

Allergies, obesity, other risk factors and survival from pancreatic cancer

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Survival from pancreatic adenocarcinoma remains extremely poor, approximately 5% at 5 years. Risk factors include smoking, high body mass index (BMI), family history of pancreatic cancer, and long-standing diabetes; in contrast, allergies are associated with reduced risk. Little is known about associations between these factors and survival. We analyzed overall survival in relation to risk factors for 475 incident cases who took part in a hospital based case-control study. Analyses were conducted separately for those who did (160) and did not (315) undergo tumor resection. Kaplan-Meier methods were used to describe survival according to smoking, BMI, family history, diabetes, and presence of allergies. Cox proportional hazards models were used to adjust for covariates. There was no association with survival based on smoking, family history, or history of diabetes in either group. Among patients with resection, those with allergies showed nonstatistically significant longer survival, a median of 33.1 months (95% CI: 19.0–52.5) vs. 21.8 months (95% CI: 18.0–33.1), $p = 0.25$. The adjusted hazard ratio (HR) was 0.72 (95% CI: 0.43–1.23), $p = 0.23$. Among patients without resection, those with self-reported allergies survived significantly longer than those without allergies: 13.3 months (95% CI: 10.6–16.9) compared to 10.4 months (95% CI: 8.8–11.0), $p = 0.04$, with an adjusted HR of 0.68 (95% CI: 0.49–0.95), $p = 0.02$. Obesity was nonsignificantly associated with poorer survival, particularly in the resected group (HR = 1.62, 95% CI: 0.76–3.44). The mechanisms underlying the association between history of allergies and improved survival are unknown. These novel results need to be confirmed in other studies.

Key words: pancreatic cancer, survival, allergies, BMI

Abbreviations: BMI: body mass index; HR: hazard ratio; MSKCC: Memorial Sloan-Kettering Cancer Center; OR: odds ratio; Th2: helper T cells type 2; Th1: helper T cells type 1; T_{regs}: T regulatory cells

Novelty and impact: Few studies have investigated whether established risk factors for pancreatic cancer are related to survival. We report on results from a study of 475 patients at our institution who took part in an epidemiologic study and were followed for outcome. Self-reported allergies, known to be associated with reduced risk of pancreatic cancer, were found to be associated with improved survival: the adjusted hazard ratio was 30% lower than for those without allergies. This is a novel finding that is of great interest because it suggests that this aspect of the immune system can potentially be harnessed to improve outcomes for these patients.
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Pancreatic adenocarcinoma is the fifth leading cause of cancer mortality. The estimated number of new cases in the US in 2009 is 42,470 and the estimated number of deaths is nearly as high, 35,240.¹ The high mortality is due to the advanced disease stage at the time of diagnosis and the limited effectiveness of systemic therapies. Only a small percentage of patients, about 15–20%, have a resectable tumor.² Five-year survival is approximately 5.5%,³ although recent years have seen a small improvement in 2-year survival from 6.1% in 1973 to 10.2% in 2002. This is thought to be attributable to increased use of resection, improved surgical techniques leading to lower perioperative mortality, and increased use of adjuvant chemotherapy.^{2,4} Although resection is the most effective therapy for pancreatic cancer, recurrence and death from disease occur in the vast majority of patients.

Little is known about the relationship between established risk factors for pancreatic cancer and survival. Smoking is associated with about 2- to 3-fold increased risk.^{5–8} Obesity is also a risk factor, considered “convincing” by the recent World Cancer Research Fund report, based on data from 28 studies.⁹ Long-standing diabetes^{5–8,10} and high plasma glucose concentration without overt diabetes¹¹ have been reported to be positively associated with disease; in addition, new onset diabetes may be an early marker of pancreatic cancer.^{12–14} Family history increases risk,¹⁵ accounts for 4–16%

of cases,¹⁶ and interacts with smoking.^{17–19} In contrast, studies have consistently shown reduced risk for pancreatic cancer among individuals with allergies, particularly respiratory allergies.^{20–23} The mechanisms through which this protective effect works remain unknown.

The purpose of this study was to evaluate the association of established risk factors for pancreatic cancer with outcome. In cases recruited to a case-control study of pancreatic cancer at a large referral center, we investigated the association of smoking history, obesity, diabetes, family history of pancreatic cancer, and allergies on survival, controlling for clinical factors known to influence outcome.

Material and Methods

Study population and data collection

Cases in this analysis came from an ongoing hospital-based case-control study and Familial Pancreatic Cancer Registry at Memorial Sloan-Kettering Cancer Center (MSKCC). Patients were eligible if they were over age 21 years, spoke English, and had pathologically or cytologically confirmed adenocarcinoma of the pancreas. Patients were recruited from the surgical, medical oncology, and gastroenterology clinics at MSKCC when seen for initial diagnosis or follow-up, including post-surgical care or chemotherapy. The 475 patients in this analysis were recruited between April 1, 2004, and May 1, 2008 and consented to the study within 6 months of diagnosis. Among those cases approached and eligible, 77% have enrolled. The study was approved by the MSKCC Institutional Review Board and all enrolled participants signed informed consent.

The study questionnaire was administered by the research study assistant by telephone or in person and covered known and potential risk factors for pancreatic cancer. Detailed smoking history was collected, as well as information about height and weight at different times and history of diabetes. The question on allergies asked the respondent if he or she “ever had allergies to foods, animals, pollen or hay fever, plants such as poison ivy, bee stings, molds, medicine or vaccines.” The interviewer recorded a “yes” or “no” response to this question and those who said “yes” were asked “What are you or have you been allergic to? Anything else?” The question was open ended and there was no restriction on the number or type of allergies patients could name. There was not a specific question on asthma. Detailed family history of cancer was collected in a separate questionnaire.

Statistical analyses

The outcome was overall survival. Because outcome and the clinical factors associated with outcome varied substantially according to whether patients had resection, analyses were conducted separately for patients who underwent resection ($n = 160$) and those who did not ($n = 315$). For the resected patients, the baseline from which overall survival was calculated was the date of surgery; for the nonresected patients, the baseline was the date of diagnosis. Patients were followed to

date of death or last follow up. The chi-square test was used to examine differences in characteristics between the resected and nonresected cohorts. Chemotherapy treatment was initiated at different times from the baseline; therefore, a landmark analysis was used in which the start date for calculation of survival was 2 months from the baseline. Eighteen patients from the resected cohort and 37 patients from the nonresected cohort died or were lost to follow-up in that time period and were excluded from analyses of the chemotherapy variable. Patients who did not start chemotherapy within 2 months of the baseline dates were considered not to have had chemotherapy.

Survival probabilities were estimated using Kaplan-Meier methods and strata were compared using the log-rank test. Univariate analyses were conducted to evaluate the association of clinical variables and risk factors with overall survival. Clinical variables included: Eastern Cooperative Oncology Group performance status (>1 vs. ≤ 1), with higher score representing poorer performance; nodal status (N1 vs. N0) and tumor stage (T3/T4 vs. T1/T2) in the resected patients; metastatic disease in the nonresected patients [metastasis (M1) vs. no metastasis (M0)]; and chemotherapy at 2 months after baseline (yes/no). Risk factors included age, gender, smoking history (never, past, current, with current smokers including those who smoked within the year before diagnosis), body mass index [BMI, weight (kg)/height (m^2) based on usual adult weight, classified as normal (<25), overweight (25 to <30), and obese (≥ 30)], diabetes diagnosed ≥ 3 years before the pancreatic cancer diagnosis (yes/no), family history of pancreatic cancer (any first-degree relative vs. none), history of any allergies (yes/no) and history of hay fever, seasonal allergies, or allergies to grass or pollen (yes/no; *i.e.*, any mention of these or similar allergies), and history of allergy to medications (yes/no; *i.e.*, mention of allergy to any medication). Presence of any allergies, BMI, and those variables that were significant in the univariate analyses were included in Cox regression models to adjust for covariates. In separate models, allergies to medications or hay fever were included with the same covariates, excluding the presence of any allergies. SAS 9.2 was used for all analyses.

Results

As shown in Table 1, the mean age of patients in this study was 64 and 52% were male. They were primarily Caucasian (88%) and Catholic (45%). Fifty-three percent had ever smoked cigarettes and 12% were current smokers. Forty-three percent were overweight and 23% were obese; 10% had diabetes diagnosed at least 3 years before the pancreatic cancer diagnosis. Ten percent reported a first-degree relative with pancreatic cancer, with resected patients more likely than nonresected patients to report this family history (15% vs. 8%, $p = 0.02$). Allergies were reported by 52%. Most patients had high-performance status (≤ 1). Among the resected cohort, two-thirds had positive lymph nodes and 91% had tumors classified as T3/T4. Among the nonresected cohort, 56% had metastatic disease. Seventy-seven percent received

Table 1. Patient characteristics

Characteristics	All patients (<i>n</i> = 475)		Resected (<i>n</i> = 160)		Nonresected (<i>n</i> = 315)	
	63.7 ± 10.8		64.6 ± 11.1		63.2 ± 10.7	
Mean age at diagnosis (years ± SD)	No.	%	No.	%	No.	%
Gender—male	247	52	79	49	168	53
Race						
White/Caucasian	420	88	143	89	277	88
Black/African-American	26	6	6	4	20	6
Asian	18	4	8	5	10	3
Others	11	2	3	2	8	3
Religion						
Catholic	214	45	71	44	143	45
Protestant	104	22	31	19	73	23
Jewish	09	25	43	27	76	24
Other/None	38	8	15	9	23	7
Smoking history						
Never smoked	221	47	83	52	138	44
Past smoker	197	41	63	39	134	42
Current smoker	57	12	14	9	43	14
BMI						
Normal (<25)	160	34	55	34	105	33
Overweight (25 to <30)	204	43	74	46	130	41
Obese (>30)	108	23	29	18	79	25
Diabetes	47	10	14	9	33	10
Pancreatic cancer in 1° relative	49	10	24	15	25	8
Allergies ¹	249	52	84	53	165	52
Medications	116	24	37	23	79	25
Hay fever ²	105	22	32	20	73	23
ECOG performance status						
≤1	370	78	114	71	256	81
>1	29	6	7	4	22	7
Missing	76	16	39	24	37	12
Lymph nodes						
N0 (negative)			52	33	NA	
N1 (positive)			107	67	NA	
Missing			1	1	NA	
Tumor stage						
T1/T2			14	9	NA	
T3/T4			145	91	NA	
Missing			1	1	NA	
Metastases						
M0 (negative)			NA		86	27
M1 (positive)			NA		177	56
Missing			NA		52	17
Chemotherapy ³	325	77	89	63	236	85

NA, not applicable, ECOG, Eastern Cooperative Oncology Group.

¹Includes allergies to foods, animals, pollen or hay fever, plants such as poison ivy, bee sting, molds, medicine or vaccines. ²Includes hay fever, seasonal allergies and allergies to grass or pollen. ³Chemotherapy at 2 months after baseline, among 142 in the resected cohort and 278 in the non resected cohort, 420 in total.

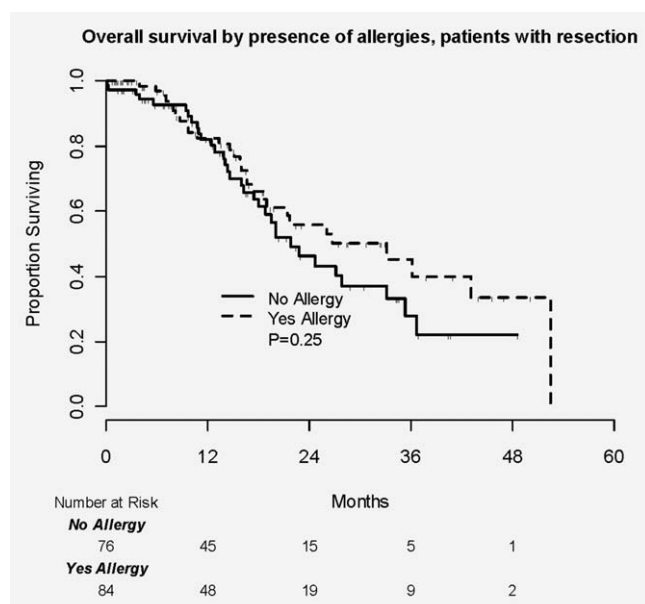


Figure 1. Overall survival of patients with resection according to presence of allergies.

chemotherapy 2 months after baseline, including 63% of the resected and 85% of the nonresected patients.

Figure 1 shows survival in the resected cohort according to the presence or absence of allergies: median survival for those with allergies was 33.1 months (95% CI: 19.0–52.5) compared to 21.8 months (95% CI: 18.0–33.1) for those without allergies ($p = 0.25$). In univariate analyses for the resected cohort (Table 2), there was no statistically significant association with survival based on any of the risk factor variables studied. The hazard ratio (HR) for allergies showed reduced risk (HR = 0.74, 95% CI: 0.45–1.23); there was also reduced risk associated with allergies to medications (HR = 0.62, 95% CI: 0.32–1.23), while hay fever was not related to risk. Increased risk was found for those who were obese (HR = 1.56, 95% CI: 0.75–3.23). The only factors significantly related to survival were the presence of positive lymph nodes (HR = 2.36, 95% CI: 1.31–4.25) and tumor stage (HR = 4.39, 95% CI: 1.07–18.0). When the presence of any allergy, BMI, nodal status, and tumor stage were included in the same model, there was little change in the HRs for allergies or BMI. Nodal status and tumor stage remained associated with overall survival although stage was not statistically significant. In separate multivariate analyses for allergies to medications and hay fever, results were similar to those reported above: for allergies to medications, HR = 0.66 (95% CI: 0.33–1.31); for hay fever, HR = 1.20 (95% CI: 0.65–2.22) (data not shown in tables).

For the nonresected cohort, median survival for those with allergies was 13.3 months (95% CI: 10.6–16.9), compared to 10.4 months (95% CI: 8.8–11.0) for those without allergies, $p = 0.04$ (Fig. 2). In univariate analysis (Table 3), a lower HR was observed for those with any allergies (HR = 0.75, 95% CI: 0.57–0.99) with little influence apparent for

Table 2. Factors related to survival from pancreatic cancer, resected patients

	Hazard ratio	95% CI	P value
Univariate analysis			
Age at diagnosis	1.00	0.98–1.03	0.80
Gender (female vs. male)	0.97	0.59–1.61	0.92
Smoking (past vs. never)	0.99	0.58–1.69	0.98
(current vs. never)	0.83	0.34–2.03	0.68
BMI (overweight vs. normal)	1.04	0.58–1.85	0.91
(obese vs. normal)	1.56	0.75–3.23	0.23
Diabetes (yes vs. no)	0.97	0.42–2.26	0.95
Family history (yes vs. no)	0.84	0.42–1.66	0.61
Any allergies ¹ (yes vs. no)	0.74	0.45–1.23	0.25
Medications (yes vs. no)	0.62	0.32–1.23	0.17
Hay fever ² (yes vs. no)	1.16	0.64–2.11	0.63
ECOG status (>1 vs. ≤1)	1.52	0.47–4.89	0.49
Lymph nodes (≥1 vs. 0)	2.36	1.31–4.25	<0.01
Tumor stage (T3/T4 vs. T1/T2)	4.39	1.07–18.0	0.04
Chemotherapy ³ (yes vs. no)	1.22	0.72–2.06	0.46
Multivariate analysis⁴			
Any allergies ¹ (yes vs. no)	0.72	0.43–1.23	0.23
Overweight vs. normal	1.02	0.56–1.88	0.94
Obese vs. normal	1.62	0.76–3.44	0.21
Lymph nodes (≥1 vs. 0)	2.12	1.16–3.88	0.01
Tumor stage (T3/T4 vs. T1/T2)	3.34	0.79–14.1	0.10

ECOG, Eastern Cooperative Oncology Group.

¹Includes allergies to foods, animals, pollen or hay fever, plants such as poison ivy, bee sting, molds, medicine or vaccines. ²Includes hay fever, seasonal allergies and allergies to grass or pollen. ³Landmark analysis was applied. ⁴Adjusted for variables shown. Analysis was based on 156 patients with data on all variables.

either allergies to medications (HR = 0.81, 95% CI: 0.58–1.13) or hay fever (HR = 0.84, 95% CI: 0.60–1.18). Obesity (HR = 1.17, 95% CI: 0.82–1.68) and other risk factors did not influence survival. Poor performance status and the presence of metastases were associated with poorer survival: HR = 2.93 (95% CI: 1.73–4.96) and HR 2.11 (95% CI: 1.49–3.00), respectively. Having chemotherapy was associated with longer survival (HR = 0.66, 95% CI: 0.47–0.94). In multivariate Cox regression models, results for both allergies and obesity were slightly strengthened. The HR for allergies was 0.68 (95% CI: 0.49–0.95), while that for obesity was 1.38 (95% CI: 0.90–2.11). In separate analyses for allergies to medications and hay fever, the adjusted HR for those allergic to medications was 0.68 (95% CI: 0.45–1.04), while for hay fever HR = 0.88 (95% CI: 0.59–1.31) (data not shown in tables).

Discussion

Among patients with pancreatic cancer who did not undergo resection, we found significantly improved survival for those

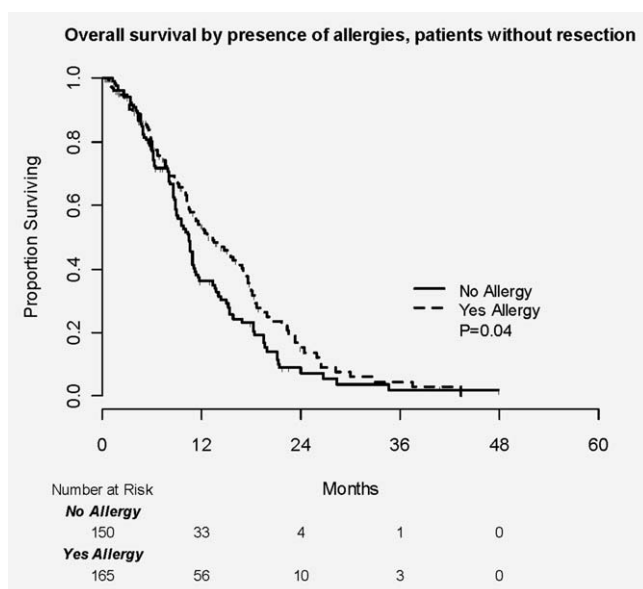


Figure 2. Overall survival of patients without resection according to presence of allergies.

who reported a history of allergies compared to those without allergies. Among those who underwent resection, survival was more favorable for those with allergies, although this difference was not statistically significant. As the HR associated with allergies was similar for the two groups, it is likely that the lack of statistical significance for the resected group was related to the smaller sample size. Post-hoc power calculations indicate that power to detect the differences observed was <30% in the resected patients. To our knowledge, our study is the first analysis of survival of pancreatic cancer in relation to allergies. Pompei *et al.*²⁴ found higher probability of cure and lower disease progression and longer survival in 92 patients with various types of cancer who had allergies compared to 182 without allergies; none of the 16 pancreatic cancer patients in that study had allergies, so comparisons could not be made in these patients.

The association of allergies with reduced risk of developing pancreatic cancer is well established. A recent review and meta-analysis of 14 studies²¹ conducted from the 1970s to the 1990s showed an overall odds ratio (OR) of 0.82 (95% CI: 0.68–0.99) for the presence of any allergies, and a stronger effect (OR = 0.75, 95% CI: 0.65–0.87) in the studies that adjusted for smoking. Reduced risk is most consistently associated with respiratory allergies, such hay fever and allergies to grass, pollen and plants.^{20,22,25–30} Studies examining risk of pancreatic cancer in relation to medications have shown inconsistent results,^{22,29,31,32} probably reflecting different patterns of medication usage in different times and locations. The present analysis indicated that allergies to medications appear to be associated with survival, while hay fever was not. Among our patients with allergies to medications, about two-thirds were allergic to antibiotics and about one-quarter allergic to pain medications (data not shown). Larger studies are

Table 3. Factors related to survival from pancreatic cancer, nonresected patients

	Hazard ratio	95% CI	P value
Univariate analysis			
Age at diagnosis	1.01	1.00–1.02	0.20
Gender (female vs. male)	0.82	0.62–1.08	0.16
Smoking (past vs. never)	1.00	0.73–1.36	0.97
(current vs. never)	0.79	0.52–1.20	0.26
BMI (overweight vs. normal)	0.92	0.89–1.69	0.21
(obese vs. normal)	1.17	0.82–1.68	0.39
Diabetes (yes vs. no)	0.78	0.47–1.30	0.34
Family history (yes vs. no)	1.03	0.61–1.75	0.91
Any allergies ¹ (yes vs. no)	0.75	0.57–0.99	0.04
Medications (yes vs. no)	0.81	0.58–1.13	0.21
Hay fever ² (yes vs. no)	0.84	0.60–1.18	0.32
ECOG status (>1 vs. ≤1)	2.93	1.73–4.96	<0.0001
Metastases (M1 vs. M0)	2.11	1.49–3.00	<0.0001
Chemotherapy ³ (yes vs. no)	0.66	0.47–0.94	0.02
Multivariate analysis⁴			
Any allergies ¹ (yes vs. no)	0.68	0.49–0.95	0.02
Overweight vs. normal	1.05	0.70–1.57	0.82
Obese vs. normal	1.38	0.90–2.11	0.14
ECOG status (>1 vs. ≤1)	2.15	1.06–4.36	0.03
Metastases (M1 vs. M0)	2.18	1.48–3.21	<0.0001
Chemotherapy ³ (yes vs. no)	0.48	0.31–0.74	<0.001

ECOG, Eastern Cooperative Oncology Group.

¹Includes allergies to foods, animals, pollen or hay fever, plants such as poison ivy, bee sting, molds, medicine or vaccines. ²Includes hay fever, seasonal allergies and allergies to grass or pollen. ³Landmark analysis was applied. ⁴Adjusted for variables shown. Based on 215 patients with data on all variables.

needed to examine this further. The number of patients with other specific allergies was too small for meaningful analysis.

Although our results for the association between obesity and survival in patients with pancreatic cancer did not reach statistical significance, they are consistent with other studies. A recently reported hospital based epidemiologic study has shown that high BMI, and particularly obesity, in adulthood and the year before diagnosis is associated with poorer survival.³³ A second study in a similar setting found poorer survival for patients with usual adult BMI ≥ 35.³⁴ Increased risk of death in resected patients with BMI > 35 at the time of referral was also noted in a record-based study.³⁵ The observed HRs in our study, particularly in the resected cohort, are fairly similar to those found in other studies and point to a potential increase in risk of mortality among heavier patients. As noted above, reduced power in the resected cohort affects our ability to reach statistical significance. Our results are also consistent in finding stronger associations between BMI and survival among those with resection. In an

earlier study at our institution, we noted increased complications among resected patients with generalized obesity and visceral fat.³⁶ Further examination of the association of obesity with outcomes in patients with pancreatic cancer is warranted. Other studies in a population similar to ours have found, as we have, no difference in survival according to age, race, sex or smoking.³⁷

The mechanisms underlying a possible protective effect of allergies in cancer patients are unclear. Immune defense against tumors involves a number of different cell types, including CD8+ T cells (cytotoxic T lymphocytes) and CD4+ T cells (helper cells) from the adaptive immune system. In pancreatic cancer, presence of both these cell types among tumor-infiltrating lymphocytes appears to be important for survival.³⁸ The presence of allergies is associated with 1 subset of CD4+T cells: when sensitive individuals are exposed to environmental allergens, CD4+T cells differentiate into T helper type 2 (Th2) effector cells, rather than T helper type 1 (Th1) cells, the dominant type in nonatopic individuals. These two subgroups release different groups of cytokines: Th1 cells produce primarily IFN- γ , while Th2 cells produce primarily IL-4. In the presence of IL-4, B cells switch to production of IgE antibodies rather than IgG or IgA antibodies. IgE itself is a potential factor in cytotoxicity towards tumors. In a small *in vitro* study,³⁹ Fu *et al.* found that whole serum from patients with pancreatic cancer resulted in antibody-dependent cell-mediated cytotoxicity which was reduced when IgE was depleted. These findings are consistent with studies in a mouse model of ovarian cancer.^{40,41} In glioma, another tumor for which self-reported allergies are consistently associated with reduced risk,^{42–45} total serum IgE was strongly related to survival.⁴⁶ This aspect of immunity is addressed by the emerging field of allergeo-oncology.⁴⁷

Another potentially important factor in host immune defense against tumors is the production of T regulatory cells (T_{regs}) by tumors. T_{regs} secrete immunosuppressive cytokines and suppress cytotoxic T lymphocytes, thereby protecting tumors from attack. It has been observed that immunosuppressive T_{regs} are elevated in peripheral blood cells of patients with pancreatic cancer^{48,49} and that depletion of T_{regs} in a mouse model of pancreatic cancer led to stronger immune response.⁵⁰ In a genetic mouse model with a mutation in codon 12 of *kras*, mimicking the majority of human pancreatic tumors, the immune response is dominated by immunosuppressive cells, including T_{regs}, that are likely to suppress tumor infiltrating effector T cells.⁵¹ This was observed at both preinvasive and later stages of tumor growth. In addition, there is a strong desmoplastic response in pancreatic

cancer, resulting in cytotoxic T cells' being trapped in the stroma and isolated from the tumor.^{52,53} We can speculate that these failures of the usual immune response to pancreatic tumors may allow for a role for other immune mechanisms, such as those represented by the IgE/Th2 pathway.

Strengths of our study include the availability of extensive epidemiologic and clinical data on our patients. Prevalence of allergies was high in our population, with about half the patients reporting some allergy, and it is possible that some reported allergies have other types of causes. Published reports from case-control studies of allergy and risk show a wide range in prevalence of allergies,^{20–22} attributable to several factors. There has been a well-documented increase in prevalence of allergies in western countries.^{54–59} The studies covered different populations (Europe, Asia, various regions in North America), so that both environmental exposures and genetic background of the population are likely to be different. In addition, the specific questions asked about allergies differed among studies.

Our patient population is not typical, since a larger proportion (34%) were resected than among most patients with pancreatic cancer and overall survival is longer than expected, even in the nonresected patients. This reflects selection of a specialized tertiary-care institution such as ours by patients with treatable disease and the bias towards longer term survivors in all case-control studies of pancreatic cancer. These factors are similar in other epidemiologic studies of survival in relation to patient characteristics.^{33,35,37} Among eligible patients who were approached for this study, those who were aged >70 years were more likely to refuse to participate, particularly among the women (data not shown). We did not ascertain cause of death, so it is possible that for some patients who died, there was a cause other than pancreatic cancer. Further, it is possible that there were differences between in-person and telephone interviews in the health of the respondents and likelihood of recalling allergies, which could have led to biased results; since we did not record the interview method, we were unable to evaluate this possibility.

In conclusion, the very poor outcome for pancreatic cancer and the possibility of new therapeutic avenues raised by the findings on allergies suggest that this is a promising area for future research. Such research should be directed towards further prospective studies to evaluate associations of allergies with survival to replicate these results, and mechanistic studies to help explain the biologic basis of these observations. Our results for the association of obesity with survival support those of other investigators, and indicate the importance of continuing work in this area as well to understand the mechanisms involved.

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