0	Reference
	MUC2	89	Positive	11.0	1.5	(1.1-2.1)	1.5	(1.0-2.1)
		65	Negative	5.0	1.0	Reference	1.0	Reference
	MUC5AC	99	Positive	10.0	1.3	(0.9-1.8)	1.4	(1.0-2.1)
		55	Negative	5.0	1.0	Reference	1.0	Reference
Well- and moderately differentiated ductal AC	All three mucins combined	68	Positive	5.0	1.8	(1.2-2.6)	1.8	(1.2-2.6)
		52	Negative	12.5	1.0	Reference	1.0	Reference
(75% of tumors in the TMA)	MUC1	112	Positive	6.0	2.7	(1.2-6.2)	2.5	(1.1-5.7)
		8	Negative	25.0	1.0	Reference	1.0	Reference
	MUC2	75	Positive	5.0	1.6	(1.1-2.3)	1.6	(1.1-2.4)
		45	Negative	13.0	1.0	Reference	1.0	Reference
	MUC5AC	82	Positive	5.0	1.3	(0.9-2.0)	1.5	(1.0-2.4)
		38	Negative	12.0	1.0	Reference	1.0	Reference

NOTE: Associations not shown for 24 poorly differentiated ductal AC, 7 neuroendocrine, and 10 specialized adenocarcinomas.

*Survival time in months from diagnosis to death.

†Adjusted for gender, time period, age (<75 versus 75+ y), race (Asian versus non-Asian), stage (local and regional versus distant and unstaged), pancreatic versus metastatic tissue, and ever versus never surgical or radiation treatment for pancreatic cancer.

Table 4

Cox-Proportional hazard ratios, time from diagnosis to death in months for 120 well-differentiated adenocarcinomas (75% of tumors in cohort) by MUC2 expression (negative versus weak, moderate, and strong)

Histology	% of all tumors	No	MUC2 expression	Median survival*	Unadjusted Model HR (95% CI)		Adjusted Model† HR (95% CI)	
Differentiated ductal AC	75%	94	Signal	5.0	1.9	(1.2, 2.9)	1.9	(1.2, 3.2)
		26	No Signal	17.5	1.0	Reference	1.0	Reference

NOTE: Associations not shown for 24 poorly differentiated ductal AC, 7 neuroendocrine, and 10 specialized adenocarcinomas.

*Survival time in months from diagnosis to death.

†Adjusted for gender, time period, age (<75 versus 75+ y), race (Asian versus non-Asian), stage (local and regional versus distant and unstaged), pancreatic versus metastatic tissue, and ever versus never surgical or radiation treatment for pancreatic cancer.