Prediagnostic Body Mass Index and Pancreatic Cancer Survival

Chen Yuan, Ying Bao, Chen Wu, Peter Kraft, Shuji Ogino, Kimmie Ng, Zhi Rong Qian, Douglas A. Robinson, Meir J. Stampfer, Edward L. Giovannucci, and Brian M. Wolpin

ABSTRACT

Purpose

Although obesity is associated with increased incidence of pancreatic cancer, studies have not prospectively evaluated prediagnostic body mass index (BMI) and survival.

Patients and Methods

We analyzed survival by prediagnostic BMI assessed in 1986 among 902 patients from two large prospective cohorts diagnosed from 1988 to 2010. We estimated hazard ratios (HRs) for death using Cox proportional hazards models, with adjustment for age, sex, race/ethnicity, smoking, diagnosis year, and stage. We evaluated the temporal association of BMI with survival by grouping reported BMI by 2-year lag-time intervals before diagnosis.

Results

The multivariable-adjusted HR for death was 1.53 (95% CI, 1.11 to 2.09) comparing patients with BMI ≥ 35 kg/m² with those with BMI < 25 kg/m² (P trend = .001), which was similar after adjustment for stage. The association of BMI with survival was stronger with longer lag times between reported BMI and cancer diagnosis. Among patients with BMI collected 18 to 20 years before diagnosis, HR for death was 2.31 (95% CI, 1.48 to 3.61; P trend $< .001$), comparing obese with healthy-weight patients. No statistically significant differences were seen by cohort, smoking status, or stage, although the association was stronger among never-smokers (HR, 1.61; 95% CI, 1.01 to 2.57; P trend = .002) than ever-smokers (HR, 1.36; 95% CI, 0.86 to 2.15; P trend = .63), comparing BMI ≥ 35 kg/m² with BMI < 25 kg/m². Higher prediagnostic BMI was associated with more advanced stage at diagnosis, with 72.5% of obese patients presenting with metastatic disease versus 59.4% of healthy-weight patients ($P = .02$).

Conclusion

Higher prediagnostic BMI was associated with statistically significantly decreased survival among patients with pancreatic cancer from two large prospective cohorts.

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INTRODUCTION

Pancreatic cancer is the fourth-leading cause of cancer-related death in the United States.¹ Among patients who develop pancreatic adenocarcinoma, only 5% will survive 5 years after diagnosis, and most patients live < 12 months. The length of patient survival is greatly influenced by disease stage at presentation, but few other markers of survival have been well characterized.²

Multiple studies have demonstrated that high body mass index (BMI) is associated with increased risk of developing pancreatic cancer.³⁻⁵ Subsequent work has suggested that alterations in systemic metabolism as a consequence of peripheral insulin resistance may underlie the association of excess weight with disease risk.⁶⁻⁹ Additionally, chronic inflammation that can be induced by obesity may be

related to the observed associations.^{10,11} However, few studies have evaluated the impact of BMI on survival of patients with pancreatic cancer, and no studies have used prospectively collected data on BMI.

Early manifestations of subclinical pancreatic cancer include weight loss and hyperglycemia, and these symptoms are commonly seen 12 to 24 months before the clinical diagnosis of pancreatic cancer.^{12,13} Therefore, measurement of BMI at the time of diagnosis does not provide accurate representation of a patient's long-term exposure to obesity and insulin resistance. Furthermore, retrospective studies are subject to biases related to patient recall and proxy respondents. Prospective cohort studies provide a unique opportunity to evaluate repeated BMI evaluations collected over many years before the diagnosis of pancreatic cancer. In

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the current study, we prospectively evaluated the association of prediagnostic BMI with survival among participants diagnosed with pancreatic cancer from two large prospective cohort studies.

PATIENTS AND METHODS

Study Population

We assessed the association of prediagnostic BMI with survival among participants with pancreatic cancer from the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS). NHS was initiated in 1976 when 121,700 female registered nurses age 30 to 55 years returned a mailed questionnaire describing demographics, lifestyle choices, and medical history.¹⁴ HPFS began in 1986 when 51,529 men age 40 to 75 years working as dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, or podiatrists returned a mailed questionnaire on health-related behaviors and medical history.¹⁵ Participants have updated information on exposures and medical history through biennial follow-up questionnaires. The studies are approved by the Human Research Committee at Brigham and Women's Hospital (Boston, MA), and participants provided informed consent.

Exposure Data

The primary exposure of baseline prediagnostic BMI (weight [kg] divided by square of height [m]) was calculated from weight reported on the 1986 questionnaire in NHS and HPFS and height reported on the 1976 questionnaire in NHS and 1986 questionnaire in HPFS. For participants in NHS without weight available on the 1986 questionnaire, we carried forward the weight from 1980 to 1984, if available. For secondary analyses, we used weight reported on biennial follow-up questionnaires to calculate BMI at additional time points before diagnosis. BMI was categorized using WHO criteria for healthy weight (18.5 to 24.9 kg/m²), overweight (25.0 to 29.9 kg/m²), and obese (≥ 30 kg/m²). For some analyses, sample size was adequate to further classify the obese group into two categories: BMI 30.0 to 34.9 kg/m² and BMI ≥ 35 kg/m². In a validation subsample, questionnaire-reported and staff-measured weights were highly correlated ($r = 0.96$; mean difference, 3.3 lbs).¹⁶

Detailed covariate data, including age, race/ethnicity (white, black, other, unknown), smoking status (never, past, current, missing), multivitamin use (yes, no), physical activity (MET-hr/wk), alcohol intake (g/d), energy intake (kcal/d), and history of diabetes mellitus (yes, no), were obtained from 1986 and subsequent questionnaires. Date and pancreatic cancer stage at diagnosis were obtained from medical record review. Cancer stage was classified as: local disease amenable to surgical resection; locally advanced disease with extra-pancreatic extension rendering it unresectable, but without distant metastases; distant metastatic disease; or unknown.

Patients With Pancreatic Cancer

Incident patient cases of pancreatic cancer were identified through May 31, 2010, in NHS and January 31, 2010, in HPFS by self-report or during follow-up of a participant's death. Deaths were ascertained from next of kin or postal service and by searching the National Death Index; this method has been shown to capture $> 98\%$ of deaths.¹⁷ Diagnoses were confirmed by review of medical records, death certificates, and/or tumor registry data. Those with nonadenocarcinoma histology were excluded.

During 24 years of follow-up, we identified 958 patient cases of pancreatic cancer in NHS and HPFS with available BMI from the baseline questionnaires. Fifty-eight participants who developed pancreatic cancer did not report BMI on baseline questionnaires and therefore were not included in the analysis. Because pancreatic cancer can lead to significant weight loss and metabolic derangements in 12 to 24 months before diagnosis,^{9,10} we excluded 48 participants diagnosed with pancreatic cancer within 2 years of return of the 1986 questionnaire. We also excluded eight participants with BMI < 18.5 kg/m² because of concerns regarding coexistent illness that might limit survival. Therefore, the current analysis included 902 patients with pancreatic cancer, including 561 participants from NHS and 341 from HPFS.

Statistical Analysis

We examined the association of prediagnostic BMI with survival using Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% CIs for mortality by category of BMI. Overall survival time was calculated from pancreatic cancer diagnosis to death or May 31, 2010, in NHS and to death or January 31, 2010, in HPFS, whichever came first. Two-sided tests for trend across BMI categories were calculated by entering median values from each BMI category into Cox models as continuous variables. The proportionality of hazards assumption was satisfied by evaluating a time-dependent variable, which was the cross-product of BMI and time ($P = .73$). Survival curves were

Table 1. Baseline Characteristics of Patients With Pancreatic Cancer

Characteristic	NHS (n = 561)		HPFS (n = 341)		Total (N = 902)	
	No.	%	No.	%	No.	%
Age at baseline BMI, years						
Mean	56.5		60.1		57.8	
SD	6.2		8.3		7.3	
Age at cancer diagnosis, years						
Mean	71.2		72.8		71.8	
SD	7.6		8.7		8.1	
Race/ethnicity						
White	547	97.5	308	90.3	855	94.8
Black	6	1.1	7	2.1	13	1.4
Other	8	1.4	11	3.2	19	2.1
Unknown	0	0.0	15	4.4	15	1.7
BMI, kg/m ²						
Mean	26.1		25.6		25.9	
SD	5.2		3.1		4.5	
< 25	290	51.7	153	44.9	443	49.1
25 to 29.9	162	28.9	161	47.2	323	35.8
≥ 30	109	19.4	27	7.9	136	15.1
Physical activity, MET-hr/wk						
Mean	13.6		17.8		15.4	
SD	18.3		20.8		19.6	
Smoking status						
Never	234	41.7	126	37.0	360	39.9
Past	162	28.9	151	44.3	313	34.7
Current	159	28.3	53	15.5	212	23.5
Missing	6	1.1	11	3.2	17	1.9
History of diabetes mellitus	24	4.3	17	5.0	41	4.6
Multivitamin use	172	30.7	149	43.7	321	35.6
Alcohol intake, g/d						
Mean	6.9		12.0		9.2	
SD	11.8		17.2		14.7	
Cancer stage						
Localized	75	13.4	58	17.0	133	14.8
Locally advanced	48	8.6	55	16.1	103	11.4
Metastatic	272	48.5	167	49.0	439	48.7
Unknown	166	29.6	61	17.9	227	25.2
Diagnosis period						
1988 to 1995	108	19.3	104	30.5	212	23.5
1996 to 2000	125	22.3	98	28.7	223	24.7
2001 to 2005	185	33.0	94	27.6	279	30.9
2006 to 2010	143	25.5	45	13.2	188	20.8
Median time baseline BMI to diagnosis, years	15.7		12.9		14.7	
Median survival time, months	5		5		5	

Abbreviations: BMI, body mass index; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; SD, standard deviation.

generated using the Kaplan-Meier method, and statistical significance was measured using the log-rank test.

A priori, we included in multivariable-adjusted models the covariates with the greatest likelihood for confounding, including age at diagnosis, race/ethnicity, sex, smoking status, and cancer stage. We also included the time period of diagnosis to account for changes in survival over time. We evaluated physical activity, alcohol intake, and multivitamin use as additional possible confounders, but none were associated with survival (all $P > .1$). History of diabetes mellitus was not included in our multivariate model, because it may lie within the causal pathway of BMI and survival. However, in additional analyses, our results were similar after inclusion of diabetes as a covariate in our multivariate model and after removal of patients with diabetes at baseline or who developed diabetes before diagnosis. Given a prior study suggesting an association between metabolic syndrome and pancreatic cancer stage at diagnosis,¹⁸ we created two multivariable-adjusted models with and without stage to investigate whether adjustment for stage might alter an association between BMI and pancreatic cancer survival. We noted similar results in a sensitivity analysis in which we removed patients with unknown stage.

The aim of this analysis was to characterize the association between pancreatic cancer survival and chronic overweight/obesity, before weight loss that often accompanies subclinical or newly diagnosed pancreatic malignancy. Therefore, primary analyses evaluated baseline BMI in 1986 without cumulative updating during follow-up. We also excluded patients diagnosed within 2 years of responding to the 1986 questionnaire to achieve a minimum 2-year lag time between assignment of exposure and diagnosis. We subsequently performed two secondary analyses using full available data for BMI collected from participants every 2 years. First, we grouped reported BMI by 2-year time intervals before cancer diagnosis and evaluated whether the association of BMI with pancreatic cancer survival differed by lag time between BMI measurement and cancer diagnosis. Second, we investigated a cumulative average BMI for each participant, which was average BMI weighted by exposure time from 1986 until the most recent questionnaire returned > 2 years before diagnosis.

We assessed heterogeneity in the association between BMI and pancreatic cancer survival in NHS and HPFS using Cochran's Q statistic¹⁹; the Cochran's Q statistic P value was .79 for the comparison of BMI ≥ 30 kg/m² with BMI < 25 kg/m² across the cohorts. We also evaluated stratified analyses by cohort (also stratified by sex), smoking status, disease stage, and diagnosis period. We assessed statistical interaction by entering main effect terms and a cross-product term of continuous BMI and stratification variable into the model, evaluating likelihood ratio tests. All statistical analyses were performed using SAS 9.3 statistical package (SAS Institute, Cary, NC), and all P values are two sided.

RESULTS

Baseline characteristics of 902 patients with pancreatic cancer are listed in Table 1. Mean age at baseline BMI measurement was 57.8 years, and median time between baseline BMI and pancreatic cancer diagnosis was 14.7 years. Mean baseline BMI was 25.9 kg/m², with 36% of patients classified as overweight and 15% as obese. Among those with known disease stage, 19.7% had localized disease, 15.3% had locally advanced disease, and 65.0% had metastatic disease. Median survival by cancer stage was 16 months for those with localized disease, 8 months for those with locally advanced disease, and 3 months for those with metastatic disease. At the end of follow-up, 868 patients (96%) were deceased.

Higher baseline BMI was associated with reduced survival (Table 2). In Cox regression models adjusted for age, cohort (also adjusted for sex), race/ethnicity, smoking status, and time period of diagnosis, the HR for death was 1.53 (95% CI, 1.11 to 2.09), comparing BMI ≥ 35 kg/m² with BMI < 25 kg/m² (P trend = .001). In multivariate models further adjusted for disease stage, the association was mildly attenuated, with HR for death of 1.45 (95% CI, 1.05 to 1.99), comparing BMI ≥ 35 kg/m² with BMI < 25 kg/m² (P trend = .01). Kaplan-Meier curves are shown in Figure 1 (log-rank $P = .03$). Furthermore, we divided participants into quintiles based on survival time to examine the proportion of healthy-weight individuals across categories of survival time (Appendix Table A1, online only). Notably, 44.1% of those in the bottom 20% of survival time (< 2 months) and 55.7% of those in the top 20% of survival time (> 13 months) were of healthy weight.

Higher baseline BMI was associated with more advanced stage of disease at diagnosis (Table 3). Patients had mean baseline BMI of 25.2 kg/m² when presenting with localized disease, 25.5 kg/m² with locally advanced disease, and 26.3 kg/m² with metastatic disease (analysis of variance $P = .03$). This corresponded to 72.5% of patients with baseline BMI ≥ 30 kg/m² having metastatic disease at presentation compared with only 59.4% of patients with BMI < 25 kg/m² (Table 3; χ^2 $P = .02$).

In secondary analyses, cumulatively updated BMI was similarly associated with pancreatic cancer survival. In our multivariate model adjusted for disease stage, HR for death was 1.37 (95% CI, 1.00 to 1.88), comparing those with cumulatively updated BMI ≥ 35 kg/m²

Table 2. HRs for Death Resulting From Pancreatic Cancer by Baseline BMI

Variable	BMI (kg/m ²)									P ^a
	< 25.0	25.0 to 26.9		27.0 to 29.9		30.0 to 34.9		≥ 35.0		
	HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
Person-months	4,592	1,820		1,326		831		357		
No. of deaths	421 of 443	156 of 167		155 of 156		92 of 92		44 of 44		
Age adjusted	1.0	1.00	0.84 to 1.21	1.24	1.03 to 1.50	1.16	0.93 to 1.46	1.47	1.07 to 2.00	.003
MV adjusted I†	1.0	0.98	0.82 to 1.18	1.23	1.02 to 1.49	1.22	0.96 to 1.54	1.53	1.11 to 2.09	.001
MV adjusted II‡	1.0	0.88	0.73 to 1.06	1.04	0.86 to 1.26	1.21	0.96 to 1.53	1.45	1.05 to 1.99	.01

Abbreviations: BMI, body mass index; HR, hazard ratio; MV, multivariable.

* P for trend; tests calculated by entering stratum-specific median values for BMI as continuous variables in Cox proportional hazards models.

†Adjusted for age at diagnosis, cohort (also adjusted for sex), race/ethnicity (white, nonwhite, unknown), smoking status (current, past, never, missing), and year of diagnosis (1988 to 1995, 1996 to 2000, 2001 to 2005, 2006 to 2010).

‡Adjusted for age at diagnosis, cohort (also adjusted for sex), race/ethnicity (white, nonwhite, unknown), smoking status (current, past, never, missing), year of diagnosis (1988 to 1995, 1996 to 2000, 2001 to 2005, 2006 to 2010), and stage at diagnosis (localized, locally advanced, metastatic, unknown).

Fig 1. Kaplan-Meier curves of overall survival by baseline body mass index (BMI).

with BMI < 25 kg/m² (P trend = .06). To further investigate the temporal association of prediagnostic BMI with pancreatic cancer survival, we grouped reported BMI by 2-year time intervals before cancer diagnosis. In these analyses, we noted a stronger association with greater time between BMI assessment and cancer diagnosis (Table 4). Among participants with BMI reported between 18 and 20 years before cancer diagnosis, HR for death was 2.31 (95% CI, 1.48 to 3.61), comparing those with BMI ≥ 30 kg/m² with BMI < 25.0 kg/m² (P trend < .001).

No statistically significant effect modification was seen by cohort (also stratified by sex), disease stage, smoking status, or diagnosis period (Table 5), although the association did seem stronger among never-smokers than ever-smokers (P interaction = .06).

DISCUSSION

In this large study with prospectively collected BMI, we noted reduced survival for patients with pancreatic cancer who were obese years before their diagnosis. We also observed a statistically significant association between prediagnostic BMI and cancer stage, with more obese patients presenting with metastatic disease than patients with healthy weight. Nevertheless, the association of prediagnostic BMI was independent of other predictors of survival, including cancer stage. Fur-

thermore, the association of prediagnostic BMI with pancreatic cancer survival was strongest when BMI was measured many years before diagnosis, suggesting the importance of chronic exposure to elevated BMI in the association with survival. In aggregate, these results suggest that chronic alterations in systemic metabolism may affect survival of patients with pancreatic adenocarcinoma.

Three hospital-based studies have evaluated BMI and survival among patients with pancreatic cancer.²⁰⁻²² In these studies, patients were queried about height and weight at the time of diagnosis and were asked to recall their usual weight during adulthood or at different time points during their life. At MD Anderson Cancer Center,²⁰ patients with recalled usual adult BMI ≥ 30 kg/m² had HR of death of 1.75 (95% CI, 1.23 to 2.50), compared with those with a healthy weight from ages 30 to 39 to 50 to 59 years. In a study of patients from Memorial Sloan-Kettering Cancer Center,²¹ those with recalled BMI classified as obese had a nonstatistically significant elevated risk of death. Among patients from Mayo Clinic who completed a questionnaire at diagnosis,²² BMI was inversely associated with survival (P trend = .009). Patients with recalled usual adult BMI of 35 to 39.9 kg/m² and ≥ 40 kg/m² had HRs for death of 1.32 (95% CI, 1.02 to 1.72) and 1.67 (95% CI, 1.19 to 2.33), respectively, compared with those with healthy weight.

The associations of prediagnostic BMI with pancreatic cancer survival noted in these retrospective case-control studies are generally consistent with results from our study. However, prospective cohort studies have several design advantages over hospital-based, retrospective case-control studies, lending additional validity to their results. In retrospective case-control studies, patients are asked to recall their weight from many years before diagnosis or provide their usual weight during adulthood. Therefore, misclassification can occur because of incorrect recall of weight. Furthermore, if systematic differences in recall exist by the patient's performance status at diagnosis, recall bias can be introduced. Prospective study designs, such as that in our analysis, limit issues with misclassification and recall bias by soliciting BMI years before diagnosis, such that participants provide their current weight and are not influenced by their degree of illness at diagnosis.

Another limitation of hospital-based case-control studies relates to generalizability to the full population of patients presenting with pancreatic cancer. Tertiary centers attract patients who are younger, have fewer comorbidities, and present with earlier-stage disease.²⁰⁻²³ Furthermore, patients who consent to participate in large hospital-based case-control studies may not represent the full patient panel of the center. Some patients may be too ill or pass away before completing the necessary consents and questionnaires, therefore leading to an under-representation of patients with more aggressive tumor biology. This is of particular importance in studies of rapidly fatal malignancies, such as pancreatic cancer. Prospective study designs, such as that in our analysis, more fully capture the spectrum of patients with pancreatic cancer in terms of disease aggressiveness and stage of disease, because individuals are enrolled before their diagnosis. Notably, survival times for patients in the current study were highly similar to those of 121,713 patients included in the National Cancer Data Base, which is thought to capture 76% of patient cases of pancreatic cancer diagnosed in the United States each year.²³ Median survival time for all patients with pancreatic cancer in the National Cancer Data Base was 4.4 months; by stage, survival times were 2.5 months for metastatic disease, 7.7 months for locally advanced disease, and 12.7 to 24.1

Table 3. Baseline BMI and Pancreatic Cancer Stage at Diagnosis

Baseline BMI (kg/m ²)	Stage*					
	Localized		Locally Advanced		Metastatic	
	No.	%	No.	%	No.	%
< 25.0	79	24.3	53	16.3	193	59.4
25.0 to 29.9	39	15.1	40	15.4	180	69.5
≥ 30.0	15	16.5	10	11.0	66	72.5

Abbreviation: BMI, body mass index.

* $\chi^2 P = .02$.

Table 4. Temporal Association of Prediagnostic BMI and HR for Death Resulting From Pancreatic Cancer

Years Between Reported BMI and Diagnosis Date	No. of Patients	BMI (kg/m ²)					P*
		< 25.0 HR†	25.0 to 29.9		≥ 30.0		
			HR†	95% CI	HR†	95% CI	
2 to < 4	731	1.0	0.99	0.84 to 1.17	1.29	1.04 to 1.60	.04
4 to < 6	696	1.0	0.96	0.81 to 1.14	1.29	1.02 to 1.61	.06
6 to < 8	664	1.0	1.08	0.90 to 1.28	1.18	0.94 to 1.49	.14
8 to < 10	611	1.0	1.03	0.86 to 1.24	1.26	0.99 to 1.60	.08
10 to < 12	548	1.0	1.08	0.89 to 1.31	1.16	0.90 to 1.49	.23
12 to < 14	496	1.0	1.04	0.84 to 1.27	1.28	0.99 to 1.67	.07
14 to < 16	401	1.0	1.33	1.05 to 1.68	1.40	1.04 to 1.89	.01
16 to < 18	300	1.0	1.08	0.82 to 1.41	1.60	1.12 to 2.27	.02
18 to < 20	202	1.0	1.36	0.96 to 1.93	2.31	1.48 to 3.61	< .001

Abbreviations: BMI, body mass index; HR, hazard ratio.

*P for trend; tests calculated by entering stratum-specific median values for BMI as single variables in Cox proportional hazards models.

†Adjusted for age at diagnosis, cohort (also adjusted for sex), race/ethnicity (white, nonwhite, unknown), smoking status (current, past, never, missing), year of diagnosis (1988 to 1995, 1996 to 2000, 2001 to 2005, 2006 to 2010), and stage at diagnosis (localized, locally advanced, metastatic, unknown).

months for localized disease. In the current study, median overall survival was 5 months among all patients, and survival times by stage were 3 months for metastatic disease, 8 months for locally advanced disease, and 16 months for localized disease.

Because of the prospective study design, we also could evaluate the association of biennially updated data on BMI with pancreatic cancer survival. Interestingly, BMI reported a greater number of years before cancer diagnosis was more strongly associated with pancreatic cancer survival. These data suggest that chronic exposure to the consequences of obesity may be important in affecting patient survival. Recent experimental data suggest that pancreatic tumors develop and spread over years, providing opportunities for chronic alterations in systemic metabolism and inflammation to influence malignant characteristics and growth.^{24,25} In this regard, multiple metabolic and inflammatory alterations related to obesity have been shown to have

an impact on tumor growth in preclinical models,^{11,26-28} providing experimental rationale for these findings in patients. Additionally, fatty infiltration of the pancreas may supply growth-promoting signals locally to adjacent malignant cells.^{29,30} Nevertheless, we cannot rule out that survival in patients with chronic obesity may also be affected by increased complication rates from surgery or systemic therapies or greater degree of comorbidity that limits aggressiveness of care.^{31,32} Importantly, stratified analyses by stage at diagnosis did not suggest that our results were primarily driven by those with localized disease, the population of patients for whom surgical resection is generally pursued. We also noted that obese patients were more likely to be diagnosed with advanced-stage disease, which may contribute to their worse survival. However, even after adjustment for stage, prediagnostic BMI remained associated with survival, suggesting additional mechanisms aside from more advanced stage at diagnosis.

Table 5. HRs for Death Resulting From Pancreatic Cancer by Baseline BMI Stratified by Covariates

Stratification Covariate	No. of Patients	BMI (kg/m ²)									P ^a
		< 25.0 HR†	25.0 to 26.9		27.0 to 29.9		30.0 to 34.9		≥ 35.0		
			HR†	95% CI	HR†	95% CI	HR†	95% CI	HR†	95% CI	
Cohort study											.59
HPFS (male)	341	1.0	1.12	0.85 to 1.48	1.07	0.79 to 1.45	1.22	0.76 to 1.95	2.23	0.88 to 5.66	
NHS (female)	561	1.0	0.67	0.50 to 0.88	1.10	0.86 to 1.41	1.17	0.89 to 1.54	1.37	0.97 to 1.93	
Smoking status											.06
Never-smoker	360	1.0	0.95	0.70 to 1.29	1.65	1.21 to 2.24	1.48	1.02 to 2.13	1.61	1.01 to 2.57	
Ever-smoker	525	1.0	0.81	0.63 to 1.03	0.80	0.62 to 1.03	1.07	0.78 to 1.46	1.36	0.86 to 2.15	
Diagnosis period											.09
1988 to 2000	435	1.0	0.72	0.56 to 0.94	0.90	0.68 to 1.19	0.88	0.63 to 1.24	1.23	0.80 to 1.91	
2001 to 2010	467	1.0	1.04	0.79 to 1.38	1.16	0.89 to 1.52	1.53	1.10 to 2.14	1.49	0.92 to 2.40	
Cancer stage											.85
Localized	133	1.0	0.97	0.56 to 1.68	1.09	0.60 to 1.95	1.01	0.56 to 1.82			
Locally advanced	103	1.0	0.39	0.22 to 0.70	0.77	0.39 to 1.54	1.42	0.68 to 2.97			
Metastatic	439	1.0	1.01	0.78 to 1.32	1.14	0.88 to 1.48	1.32	0.98 to 1.78			

Abbreviations: BMI, body mass index; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; NHS, Nurses' Health Study.

*P for interaction.

†Adjusted for age at diagnosis, cohort (also adjusted for sex), race/ethnicity (white, nonwhite, unknown), smoking status (current, past, never, missing), year of diagnosis (1988 to 1995, 1996 to 2000, 2001 to 2005, 2006 to 2010), and stage at diagnosis (localized, locally advanced, metastatic, unknown), excluding stratification covariate.

Limitations of our study also require consideration. Among study participants, treatment programs likely varied, and we could not control for differences in treatment, because this information was not collected in our cohorts. Nevertheless, chemotherapy and irradiation have had only a modest impact on patient survival,² and treatment programs were unlikely to have varied greatly by baseline BMI measured years before diagnosis. We used overall mortality data in our analyses, as opposed to pancreatic cancer–specific mortality. However, pancreatic cancer is a highly lethal malignancy with cure rates < 5%, such that overall mortality is a good surrogate for cancer-specific mortality. This approach has been used in other studies of pancreatic cancer survival.²⁰⁻²² We cannot rule out that our findings may have been influenced in part by residual confounding. Nonetheless, we collected information on multiple other exposures and included possible confounding covariates in multivariate models without observing meaningful changes in risk estimates. Finally, our study participants were predominantly individuals of European descent, and additional studies in other populations are warranted.

In conclusion, higher prediagnostic BMI was associated with statistically significantly decreased survival among patients with pancreatic cancer from two large prospective cohort studies. This associ-

ation was similar across patient subgroups and seemed stronger for BMI measured a greater number of years before cancer diagnosis. These data emphasize the link between chronic alterations in systemic metabolism and pancreatic cancer survival and suggest obesity-related metabolic pathways for possible therapeutic intervention in patients with pancreatic adenocarcinoma.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: All authors

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Appendix

Table A1. Proportion of Patients With Healthy Weight by Quintiles of Survival Time

Quintile of Survival Time	Survival Time Range (months)	No. of Patients	No. of Patients With Healthy Weight*	
			No.	%
1	< 2	211	93	44.1
2	2 to 3	157	75	47.8
3	4 to 7	199	96	48.2
4	8 to 13	156	79	50.6
5	> 13	167	93	55.7

Abbreviation: BMI, body mass index.

*Healthy weight defined as baseline BMI of 18.5 to 24.9 kg/m².