Circulating Insulin-Like Growth Factor Binding Protein-1 and the Risk of Pancreatic Cancer

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Abstract

Insulin-like growth factor (IGF)-I has growth-promoting effects on pancreatic cancer cells, and elevated fasting serum insulin has been linked to pancreatic cancer risk. IGF binding protein-1 (IGFBP-1) is a downstream target of insulin and inhibits IGF-I activity. To investigate whether prediagnostic plasma levels of IGFBP-1 are associated with pancreatic cancer risk, we did a prospective, case-control study nested within the Health Professionals Follow-up Study, the Nurses' Health Study, the Physicians' Health Study, and the Women's Health Initiative. We assayed circulating IGFBP-1 among 144 pancreatic cancer cases that occurred ≥4 years after plasma collection and in 429 controls, matched for date of birth, prospective cohort, smoking status, and fasting status. When compared with participants in the three highest quartiles of plasma IGFBP-1, those in the lowest quartile experienced a relative risk (RR) for pancreatic cancer of 2.07 [95% confidence intervals (95% CI), 1.26–3.39], after adjusting for other risk factors, including circulating IGF-I, IGF binding protein-3, and C-peptide. Only participants in the lowest quartile of plasma IGFBP-1 showed an elevated risk of pancreatic cancer. The influence of low plasma IGFBP-1 became progressively stronger with time; among cases diagnosed ≥8 years after blood collection, the adjusted RR was 3.47 (95% CI, 1.48–8.14), comparing the bottom versus the top three quartiles. The influence of plasma IGFBP-1 was most marked among participants who never smoked cigarettes (RR, 3.30; 95% CI, 1.48–7.35). Among participants in four U.S. prospective cohort studies, low plasma IGFBP-1 levels significantly predicted an increased risk of pancreatic cancer. [Cancer Res 2007;67(16):7923–8]

Introduction

Obesity and sedentary lifestyle have been implicated as possible risk factors for the development of pancreatic cancer (1–5). Perturbations in insulin and the insulin-like growth factor (IGF) axis have been posited as an underlying biological mechanism for the association of these lifestyle factors with an increased risk of malignancy (6, 7). In support of this hypothesis, elevated fasting serum insulin predicted an increased risk of pancreatic cancer in a prospective cohort study of male, Finnish smokers (8). Nonetheless, the cancer-promoting effects of insulin are likely to act through one or more mediators, as supraphysiologic levels of insulin are required to stimulate cell proliferation (9).

The IGF axis includes two growth factors, IGF-I and IGF-II, and several IGF binding proteins (IGFBP), which together work to regulate the amount of free, biologically active IGF available to interact with target cells (9). IGF-I and the IGF-I receptor are highly expressed in pancreatic cancer cell lines, where initiation of intracellular signaling through the IGF-I receptor increases proliferation, invasion, and expression of mediators of angiogenesis (10–15). Although elevated plasma levels of IGF-I and IGF-II have been linked to an increased risk for several solid malignancies (16, 17), this association has not been noted in participants with pancreatic cancer (18, 19). In a previous study of the current cohort, no associations between prediagnostic plasma levels of IGF-I, IGF-II, or IGFBP-3 and pancreatic cancer risk were noted (20).

In contrast to IGF-I, IGF-II, and IGFBP-3, plasma levels of IGFBP-1 are altered acutely with meals and regulated by several hormones involved in glucose and energy homeostasis, including insulin, glucagon, and cortisol (21–24). Chronically, low plasma levels of IGFBP-1 have been noted with obesity and sedentary lifestyle (22).

Using the combined resources of four large prospective cohort studies with blood samples collected prior to cancer diagnosis, we did a nested case-control study to assess plasma IGFBP-1 levels and the risk of pancreatic cancer. To reduce the potential influence of subclinical cancer on IGFBP-1 concentrations, only participants alive and without clinical evidence of cancer during the first 4 years of follow-up were included in our analysis.

Materials and Methods

Populations. To obtain a sufficient number of participants with prediagnostic blood samples for our analysis, we drew on four large prospective studies: the Health Professionals Follow-up Study (HPFS), the Nurses' Health Study (NHS), the Physicians' Health Study (PHS), and the Women's Health Initiative-Observational Study (WHI-OS). The HPFS was initiated in 1986 when 51,529 U.S. men ages 40 to 75 years working as dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, or podiatrists responded to a mailed questionnaire. The NHS was established in 1976 when 121,700 female registered nurses ages 30 to 55 years responded to a mailed questionnaire. The PHS was a randomized,

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double-blind trial of aspirin and β-carotene initiated in 1982 among 22,071 male physicians between 40 and 84 years of age. The aspirin component of the trial was terminated in 1988. The β-carotene component was terminated in 1995 and all study participants are actively followed as an observational cohort. The WHI-OS consists of 93,676 postmenopausal women, ages 50 to 79 years, who were enrolled between 1994 and 1998. The health of these participants was tracked over an average of 8 years via annual health forms and a clinic visit 3 years after enrollment.

For each study, individual characteristics and habits, including weight, height, smoking status, physical activity, and history of diabetes were either obtained on the baseline questionnaires, or on subsequent questionnaires. Weight and height were measured at the baseline clinic visit in the WHI-OS. Additional details for these studies are available elsewhere [NHS, ref. (25); HPFS, ref. (26); PHS, ref. (27); WHI-OS, ref. (28)]. The National Death Index was searched for nonrespondents; this method has been shown to have a sensitivity of 98% (29). The current study was approved by the Human Research Committee at Brigham and Women's Hospital (Boston, MA), and all participants provided consent for questionnaire and blood data to be used in research studies.

Blood collection. Blood samples were collected from 18,225 men in the HPFS between 1993 and 1995, 32,826 women in the NHS from 1989 to 1990, 14,916 men in the PHS from 1982 to 1984, and 93,676 women in the WHI between 1994 and 1998. All blood samples were continuously stored in well-monitored liquid nitrogen freezers from blood collection to their retrieval for analysis. Details on blood draw, transportation, and storage of plasma samples in these cohorts are provided elsewhere [NHS, ref. (30); HPFS, ref. (31); PHS, ref. (32); WHI, ref. (33)].

Pancreatic cancer cases and matched controls. We included all cases of pancreatic cancer with an available plasma specimen through 2004. Consistent with previous studies (8, 34), to avoid the influence of subclinical cancer on IGFBP-1 plasma concentrations, which are sensitive to weight, exercise, and nutritional status, we excluded all cases diagnosed <4 years after blood draw. As such, all eligible participants were alive and without clinical evidence of cancer during the first 4 years of cohort follow-up. Incident cases of pancreatic cancer were initially self-reported by cohort participants on annual or biennial questionnaires and then confirmed with medical records or pathology reports. In addition, given the high fatality rate of pancreatic cancer, cases were identified through follow-up of reported deaths (notified by postal authorities or next of kin) or when searching the National Death Index for nonrespondents. Medical records were also requested for deceased cases. Pancreatic cancer cases with a prior history of malignancy (other than nonmelanoma skin cancer) were excluded from these analyses. Based on these criteria, 144 cases with pancreatic cancer and stored plasma were available for analysis.

Eligible controls were cohort participants who were still alive and free of cancer at the date of the case's diagnosis and who had provided a blood sample. From these participants, we randomly selected three controls for each case, matching on cohort (which concurrently matched on sex), year of birth, smoking status (current, past, or never), fasting status, and month of blood draw. On this basis, 432 control participants were chosen. One control who developed pancreatic cancer and two controls for whom the IGFBP-1 assay was unsuccessful were removed from the analysis, resulting in 429 eligible controls.

Plasma assays. Plasma levels of IGFBP-1, IGF-I, C-peptide, and IGFBP-3 were assayed in the laboratory of Dr. Michael N. Pollak (Lady Davis Research Institute of the Jewish General Hospital and McGill University). Samples from case subjects and their matched control subjects were assayed in the same batch to minimize interassay variability, and aliquots from a pool of quality control plasma were inserted randomly. Laboratory personnel were unable to distinguish among case, control, and quality control samples. Plasma levels were assayed by ELISA with reagents from Diagnostic Systems Laboratory. The mean intraassay coefficients of variation for IGFBP-1, IGF-I, C-peptide, and IGFBP-3 from the blinded quality control samples were <11%, 11%, 8%, and 5%, respectively.

Statistical analysis. We square root–transformed the plasma biomarkers to improve normality and compared values for cases and controls using paired *t* tests. Continuous and categorical covariates were compared using Wilcoxon signed rank, and χ^2 tests, respectively. For plasma IGFBP-1, quartile cut-points were generated among the controls only and were determined separately for each prospective cohort. Spearman correlation coefficients were calculated to examine the relationships among IGFBP-1, IGF-I, C-peptide, and selected covariates.

We computed odds ratios to estimate relative risks (RR) and 95% confidence intervals (95% CI) for the association of IGFBP-1 and pancreatic cancer risk using conditional logistic regression. Tests for trend using two-sided *P* values were calculated by entering the quartile-specific median values for IGFBP-1 as a continuous variable in logistic regression models. Cochran's Q statistic was used to test for heterogeneity in the relation between relevant plasma factors and pancreatic cancer risk in the four cohorts by comparing the RRs of the top versus the bottom quartiles for each plasma marker. The resultant *P* values for the comparison of these RRs for each biomarker were >0.05 (0.63 for IGFBP-1, 0.58 for IGF-I, 0.42 for C-peptide, and 0.48 for IGFBP-3). Based on the absence of heterogeneity for

Table 1. Baseline characteristics of pancreatic cancer cases and matched controls

Variable	Cases (n = 144)	Controls (n = 429)	P*
Cohort			Matched
HPFS	17	51	
PHS	52	156	
NHS	40	119	
WHI-OS	35	103	
Age (y)	61.4 ± 8.6	60.6 ± 8.6	Matched
Gender			Matched
Female (%)	52	52	
Male (%)	48	48	
BMI (kg/m^2)	26.1 ± 4.4	25.8 ± 4.6	0.15
Height (in.)	67.1 ± 3.6	67.3 ± 3.7	0.68
Smoking status			Matched
Never (%)	38	39	
Past (%)	40	42	
Current (%)	22	19	
History of diabetes mellitus			0.54
Yes (%)	5	4	
No (%)	95	96	
History of regular multivitamin use			0.25
Yes (%)	42	37	
No (%)	58	63	
Physical activity †			0.18
Low (%)	60	53	
High (%)	40	47	
Fasting status			Matched
≤8 h or unknown (%)	37	38	
>8 h (%)	63	62	
IGFBP-1 (ng/mL)	25.5 ± 24.7	26.8 ± 22.3	0.19
IGF-I (ng/mL)	167.5 ± 64.9	173.3 ± 71.0	0.40
C-peptide (ng/mL)	2.3 ± 1.7	2.0 ± 1.7	0.11
IGFBP-3 (ng/mL)	4,335.7 ± 933.1	4,317.4 ± 887.6	0.93

*IGFBP-1, IGF-1, C-peptide, and IGFBP-3 were square root–transformed to improve normality and analyzed using paired *t* tests. Remaining covariates were analyzed using Wilcoxon signed rank for continuous variables and χ^2 for categorical variables.

† Below (low) or above (high) the median level of physical activity.

Table 2. Spearman correlation coefficients between plasma markers and covariates among matched pancreatic cancer controls

Variable	IGFBP-1	IGF-I	C-peptide	Age	BMI	Physical activity	Height
IGFBP-1	1.0						
IGF-I	−0.30*	1.0					
C-peptide	−0.50*	0.11 †	1.0				
Age	0.26*	−0.37*	−0.04	1.0			
BMI	−0.30*	−0.09	0.28*	0.12*	1.0		
Physical activity	0.16*	0.03	−0.11 †	0.05	−0.11 †	1.0	
Height	−0.40*	0.22*	0.20*	−0.32*	−0.12 †	−0.04	1.0

*$P < 0.001$.
† $P < 0.05$.

the influence of the plasma factors on pancreatic cancer risk in the four cohorts, results are presented for all four cohort combined.

We adjusted for covariates that were associated with cancer risk in these cohorts, including body mass index [(BMI) weight in kilograms / (height in meters)^2], level of physical activity, history of diabetes mellitus, and history of regular multivitamin use. BMI and level of physical activity were included in models after division into quartiles. To assess the independent effect of plasma IGFBP-1 on the risk of pancreatic cancer, we included plasma IGF-I, C-peptide, and IGFBP-3 levels in our models as continuous variables.

To evaluate the association of IGFBP-1 and pancreatic cancer risk with longer follow-up, we sequentially excluded cases and matched controls, requiring longer time periods between plasma collection and cancer diagnosis. Stratified analyses were conducted using unconditional logistic regression to determine whether the influence of IGFBP-1 was modified by plasma levels of IGF-I, C-peptide, and IGFBP-3 or other risk factors for pancreatic cancer. To test for statistical interaction, we entered the main effect terms and a cross-product term into the model and evaluated the coefficient by the Wald test. All statistical analyses were done with the SAS 8.2 statistical package (SAS Institute). All P values are two-sided.

Results

Among eligible participants with baseline plasma samples who were alive and without clinical evidence of cancer during the first 4 years of cohort follow-up, 144 pancreatic cancer cases and 429 matched controls were available for analysis. Baseline characteristics of the cases and matched controls are shown in Table 1. Compared with controls, cases were somewhat less likely to exercise regularly, more likely to regularly use multivitamins, and had slightly higher levels of circulating C-peptide, but these differences were not statistically significant. Age, smoking status, and fasting status were matching factors.

Table 2 shows the degree of correlation between circulating levels of IGFBP-1, IGF-I, C-peptide and selected baseline covariates among control subjects. Plasma IGFBP-1 was positively correlated with age (Pearson correlation coefficient, $r = 0.26$) and inversely correlated with IGF-I ($r = -0.30$), C-peptide ($r = -0.50$), BMI ($r = -0.30$), and height ($r = -0.40$).

In conditional logistic regression models, circulating IGFBP-1 was inversely associated with the risk of pancreatic cancer (Table 3). Compared with participants in the highest quartile of plasma IGFBP-1, those in the third, second, and first quartiles experienced RRs of 0.93 (95% CI, 0.53–1.65), 0.80 (95% CI, 0.45–1.43), and 1.75 (95% CI, 1.02–3.00), respectively. The influence of circulating IGFBP-1 on risk remained essentially unchanged when further adjusted for other risk factors for pancreatic cancer and plasma levels of IGF-1, C-peptide, and IGFBP-3 (Table 3). In addition, our results remained unchanged after excluding participants with a history of diabetes mellitus ($n = 7$ cases) or controlling for hours

Table 3. RR of pancreatic cancer according to quartiles of IGFBP-1

	Quartiles of IGFBP-1				P, trend
	Quartile 4	Quartile 3	Quartile 2	Quartile 1	
No. of cases/controls	35/109	30/107	26/106	53/107	
Median (ng/mL)	51.8	27.8	16.0	5.3	
RR* (95% CI)	1.0	0.93 (0.53–1.65)	0.80 (0.45–1.43)	1.75 (1.02–3.00)	0.14
RR† (95% CI)	1.0	0.87 (0.48–1.56)	0.76 (0.42–1.37)	1.78 (0.99–3.21)	0.22
RR‡ (95% CI)	1.0	0.88 (0.48–1.61)	0.78 (0.43–1.42)	1.81 (0.98–3.35)	0.24

*Matched for year of birth, smoking status, fasting status, month of blood draw, and prospective cohort.
† Matched for year of birth, smoking status, fasting status, month of blood draw, and prospective cohort and adjusted for level of physical activity, history of regular multivitamin use, history of diabetes mellitus, and BMI.
‡ Matched for year of birth, smoking status, fasting status, month of blood draw, and prospective cohort and adjusted for level of physical activity, history of regular multivitamin use, history of diabetes mellitus, BMI, plasma level of IGF-I, plasma level of C-peptide, and plasma level of IGFBP-3.

Table 4. RR of pancreatic cancer according to plasma levels of IGFBP-1 by time since plasma collection

Time since plasma collection (y)	No. of cases	Quartiles 2–4	Quartile 1, RR* (95% CI)	Quartile 1, RR† (95% CI)
≥4	144	1.0	2.05 (1.28–3.31)	2.07 (1.26–3.39)
≥6	91	1.0	2.93 (1.50–5.73)	2.76 (1.39–5.50)
≥8	66	1.0	3.47 (1.46–8.23)	3.00 (1.22–7.37)

*Matched for age, smoking status, fasting status, month of blood draw, and prospective cohort and adjusted for history of regular multivitamin use, level of physical activity, history of diabetes mellitus, and BMI.

† Matched for age, smoking status, fasting status, month of blood draw, and prospective cohort and adjusted for history of regular multivitamin use, level of physical activity, history of diabetes mellitus, BMI, plasma level of IGF-I, plasma level of C-peptide, and plasma level of IGFBP-3.

between a participant's last meal and blood draw as a continuous variable (data not shown).

To rule out the effects of subclinical cancer on circulating IGFBP-1 levels, we examined the influence of IGFBP-1 among cases diagnosed after progressively longer follow-up from the baseline plasma collection. Given the largely equivalent risk estimates for the three highest quartiles, we collapsed the second, third, and fourth quartiles of plasma IGFBP-1 into a referent category, thereby providing greater power for secondary analyses. As shown in Table 4, when compared with the upper three quartiles of plasma IGFBP-1, the risk of pancreatic cancer associated with lowest quartile progressively increased with longer periods of time between baseline plasma collection and case diagnosis. When we restricted our analysis to cases and matched controls with ≥8 years between plasma collection and cancer diagnosis, participants in the lowest quartile of circulating plasma IGFBP-1 experienced a multivariate RR of 3.47 (95% CI, 1.46–8.23). This increased risk with longer time since baseline plasma collection remained similarly strong after further controlling for plasma levels of IGF-I, C-peptide, and IGFBP-3 (Table 4).

We further assessed whether the effect of IGFBP-1 was modified by other relevant covariates. The influence of low circulating IGFBP-1 seemed greater among never smokers and among participants with nonfasting plasma samples (≤8 h of fasting), although the tests for statistical interaction did not reach statistical significance (Table 5). In addition, the inverse relation between plasma IGFBP-1 and pancreatic cancer seemed somewhat stronger with increasing levels of plasma C-peptide, although the test for interaction did not achieve statistical significance ($P = 0.07$; Table 5).

Discussion

Within four large prospective cohort studies, participants in the lowest quartile of IGFBP-1 were more than twice as likely to develop pancreatic cancer when compared with those in the upper three quartiles. The influence of low plasma IGFBP-1 increased with longer time periods since plasma collection. Moreover, the strength of the association was not substantially attenuated by the inclusion of plasma IGF-I, C-peptide, and IGFBP-3 in the multivariate models, suggesting an independent effect for IGFBP-1 on pancreatic cancer risk. Finally, the association of IGFBP-1 with pancreatic cancer risk was not significantly modified by other known or suspected risk factors for pancreatic cancer, although the influence of low IGFBP-1 seemed greater among never smokers and those with elevated plasma levels of C-peptide.

Significant inverse associations have been noted between plasma levels of IGFBP-1 and the risk of colorectal (35, 36) and endometrial cancer (37), whereas such associations were not observed with postmenopausal breast cancer or lung cancer (38, 39). In the studies of colon cancer, as in the current study, a threshold effect was noted with an increased risk only in the lowest plasma IGFBP-1 grouping (35, 36). A mechanistic explanation for this pattern of risk reduction is not entirely clear, but it does seem to identify a subgroup of people at elevated risk for the development of these two common malignancies.

Obesity and sedentary lifestyle have been identified as possible risk factors for pancreatic cancer (1–5). Perturbations of insulin and the IGF axis have been suggested as mechanisms by which these factors may initiate and propagate pancreatic tumorigenesis (40). In the laboratory, IGF-I and the IGF-I receptor have been implicated in multiple facets of the malignant behavior of pancreatic cancer cells, including growth, invasion, and neoangiogenesis (10–12, 15). Yet in prospective clinical studies, no clear association has been noted between plasma IGF-I, IGF-II, or IGFBP-3 levels and the development of pancreatic cancer (18–20). A study of 93 pancreatic cancer cases from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study found no association between IGF-I or IGFBP-3 and the risk of pancreatic cancer, whereas a study of 69 pancreatic cancer cases from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk reported a nonsignificant increase in the risk of death from pancreatic cancer in the top versus the bottom quartiles of IGF-I and IGFBP-3 (18, 19). We recently completed an analysis of IGF-I, IGF-II, and IGFBP-3 in the current cohort, with RRs for the highest versus the lowest quartiles of IGF-I, IGF-II, and IGFBP-3 of 0.94 (95% CI, 0.60–1.48), 0.96 (95% CI, 0.61–1.52), and 1.21 (95% CI, 0.75–1.92), respectively (20).

In contrast, elevated fasting serum glucose (41), postload plasma glucose concentration (42), and fasting serum insulin (8) have been linked to the risk of pancreatic cancer in prospective observational cohort studies. The tumorigenic effects of insulin are likely to require the modification of an intermediary pathway, as supraphysiologic levels of insulin are required to stimulate cell division and activate the IGF receptor (9). Insulin's reduction in circulating levels of IGFBP-1 is a strong candidate mechanism for hyperinsulinemia's contribution to carcinogenesis, either by increasing free, biologically active IGF-I (40) or by direct inhibitory effects of IGFBP-1 on cell proliferation (43, 44).

Although plasma IGFBP-1 levels are altered by insulin, they are also regulated by other hormones involved in glucose and energy homeostasis, such as glucagon and cortisol (22–24). In the current study, a similar effect of circulating IGFBP-1 on pancreatic cancer risk was noted after controlling for C-peptide in multivariate models. Because insulin and IGFBP-1 are modulated by similar

clinical characteristics, such as obesity and sedentary lifestyle, it is interesting to note that stratified analyses suggest a possible additive effect of high plasma levels of C-peptide and low plasma levels of IGFBP-1 on pancreatic cancer risk. Consequently, BMI and physical activity may increase the risk of pancreatic cancer by changing the levels of these two important plasma proteins with consequences for pancreatic ductal cell growth and survival.

Several features of the current study lend credibility to these results, including its prospective design, high follow-up rates in the four participating cohorts, relatively large sample size for studies of pancreatic cancer, matching on potential confounders to increase efficiency, and controlling for plasma levels of C-peptide, IGF-I, and IGFBP-3. In addition, the association observed for low circulating IGFBP-1 is unlikely to be a consequence of pancreatic cancer, given that the prospective study design excluded cases diagnosed within 4 years after blood collection.

With the known regulation of IGFBP-1 by insulin, a potential limitation of our study is the possibility of IGFBP-1 acting as a surrogate measure for insulin, which may be the true pathologic factor leading to an increased risk of pancreatic cancer. To address this possibility, we attempted to control for insulin by simultaneously measuring plasma C-peptide levels and including this marker in our multivariate models. Although the inclusion of C-peptide may not completely adjust for transient changes in insulin secretion, we continued to observe a strong association between plasma IGFBP-1 and pancreatic cancer risk even after controlling for plasma C-peptide, providing support for an independent role of IGFBP-1 in the development of pancreatic cancer.

IGFBP-1 levels are modified by recent food intake (21, 22), and in the current study, approximately one-third of plasma samples were collected <8 h after the participants' last meal. To minimize the effect of differences in fasting status, cases and controls were matched by blood draw ≤8 h or >8 h from the last meal, and the time since the last meal in hours was controlled for in multivariate models. Interestingly, the association of pancreatic cancer with circulating IGFBP-1 seemed to be stronger among participants with plasma collected in a nonfasting state. This finding is consistent with a growing body of literature suggesting that postprandial peaks in glucose, insulin, and related hormones following a high glycemic index meal, rather than fasting levels, may better reflect cumulative hormone exposure and correlate more accurately with pathologic outcomes (45–47).

Table 5. RR of pancreatic cancer according to plasma levels of IGFBP-1 and other potential pancreatic cancer risk factors

Covariate	Cases/controls	Quartiles 2–4	Quartile 1, RR (95% CI)	*P*, interaction
Age (y)*				
≤62	77/251	1.0	2.15 (1.15–4.03)	0.86
>62	67/178	1.0	1.85 (0.90–3.78)	
Gender				
Male	69/207	1.0	2.20 (1.10–4.37)	0.47
Female	75/222	1.0	1.88 (0.99–3.56)	
Smoking status				
Never	55/166	1.0	3.33 (1.49–7.41)	0.19
Past	58/183	1.0	1.82 (0.90–3.71)	
Current	31/80	1.0	1.15 (0.39–3.37)	
Physical activity*				
Low	86/228	1.0	1.93 (1.06–3.53)	0.95
High	58/201	1.0	2.09 (1.01–4.33)	
BMI (kg/m^2)				
<25	62/210	1.0	2.34 (1.08–5.09)	0.27
≥25	82/219	1.0	1.77 (1.01–3.09)	
Fasting status				
≤8 h or unknown	53/162	1.0	2.69 (1.31–5.50)	0.29
>8 h	91/267	1.0	1.50 (0.81–2.78)	
IGF-I †				
Tertile 1	45/142	1.0	2.13 (0.83–5.48)	0.75
Tertile 2	52/143	1.0	1.87 (0.85–4.12)	
Tertile 3	47/144	1.0	2.31 (1.01–5.30)	
C-peptide †				
Tertile 1	43/141	1.0	0.99 (0.16–6.04)	0.07
Tertile 2	38/144	1.0	1.80 (0.70–4.65)	
Tertile 3	63/144	1.0	2.32 (1.17–4.60)	
IGFBP-3 †				
Tertile 1	50/141	1.0	1.22 (0.49–3.02)	0.15
Tertile 2	46/144	1.0	1.72 (0.74–4.03)	
Tertile 3	48/144	1.0	3.17 (1.39–7.23)	

NOTE: Multivariate RRs adjusted for year of birth, smoking status, fasting status, prospective cohort, level of physical activity, history of regular multivitamin use, history of diabetes mellitus, and BMI. In each case, the stratification variable was excluded from the model.

*Above or below the median level of age and physical activity in matched pancreatic cancer controls.

† Plasma levels of IGF-I, C-peptide, and IGFBP-3 in tertiles with cut-points based on matched pancreatic cancer controls.

In conclusion, this prospective, nested case-control study suggests that low circulating levels of IGFBP-1 significantly predict the subsequent risk of pancreatic cancer, independent of other known or suspected risk factors for this malignancy. Further studies of the interaction of insulin and the IGF axis in pancreatic cancer are needed to better understand the mechanisms by which anthropometric factors and plasma levels of insulin and IGFBP-1 alter the risk for this highly lethal malignancy.

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