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Obesity Adversely Affects Survival in Pancreatic Cancer Patients

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Abstract

Purpose—Higher body-mass index (BMI) has been implicated as a risk factor for developing pancreatic cancer, but its effect on survival has not been thoroughly investigated. We assessed the association of BMI with survival in a sample of pancreatic cancer patients and utilized epidemiologic and clinical information to understand the contribution of diabetes and hyperglycemia.

Methods—A survival analysis using Cox proportional hazards by usual adult BMI was performed on 1,861 unselected patients with pancreatic adenocarcinoma; analyses were adjusted for covariates that included clinical stage, age, and sex. Secondary analyses incorporated self reported diabetes and fasting blood glucose in the survival model.

Results—BMI as a continuous variable was inversely associated with survival from pancreatic adenocarcinoma [hazard ratio 1.019 for each increased unit of BMI (kg/m^2), $p < 0.001$] after adjustment for age, stage, and sex. In analysis by National Institutes of Health BMI category, BMI of 30–34.99 kg/m^2 (HR 1.14, 95% confidence interval 0.98–1.33), 35–39.99 kg/m^2 (HR 1.32, 95% CI 1.08–1.62), and ≥40 (HR 1.60, 95% CI 1.26–2.04) were associated with decreased survival compared to normal BMI of 18,5–24.99 kg/m^2 (overall trend test $p<0.001$). Fasting blood glucose and diabetes did not affect the results.

Conclusions—Higher BMI is associated with decreased survival in pancreatic cancer. Although the mechanism of this association remains undetermined, diabetes and hyperglycemia do not appear to account for the observed association.

Introduction

High body mass index (BMI) has been consistently reported as a risk factor for pancreatic cancer[1–7]. Though the mechanism for this increased risk is not yet established, hyperinsulinemia and insulin resistance have been hypothesized.[1, 6] In one study using lean and obese mice inoculated with murine pancreatic cancer cells, higher serum insulin and

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lower adiponectin in obese mice correlated with increased tumor cell proliferation, but there was no change in apoptosis indices.[8] The same group has also reported that steatosis in human pancreas at the time of surgical tumor resection correlated with increased likelihood of lymph node metastasis, and hypothesized that steatosis affects the tumor microenvironment.[9]

Obesity has been reported to be associated with poorer prognosis in multiple cancers[10, 11], perhaps most notably breast cancer[12–15] In breast cancer, it is possible that increased peripheral estrogens related to obesity may contribute to risk of recurrent disease, although this mechanism remains indeterminate. In pancreatic cancer, increased BMI has been reported to be an adverse prognostic factor for survival after surgery in two surgical series of 285 and 356 patients, respectively.[16, 17] However, another surgical report of 306 patients undergoing resection of pancreatic adenocarcinoma reported increased postoperative complications in obese patients, but the slight decrease in survival did not reach statistical significance.[18]

An epidemiologic study[19] has reported an association of risk of pancreatic cancer with increased BMI at various time points throughout life, and further observed decreased survival from pancreatic cancer, with the strongest effect among resected patients. It should be noted that this sample was drawn from the same institution where one of the above mentioned surgical series was reported. Another hospital-based study has also shown a decreased survival among obese patients compared to normal weight among 475 patients with pancreatic cancer, although statistical significance was not reached (HR=1.62, 95% CI 0.76–3.44).[20]

We more fully examined the effect of BMI on pancreatic cancer survival utilizing the Mayo Clinic Pancreas Biospecimen Resource, a prospective patient series that employs ultra rapid recruitment methods.

Methods

The study was reviewed and approved by the Mayo Clinic Institutional Review Board, and written, informed consent was obtained on all subjects.

Patient recruitment

Pancreatic cancer patients were rapidly and systematically identified and approached, using methodology reported previously[21] at Mayo Clinic Rochester, Mayo Clinic Arizona, or Mayo Clinic Florida between October 1, 2000 and Jan. 1, 2009. Of 2,746 adenocarcinoma patients identified during this time period, 1,898 consented to participate (69.1%). 1.9% were excluded for missing height, weight, or stage of pancreatic cancer, leaving 1,861 patients suitable for analysis. Only histologically (95%) or clinically (5%) confirmed adenocarcinoma cases providing consent were included in survival analyses. Clinically confirmed cases required a pancreatic mass on imaging consistent with adenocarcinoma, and symptoms typical of pancreatic adenocarcinoma (weight loss, abdominal pain, painless jaundice). All cases were reviewed by subspecialist physicians with expertise in pancreatic cancer (oncologist or surgeon) for coding as adenocarcinoma. At the time of enrollment, participants were asked to complete risk factor questionnaires including personal medical history, behaviors, family history, and usual adult height and weight (which were used for calculating BMI), and data from which Karnofsky performance score[22] was determined. Fasting blood glucose was obtained from the electronic medical record for all subjects at study entry. When risk factor questionnaire information was not completed (N=629), the medical record was abstracted to ascertain weight at study entry, usual adult weight, recent weight loss, ever/never smoking status, BMI, prior diagnosis of diabetes, and family history

of pancreatic cancer. We have previously reported an intermethod reliability study in which usual adult height and weight from 25 cases and 25 healthy controls was obtained from both questionnaires and abstracted from the medical record. Since usual adult weight was not usually available, weight at study entry plus reported recent weight loss was used. A high degree of intermethod reliability was noted (Pearson correlation coefficient > 0.93).[23] Staging was recorded according to AJCC 6th e0taging criteria by a physician with expertise in gastrointestinal cancer. Patients were then grouped into surgically resected, locally advanced, and metastatic disease for survival analysis. Surgical patients were also subcategorized into stages IA, IB, IIA, and IIB. Vital status of subjects was collected by multiple sources as part of routine research followup, including periodic mailings, medical records, Tumor Registry, and death indexes from online services.

Statistical methods

Age was used as a continuous variable and defined as age in years at diagnosis of pancreatic cancer. Risk factor questionnaires provided self-report of diabetes (Y/N), cigarette smoking was recorded as ever/never, and also by typical packs-per-day for smoking intensity. BMI was calculated from self-reported usual adult height and weight. Weight loss was recorded as usual adult weight minus weight at study entry. Date of diagnosis was defined as date of tissue diagnosis for those with pathology-proven disease. For those who were clinically diagnosed, date of the first clinical diagnosis was used. Date of death or last known date alive was selected from the most current data among multiple sources as described in Methods. For the primary analysis, BMI was considered as a continuous variable. Secondary analyses also examined BMI categorized according to NIH guidelines of underweight (<18.5 kg/m^2), normal weight (referent group, 18.5–24.99 kg.m^2), overweight (25.0–29.99 kg/m^2), obese class I (30.0–34.99 kg/m^2) obese class II (35.0–39.99 kg/m^2), and obese class III (≥40.0 kg/m^2).[24] In addition to age and sex, covariates showing associations ($p < 0.05$) in univariable analysis were considered for multivariable analysis.

Cox proportional hazards regression analyses were used to conduct comparisons for survival. Time to event was diagnosis of pancreatic cancer until death or last followup with individuals still alive at last followup being coded as censored for the event (death) as of that date. All analyses used SAS software, version 9.1.3.

Results

Median follow up for cases was 306 days. By the time of analysis, 1,527 patients (82.1%) were deceased. Table 1 shows the characteristics of patients included in the analysis. Patients who completed questionnaires were more likely to be female, older, earlier stage, not diabetic, and had longer survival, lower BMI, and more reported weight loss at study entry.

Kaplan-Meier survival comparisons (Figure 1) showed an association of BMI with survival (chi square p=0.011). Median survival for each BMI category (kg/m^2) was as follows: (0–18.49) 276 days, (18.5–24.99) 349 days, (25.0–29.99) 352 days, (30.0–34.99) 310 days, (35.0–39.99) 273 days, and (≥40.0) 246 days.

In multivariable survival analyses, increasing age (HR 1.017 per year, 95% confidence interval 1.012–1.022) and locally advanced (HR 2.99, 95% C.I. 2.60–3.43) or metastatic disease (HR 4.76, 95% CI 4.14–5.46) versus resectable disease were associated with decreased survival; ever/never smoking, tumor location (head vs body/tail), and family history of pancreatic cancer showed no association with survival in stepwise analysis and were not included in the final multivariable model. BMI was inversely associated with survival as a continuous variable in adjusted analysis (HR 1.019, p <0.001).

Analysis by usual adult BMI NIH category was also significantly associated with survival (p-trend <0.001), with a clear dose-dependent association with survival (first panel, Figure 2A). Adjusted hazard ratios for NIH BMI categories compared to the referent group of normal weight were underweight (HR 1.30, 95% CI 0.69–2.45), overweight (HR1.02, 95% CI 0.89–1.16), obese class I (HR 1.14, 95% CI 0.98–1.33), obese class II (1.32, 95% CI 1.08–1.62), and obese class III 1.60, 95% CI 1.26–2.04). Although the hazard ratio was increased for underweight persons, the sample size was small (N=13). For BMI above the normal range, there is a clear, steady decrease in survival with increasing BMI. A sensitivity analysis was performed including only biopsy-proven adenocarcinoma cases, and this did not alter the significance of the associations, with only minimal changes in HRs.

The dose-dependent association of usual adult BMI and survival was seen in patient groups who either completed or did not complete the questionnaire (Figure 2A, second and third panels). For those who completed questionnaires, adjusted analysis was also performed using self-reported Karnofsky performance score as a covariate. Performance score was significantly associated with survival ($p<10^{-5}$), while the overall association for BMI remained (HR 1.014, p=0.023). Among stage subgroups, BMI was significantly associated with survival in patients presenting with locally advanced (HR 1.021, p=0.005) and metastatic (HR 1.018, p=0.011) disease, but not resected patients (HR 1.012, p=0.227), though the dose-dependent pattern appeared consistent for all 3 stage groupings (Figure 2B).

Since weight loss is a prominent feature in clinical presentation of pancreatic cancer, we evaluated its effects on survival. In multivariate analysis, weight loss as a percentage of body weight was also associated with decreased survival (HR 2.03, p =0.015). In weight loss categories (None, >0 and ≤10%, or >10%), there was a significant association (p=0.009) with decreased survival seen with higher weight loss, adjusted for age, stage, and sex.

To further investigate whether a hyperglycemic state accounted for our findings, fasting blood glucose (FBG) at the time of study recruitment was examined on 1,443 cases for whom it was available. When added to the overall model, a modest association of FBG and survival was seen (HR 1.01), though this did not reach statistical significance (p=0.096). Since many diabetic patients were likely already on medication to lower FBG, we also examined the subset of patients who self-reported no history of diabetes (N=833). There was no association of FBG and survival in this group (HR 1.00, p=0.419). Self-reported diabetes at time of study entry was also not associated with survival (HR 1.07, p=0.273). None of these additions to the model changed the association of BMI and survival (Figure 3).

Discussion

In a clinic-based survival study, we observed that increasing BMI was strongly and consistently associated with a decreased survival from pancreatic cancer. The mechanism for this finding is not clearly evident, although circulating hyperinsulinemia has been hypothesized as one potential etiology.[19] For this reason, we examined both self-reported diabetes and fasting blood glucose levels of patients at presentation to our center. However, diabetes and hyperinsulinemia did not appear to explain the effect of BMI on survival, leaving the explanation for this finding currently unknown. This is in distinction to a recent letter stating diabetes was associated with worsened survival in the Li et al paper.[25]

Higher BMI is well known to be associated with altered circulating levels of estrogens [26, 27] and insulin[28]. However, since the survival of women does not substantially differ from that of men in pancreatic cancer, it is difficult to conclude that estrogens contribute to poor survival. Hyperinsulinemia and associated factors are a potential contributor, as has been reported in one recent study of colorectal cancer.[29] A recent large meta-analysis did not

show any effect of diabetes on survival in pancreatic cancer patients.[30] However, one study of 400 male Finnish smokers suggested higher insulin levels were associated with increased risk for pancreatic cancer.[6] Obesity has been associated with low grade chronic inflammation, with possibly a shift toward a Th2 (tolerant) immune state, which has been associated with carcinogenesis[31–33] and cancer progression[34–37] Therefore, an alternate possibility is decreased immune function, which could lead to more rapid tumor progression and thereby poorer survival. A third possibility would be bias in treatment determinations, such as aggressiveness of therapy (multiple agents or modalities) or decreased dosing of chemotherapy in obese patients. Resources did not permit us to fully pursue this possibility

The strengths of our study include its large size, the inclusion of only specialist-verified adenocarcinoma, the ready availability of electronic medical records when questionnaires were not completed, and the completeness of our follow-up. The dose-dependent nature of our findings, the strength of the association, and the significance of the finding after adjusting for performance score add to the internal validity of this association.

There are several potential limitations to our study. We relied on self-reported usual adult BMI, which can be problematic since weight can vary throughout life, although we felt this was a superior measure than weight at study entry, since pancreatic cancer often causes dramatic weight loss, often just prior to diagnosis. It could be argued that BMI may affect stage at presentation, or likelihood of a patient undergoing surgery, thus influencing survival. However, we observed no differences in BMI between stage groupings: median usual adult BMI for resectable, locally advanced, and metastatic tumors were 27.9, 28.2, and 28.0 kg/m^2, respectively (p=0.647). With regard to limitations of measures, BMI is but one measure of obesity, although it is perhaps the most widely accepted measure in clinical studies. FBG and self-report of diabetes are imprecise measures of hyperinsulinemia; more direct measures are required to further elucidate in this setting the relationship of BMI to hormonal changes in insulin and similar species, such as insulin-like growth factor and IGF-binding proteins. These parameters should be investigated in future studies.

Numerous studies comparing self reported to measured BMI have found that self-reported BMI is generally valid to use[38–41], though subjects may underestimate weight, which in our study would bias toward the null. We believe that usual adult BMI is a reasonable surrogate for aggregate exposure to whatever risk high BMI imposes for a given individual over their lifetime, and has similar issues for accuracy and recall as seen for usual alcohol intake or cigarette use, commonly used in epidemiologic studies. Our study did not include therapies administered. However, given the minimal impact on survival of current therapies, and the nearly uniform use of gemcitabine-based regimens for locally advanced and metastatic disease, it could be argued that therapy differences would not notably affect our findings.

Future studies will be necessary to investigate this association of elevated BMI and survival. If the mechanism is ever clearly elucidated, this may lead to potential therapeutic targeting. For instance, since elevated levels of circulating insulin can activate IGF receptors[42], blockade of these receptors through targeted therapy may represent a logical approach to improving outcomes for patients. We believe this association of BMI with survival provides an important clue to the understanding of why this cancer is so deadly and resistant to therapy. A thorough understanding of the mechanisms could lead to improving our care for these patients.

Conclusion

Increasing body mass index is associated with decreased survival in those diagnosed with pancreatic cancer, after adjusting for known confounders. Body-mass index should be

considered as a covariate in prospective studies of pancreatic cancer. The mechanism of this finding requires further study.

Acknowledgments

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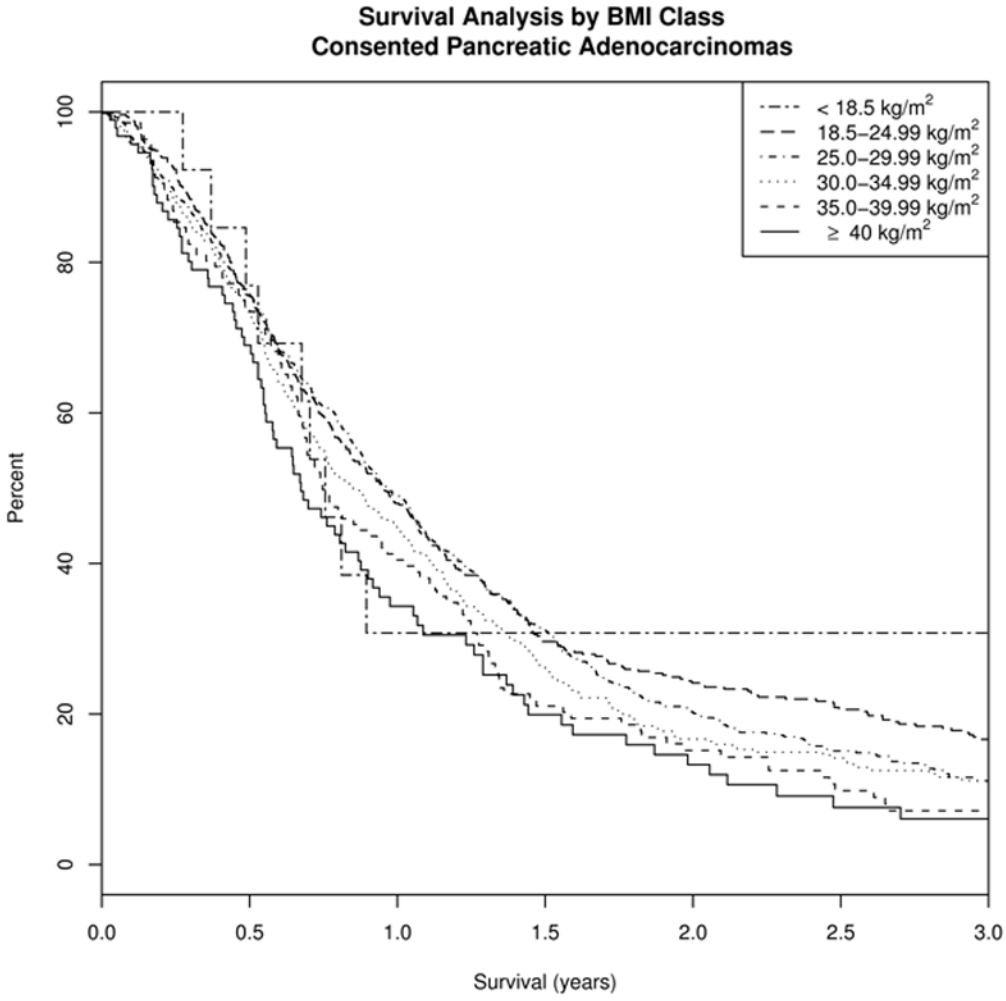

Figure 1.
Unadjusted Kaplan-Meier analysis of survival among 1,861 pancreatic cancer patients by usual adult BMI category.

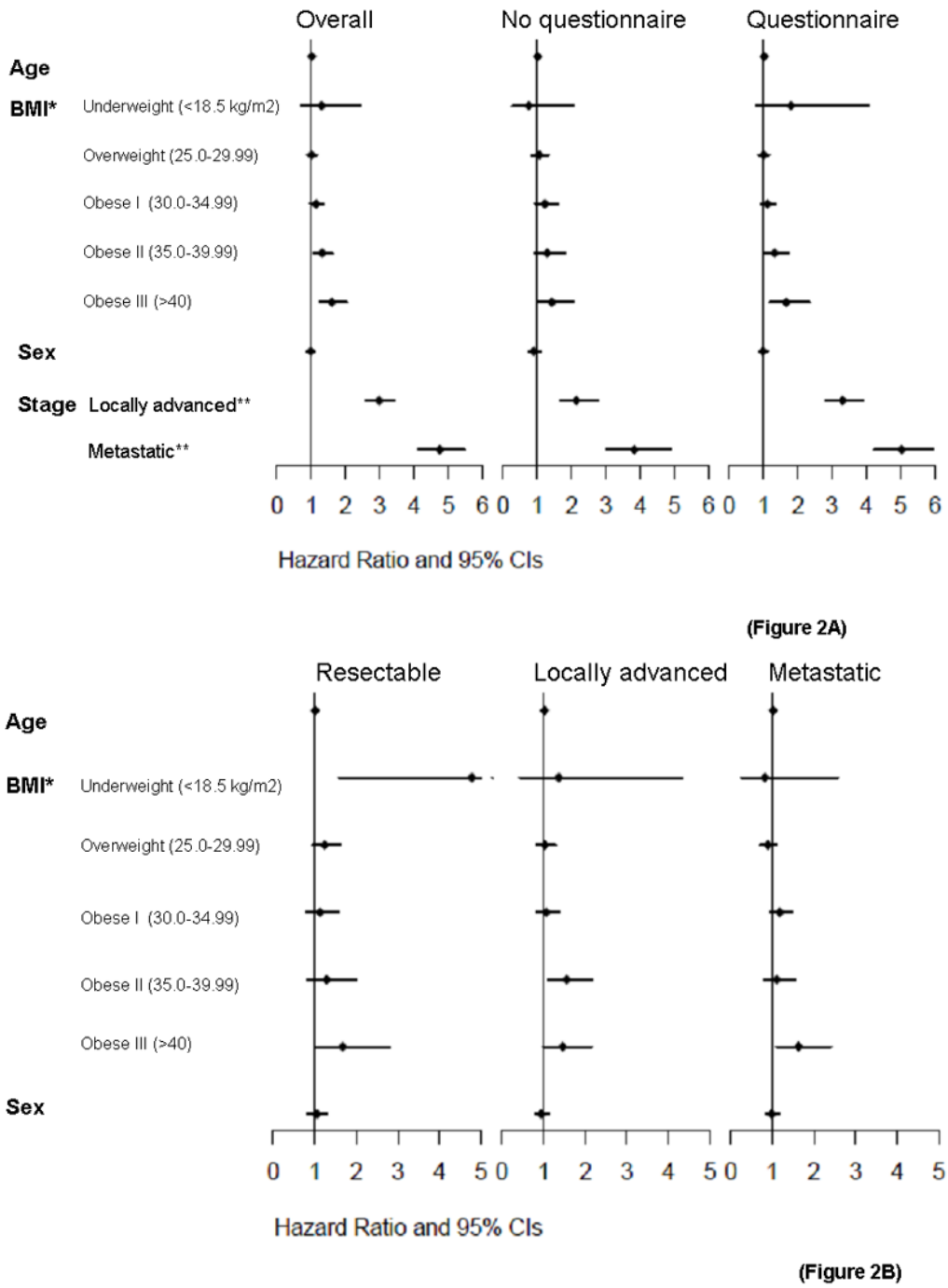

Figure 2.

Figure 2A. BMI and survival of pancreatic cancer patients by completion of risk factor questionnaire. Forest plots of multivariable Cox regression survival associations by NIH BMI category for pancreatic cancer patients overall and risk factor questionnaire completion. *Referent group for BMI is 18.5–24.99 kg/m^2. **Referent group for stage is resectable.

Figure 2B. BMI and survival of pancreatic cancer patients by stage. Forest plots within stage groupings for resectable, locally advanced, and metastatic patients at initial diagnosis of pancreatic cancer.

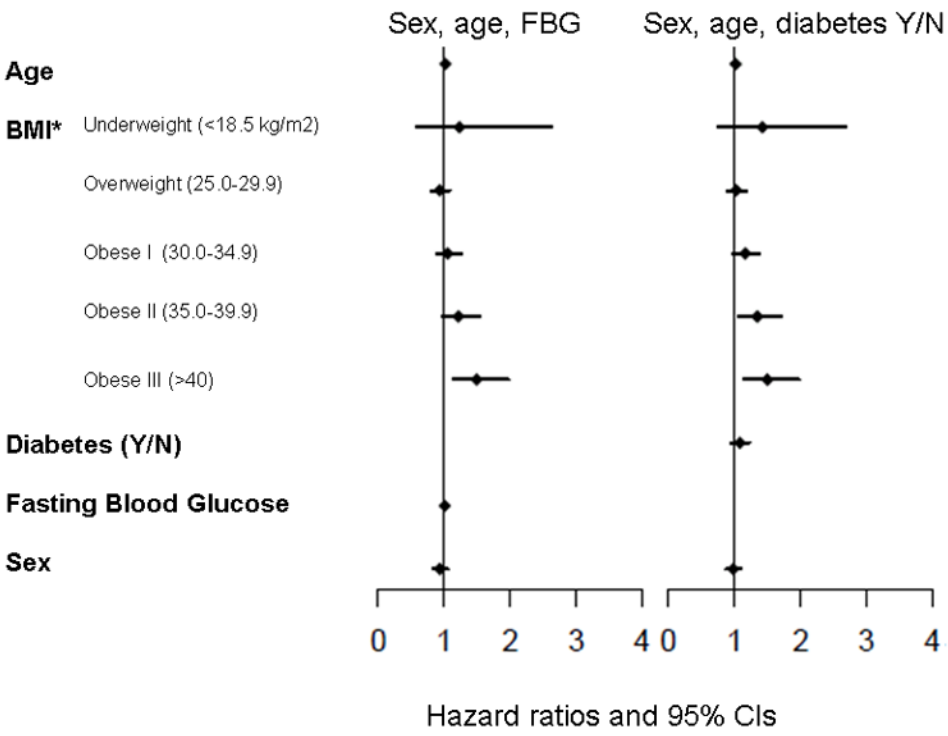

Figure 3.

Incorporation of fasting blood glucose and self reported diabetes to models of pancreatic cancer survival with BMI, adjusted for stage. Forest plots of multivariable Cox regression survival associations with fasting blood glucose (FBG) or self-reported diabetes included as covariables. *Referent group for BMI is 18.5–24.99 kg/m^2.

Table 1

Characteristics of Pancreatic Adenocarcinoma Patients, Including Completion of Risk Factor Questionnaire

	Not completed (N=629)	Completed (N=1,232)	Total (N=1,861)	p*
Sex				0.029
Male	375 (59.6%)	669 (54.3%)	1,044 (56.1%)	
Age at time of pancreatic cancer diagnosis				0.002
N	629	1,232	1,861	
Median	64.0	67.0	66.0	
Q1, Q3	56.0, 73.0	59.0, 74.0	58.0, 74.0	
Vital Status				0.164
Alive	102 (16.2%)	232 (18.8%)	334 (17.9%)	
Dead	527 (83.8%)	1,000 (81.2%)	1,527 (82.1%)	
Site of Tumor				0.943
Head	341 (54.6%)	700 (57.2%)	1,041 (56.3%)	
Body	87 (13.9%)	165 (13.5%)	252 (13.6%)	
Tail	66 (10.6%)	116 (9.5%)	182 (9.8%)	
Head & Body	43 (6.9%)	80 (6.5%)	123 (6.7%)	
Body & Tail	37 (5.9%)	79 (6.5%)	116 (6.3%)	
NOS	8 (1.3%)	16 (1.3%)	24 (1.3%)	
Uncinate Process	28 (4.5%)	45 (3.7%)	73 (4%)	
Stage Group				<0.001
Resectable				
IA	12 (1.9%)	17 (1.4%)	29 (1.6%)	
IB	12 (1.9%)	55 (4.5%)	67 (3.6%)	
IIA	28 (4.5%)	111 (9%)	139 (7.5%)	
IIB	93 (14.8%)	232 (18.8%)	325 (17.5%)	
Locally Advanced	246 (39.1%)	405 (32.9%)	651 (35%)	
Metastatic	238 (37.8%)	412 (33.4%)	650 (34.9%)	
Days Survival from Diagnosis				<0.001
N	629	1,232	1,861	
Mean (SD)	334.4 (384.51)	511.9 (578.95)	451.9 (528.02)	
Median	231.0	338.0	306.0	
Q1, Q3	107.0, 426.0	198.5, 569.5	166.0, 523.0	
Range	(0.0–3,797.0)	(1.0–5,899.0)	(0.0–5,899.0)	
Diabetes (self-reported or reported in medical record)				0.036
Missing	251	81	332	
No	245 (64.8%)	812 (70.5%)	1,057 (69.1%)	
Yes	133 (35.2%)	339 (29.5%)	472 (30.9%)	
Continuous BMI (usual adult, kg/m^2)				<0.001
N	629	1,232	1,861	
Mean (SD)	29.4 (6.58)	28.1 (5.37)	28.5 (5.83)	
Median	28.2	27.4	27.6	

	Not completed (N=629)	Completed (N=1,232)	Total (N=1,861)	p*
Q1, Q3	24.6, 32.6	24.4, 30.7	24.4, 31.2	
Range	(16.4–59.0)	(15.3–53.4)	(15.3–59.0)	
BMI by category(usual adult, kg/m^2)				<0.001
< 18.5	6 (1%)	7 (0.6%)	13 (0.7%)	
18.5–24.99 (ref)	166 (26.4%)	368 (29.9%)	534 (28.7%)	
25.0–29.99	228 (36.2%)	493 (40%)	721 (38.7%)	
30.0–34.99	123 (19.6%)	238 (19.3%)	361 (19.4%)	
35.0–39.99	58 (9.2%)	80 (6.5%)	138 (7.4%)	
≥ 40.0	48 (7.6%)	46 (3.7%)	94 (5.1%)	
Weight Loss (as a % of usual adult weight)				<0.001
None	145 (23.1%)	211 (17.1%)	356 (19.1%)	
>0, ≤10 %	255 (40.5%)	382 (31%)	637 (34.2%)	
>10%	229 (36.4%)	639 (51.9%)	868 (46.6%)	
Categorical FBG (mg/dL)				0.110
Missing	159 (%)	259 (%)	418	
<100	82 (17.4%)	133 (13.7%)	215 (14.9%)	
100–125	177 (37.7%)	349 (35.9%)	526 (36.5%)	
126–150	85 (18.1%)	195 (20%)	280 (19.4%)	
151–200	75 (16%)	199 (20.5%)	274 (19%)	
>200	51 (10.9%)	97 (10%)	148 (10.3%)	
Performance Score (Karnofsky)				
90–100	--	252 (26.8%)	252 (26.8%)	--
80	--	315 (33.7%)	315 (33.7%)	
70	--	257 (27.5%)	257 (27.5%)	
60	--	83 (8.9%)	83 (8.9%)	
<50	--	28 (3.0%)	28 (3.0%)	

BMI = Body Mass Index, FBG = Fasting blood glucose,

*comparison of subjects who did and did not complete risk factor questionnaires

Table 2

Association of pancreatic cancer survival by usual adult BMI category.

Subject group	Variable	Subcategory	N	HR (95% CI)	p-value
Overall	BMI (kg/m^2)	< 18.5	13	1.30 (0.69–2.44)	<0.001
		18.5–24.99 (ref)	534	1.00	
		25.0–29.99	721	1.02 (0.89–1.16)	
		30.0–34.99	361	1.14 (0.98–1.33)	
		35.0–39.99	138	1.32 (1.08–1.62)	
		≥ 40.0	94	1.60 (1.26–2.04)	
	Sex	Male	1,044	0.99 (0.89–1.10)	0.806
	Age	Age at diagnosis	1,861	1.02 (1.01–1.02)	<0.001
	Surgical Stage	Resectable (ref)	560	1.00	<0.001
		Locally advanced	651	2.99 (2.60–3.43)	
		Metastatic	650	4.76 (4.14–5.47)	
Completed RFQ	BMI (kg/m^2)	< 18.5	7	1.80 (0.80–4.07)	0.009
		18.5–24.99 (ref)	368	--	
		25.0–29.99	493	1.01 (0.86–1.18)	
		30.0–34.99	238	1.12 (0.93–1.35)	
		35.0–39.99	80	1.32 (1.02–1.72)	
		≥ 40.0	46	1.67 (1.19–2.33)	
Did not complete RFQ	BMI (kg/m^2)	< 18.5	6	0.75 (0.27–2.07)	0.222
		18.5–24.99 (ref)	166	1.00	
		25.0–29.99	228	1.05(0.84–1.33)	
		30.0–34.99	123	1.23 (0.95–1.59)	
		35.0–39.99	58	1.30 (0.93–1.80)	
		≥ 40.0	48	1.43 (1.0–2.05)	
Resectable	BMI (kg/m^2)	< 18.5	4	4.78 (1.59–14.37)	0.037
		18.5–24.99 (ref)	171	1.00	
		25.0–29.99	220	1.24 (0.95–1.62)	

Subject group	Variable	Subcategory	N	HR (95% CI)	p-value
		30.0–34.99	103	1.13 (0.82–1.56)	
		35.0–39.99	39	1.29 (0.84–1.99)	
		≥ 40.0	23	1.67 (1.00–2.79)	
	Sex	Male	297	1.05 (0.84–1.30)	0.687
	Age	Age at diagnosis	560	1.01 (1.00, 1.02)	0.072
Locally Advanced	BMI (kg/m^2)	< 18.5	5	1.37 (0.43–4.32)	0.067
		18.5–24.99 (ref)	179	1.00	
		25.0–29.99	254	1.03 (0.83–1.28)	
		30.0–34.99	123	1.07 (0.83–1.38)	
		35.0–39.99	50	1.56 (1.12–2.17)	
		≥ 40.0	40	1.46 (0.99–2.16)	
	Sex	Male	365	0.94 (0.79–1.12)	0.509
	Age	Age at diagnosis	651	1.02 (1.01, 1.03)	<0.001
Metastatic	BMI (kg/m^2)	< 18.5	4	0.82 (0.26–2.58)	0.018
		18.5–24.99 (ref)	184	1.00	
		25.0–29.99	247	0.89 (0.72–1.09)	
		30.0–34.99	135	1.1743 (0.93–1.48)	
		35.0–39.99	49	1.105 (0.80–1.53)	
		≥ 40.0	31	1.63 (1.10–2.40)	
	Sex	Male	382	0.98 (0.83–1.16)	0.824
	Age	Age at diagnosis	650	1.02(1.01–1.03)	<0.001
Overall model (including FBG)	BMI (kg/m^2)	< 18.5	10	1.23 (0.58, 2.62)	0.007
		18.5–24.99 (ref)	402	1.00	
		25.0–29.99	563	0.93 (0.80–1.08)	
		30.0–34.99	284	1.05 (0.89–1.25)	
		35.0–39.99	111	1.22 (0.97–1.53)	
		≥ 40.0	73	1.49 (1.13–1.97)	
	Sex	Male	834	0.93 (0.83, 1.05)	0.251
	Age	Age at diagnosis	1443	1.02 (1.01–1.02)	<0.001

Subject group	Variable	Subcategory	N	HR (95% CI)	p-value
	FBG	Fasting Blood Glucose/10	1443	1.01 (1.00–1.02)	0.082
Overall model (including DM)	BMI (kg/m^2)	< 18.5	12	1.42 (0.76, 2.68)	0.009
		18.5–24.99 (ref)	438	1.00	
		25.0–29.99	604	1.03 (0.89–1.18)	
		30.0–34.99	294	1.16 (0.98–1.37)	
		35.0–39.99	107	1.35 (1.07–1.69)	
		≥ 40.0	74	1.50 (1.13–1.98)	
	Sex	Male	864	0.98 (0.87–1.10)	0.721
	Age	Age at diagnosis	1529	1.02 (1.01–1.02)	<0.001
	Diabetes	Yes	472	1.08 (0.95–1.22)	0.229

BMI= Body-Mass Index, FBG= fasting blood glucose, DM = self reported diabetes mellitus