ORIGINAL ARTICLE

Prediagnosis Circulating Insulin-Like Growth Factors and Pancreatic Cancer Survival

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ABSTRACT

Background. Prediagnosis obesity and diabetes are associated with survival from pancreatic cancer, but the underlying mechanisms have not been characterized. Because both are associated with dysregulation in circulating insulin-like growth factor (IGF) levels, we evaluated the associations of prediagnosis IGF levels (IGF-I, IGF-II) and IGF binding protein 3 (IGFBP-3) with pancreatic cancer survival.

Methods. Participants were subjects enrolled in the intervention arm of the PLCO Cancer Screening Trial who developed exocrine pancreatic cancer during follow-up ($N = 178$, 116 men and 67 women). Participants provided blood samples at enrollment, before cancer diagnosis. Cox proportional hazards regression model, adjusted for confounders was used to investigate associations of IGF biomarkers with pancreatic cancer survival. Because of the well-documented, gender-specific differences in circulating IGF biomarkers, and differential associations of IGF biomarkers with mortality, we evaluated associations separately among males and females.

Results. Median survival was 172 days. Higher IGF-II and IGFBP-3 levels were associated with pancreatic cancer survival among males but not among females. The hazard ratios (HR) of death among men in the highest tertiles of IGF-II and IGFBP-3 compared with men in the lowest tertiles were 0.40 (95% confidence interval (CI) 0.23–0.71, $p < 0.01$) and 0.59 (95% CI 0.35–0.97, $p = 0.10$), respectively. There were no statistically significant associations between IGF-I concentrations, IGF-I/IGFBP-3, and pancreatic cancer survival.

Conclusions. Higher prediagnosis circulating IGF-II and IGFBP-3 levels are associated with better pancreatic cancer survival among men but not women. A greater understanding of how IGF signaling is related to pancreatic cancer survival could have utility in improving pancreatic cancer prognosis.

Pancreatic cancer is projected to be the second leading cause of cancer death before 2020. The only potentially curative therapy is surgery, but <20% of patients are candidates for surgery.[1] Population-based screening programs are not feasible due to the very low absolute individual risk and the lack of low-cost screening tools.[2] Hence, knowledge of factors because this could help with targeted management.

Prediagnostic obesity and a prior history of diabetes mellitus are associated with shorter pancreatic cancer survival.[3] If current obesity and diabetes epidemic trends in the United States continue, they could soon be the major modifiable factors that impact pancreatic cancer survival. However, the underlying mechanisms through which they impact pancreatic cancer survival in humans have not characterized. Obesity and diabetes are associated with insulin resistance, with resultant dysregulation in circulating insulin-like growth factors (IGF).[4–6] The IGF-axis is essential for cell proliferation and energy homeostasis.[4–6] IGFBP-3 modulates IGF-I bioavailability by limiting its access to IGF-IR.[4] Aside from modulating IGF-I bioavailability, IGFBP-3 also has IGF-I independent growth-inhibitory activities.[7]

Murine models reveal that IGF-I is associated with shorter pancreatic cancer survival, but no human studies have evaluated these associations.[8] Although studies evaluating the associations of circulating IGFs with pancreatic cancer risk have generally not reported any positive associations, high IGF-I/IGFBP3 molar ratio, an indicator of free bioavailable IGF-I levels, was associated with an increased risk of pancreatic cancer in two of the studies.[9–12] Nevertheless, because IGF-I activates pathways that accelerate carcinogenesis, enhance invasion, and metastasis, it may play a more important role in pancreatic cancer progression, than initiation.[13,14] We hypothesized that prediagnostic circulating IGF levels are associated with pancreatic cancer survival. We evaluated this hypothesis among pancreatic cancer patients enrolled in the intervention arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, where blood samples were collected before cancer diagnosis. Because of the gender-specific differences in circulating IGF biomarkers, and differential associations of IGF biomarkers with CVD and survival, we evaluated associations separately among males and females.[15–20]

MATERIALS AND METHODS

Design Overview

The PLCO Cancer Screening Trial is a randomized, two-armed, controlled trial designed to determine the effects of screening on disease-specific mortality for cancers of the prostate, lung, colorectal, and ovaries. The PLCO study design and characteristics of the participants have been described in detail elsewhere.[21] Briefly, the PLCO enrolled 154,901 men and women aged 55–74 years from ten centers in the United States between November 1993 and July 2001.[21] Participants were randomized to an intervention arm or a control arm. All study participants filled a baseline questionnaire at study entry where they provided demographic, personal, and medical information. Additionally, participants in the intervention arm had blood collected at the time of enrollment. Each eligible participant provided written informed consent.

Incident primary pancreatic adenocarcinoma (exocrine; International Classification of Disease for Oncology, 3rd edition code C250–C259) were determined from yearly questionnaires completed by participants or next of kin as well as state registries, death certificates, and physician reports and confirmed by PLCO staff.[22] We used the same IGF-axis measurements that were measured in a previous nested case control study within the PLCO evaluating the associations of IGF biomarkers with pancreatic cancer risk.[9] At the time of follow-up in December 2006, 172 incident cases of pancreatic adenocarcinomas had been diagnosed and confirmed through medical review in the intervention arm, thus included in the present analysis.

Pancreatic cancer stage was abstracted at the PLCO centers in categories of localized, locally advanced, and metastatic in 2010 from previously collected pathology reports and medical records used for cancer confirmation. Tumor stage was classified as (i) local disease amenable to surgical resection; (ii) locally advanced disease with extrapancreatic extension not amenable to surgical resection, but without distant metastases; and (iii) distant metastatic disease. The American Joint Committee on Cancer (AJCC)/International Union for Cancer Control (IUCC) tumor-lymph nodes-metastasis (TNM) staging was converted to the above categories. The AJCC/IUCC stages I and II corresponds to local disease, stage III corresponds to locally advanced disease, and stage IV corresponds to metastatic disease. Information on deaths and causes of death were obtained by linking the study population to the National Death Index. The institutional review boards of the National Cancer Institute and each of the centers that participated approved the study.

Laboratory Analyses for Circulating IGF-I, IGF-II, IGFBP-3 Nonfasting blood samples were collected in 10-mL red top blood tube at the time of baseline examination from participants in the intervention arm and processed within 2 h of collection, either on-site or at a central processing laboratory, into fractions stored at −70 °C, as previously described.[9] Serum IGF-I, IGF-II, and IGFBP-3 concentrations were quantified using enzyme-linked immunosorbent assay with reagents at Dr. Michael Pollak's laboratory. The intrabatch, and interbatch percent coefficient of variation (CV) were 10.3, 5.1, and 5.1% for IGF-I, IGF-II, and IGFBP-3, respectively.[9]

Statistical Analysis

Circulating IGF-I, IGF-II, IGFBP-3 levels, and IGF-I/IGFBP-3 molar ratio were categorized into tertiles based on the distribution within our study population. IGF-I/IGFBP-3 molar ratio, a surrogate estimate of free IGF-I was calculated (1 ng/ml IGF-I = 0.130 nM, 1 ng/ml IGFBP-3 = 0.036 nM).[9] In unadjusted analyses, Kaplan–Meier product limit survival function estimates were used to describe the survival experience by tertiles of biomarker levels. In adjusted analyses, Cox proportional hazards regression model was used to analyze the associations of the biomarkers, and IGF-I/IGFBP-3 molar ratio with pancreatic cancer survival, with age as the underlying time metric. The proportional hazard assumption was tested and satisfied through the use of time-dependent covariate method.

In line with findings from previous studies, we observed gender-related differences in the distribution of circulating IGFs.[15,16] In addition, tests for interactions by gender were significant for IGF-II; hence, we conducted analyses stratified by gender. Hazard ratios (HR) and 95% confidence intervals were calculated within each tertile of circulating biomarker. In initial analyses, we adjusted for only stage at diagnosis (localized, locally advanced, metastatic, and unknown/missing). In subsequent multivariable analyses, we additionally adjusted for age, body mass index (BMI, kg/m^2), history of diabetes (yes vs. no), and smoking status (never vs. current vs. former smokers), because these variables were significant at $p < 0.10$. Furthermore, we adjusted IGF-I analyses for IGF-II and IGF-II analyses for IGF-I. In sensitivity analyses, we excluded participants who were diagnosed with pancreatic cancer within the first 2 years of study enrollment and those who had diabetes mellitus at the time of study enrollment. We also stratified the analyses by smoking status, and time from blood draw to diagnosis in the overall study population (<5 years and ≥5 years). Trend tests were calculated by treating the median values within each tertile as a continuous variable. We assessed statistical interaction by entering the main effect terms and a cross-product term of the biomarkers and stratification variable into the model and evaluated likelihood ratio tests. All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

The mean age and BMI of study participants were 65.3 years and 27.3 kg/m^2, respectively (Table 1). In total, 116 were males, and 62 were females. Biomarker concentrations differed by gender with males having higher IGF-I but lower IGF-II and IGFBP-3. Mean biomarker concentrations were: IGF-I (male 201.47 ng/ml; female 155.43 ng/ml), IGF-II (male 1585.46 ng/ml; female 1715.08 ng/ml), and IGFBP-3 (male 3557.16 ng/ml; female 3822.83 ng/ml). A total of 171 deaths (96%) occurred during a median survival of 172 days. Median time between blood draw and diagnosis was 5.5 years.

In multivariable adjusted models, the biomarkers had divergent effects on survival among males and females, although none of the associations in females were statistically significant (Table 2). Men in the highest tertiles of IGF-II (HR 0.40, 95% CI 0.23–0.71, $p < 0.01$) and IGFBP-3 (HR 0.59, 95% CI 0.35–0.97, $p = 0.10$) had better survival compared with men in the lowest tertiles, although the trend test was statistically significant for only IGF-II. The trend test was significant for IGFBP-3 in analyses adjusted for only tumor stage (HR 0.47, 95% CI 0.29–0.76, $p < 0.01$). Further adjustment of the IGF-II analysis for

TABLE 1 Characteristics of participants in the intervention arm of the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial who developed exocrine pancreatic cancer ($N = 178$)

Characteristics	*N* (%)
Age at baseline (years)	65.30 (4.87)
≤59	26 (14.61)
60–64	47 (26.40)
65-69	69 (38.76)
≥70	36 (20.22)
Gender	
Female	62 (34.83)
Male	116 (65.17)
Race	
White, non-Hispanic	161 (90.45)
Others black, non-Hispanic	17 (9.55)
Body mass index (kg/m^2)	27.30 (4.53)
<25	55 (30.90)
25–29.99	79 (44.38)
≥30	44 (24.72)
Smoking status	
Never smoker	68 (38.20)
Current smoker	35 (19.66)
Former smoker	75 (42.13)
Mortality status	
Dead	171 (96.07)
Alive	7 (3.93)
Cancer stage	
Localized	18 (10.11)
Locally advanced	24 (13.48)
Metastatic	62 (34.83)
Unknown	74 (41.57)
History of diabetes	
No	157 (88.20)
Yes	21 (11.80)
IGF-I (ng/ml), mean (SD)	185.43 (67.60)
Female	155.43 (58.78)
Male	201.47 (66.75)
IGF-II (ng/ml), mean (SD)	1630.61 (388.27)
Female	1715.08 (378.76)
Male	1585.46 (387.34)
IGFBP-3 (ng/ml), mean (SD)	3649.70 (855.58)
Female	3822.83 (865.00)
Male	3557.16 (839.63)
Median survival, days	171.50
Time between blood draw and diagnosis, median (IQR), year	5.5 (4.9)

TABLE 2 Hazard ratios and 95% confidence intervals (HR, 95% CI) of pancreatic cancer survival by tertiles of IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio among participants in the intervention arm of PLCO

	HR (95% CI) Tertile 1	HR (95% CI) Tertile 2	HR (95% CI) Tertile 3	*p*-trend	*p*-int
IGF-I (ng/ml)					
Female	(<117)	(117–173)	(>173)		
Number of cases	20	21	21		
Model 1[a]	1.00 (ref)	0.97 (0.48–1.99)	1.61 (0.84–3.10)	0.09	
Model 2[b]	1.00 (ref)	1.15 (0.52–2.55)	1.84 (0.92–3.71)	0.07	
Model 3[c]	1.00 (ref)	0.98 (0.39–2.45)	1.46 (0.57–3.78)	0.29	
Male	(<172)	(172–223)	(>223)		0.74
Number of cases	38	39	39		
Model 1	1.00 (ref)	0.64 (0.40–1.02)	0.73 (0.47–1.15)	0.67	
Model 2	1.00 (ref)	0.83 (0.49–1.38)	0.83 (0.52–1.32)	0.65	
Model 3	1.00 (ref)	1.07 (0.60–1.90)	1.10 (0.64–1.89)	0.78	
IGF-II (ng/ml)					
Female	(<1533)	(1533–1844)	(>1844)		
Number of cases	20	21	21		
Model 1	1.00 (ref)	1.85 (0.97–3.53)	1.44 (0.74–2.82)	0.84	
Model 2	1.00 (ref)	2.08 (1.04–4.14)	1.60 (0.79–3.23)	0.73	
Model 3	1.00 (ref)	1.89 (0.93–3.86)	1.18 (0.51–2.74)	0.68	
Male	(<1409)	(1409–1678)	(>1678)		0.03
Number of cases	38	39	39		
Model 1	1.00 (ref)	0.74 (0.46–1.20)	0.40 (0.24–0.65)	<0.01	
Model 2	1.00 (ref)	0.76 (0.47–1.24)	0.47 (0.29–0.78)	<0.01	
Model 3	1.00 (ref)	0.70 (0.42–1.16)	0.40 (0.23–0.71)	<0.01	
IGFBP-3 (ng/ml)					
Female	(<3334)	(3334–4141)	(>4141)		0.09
Number of cases	20	21	21		
Model 1	1.00 (ref)	1.64 (0.85–3.15)	1.48 (0.75–2.90)	0.63	
Model 2	1.00 (ref)	1.96 (1.00–3.87)	1.58 (0.76–3.27)	0.72	
Male	(<3136)	(3136–3761)	(>3761)		
Number of cases	38	39	39		
Model 1	1.00 (ref)	0.66 (0.41–1.06)	0.47 (0.29–0.76)	0.01	
Model 2	1.00 (ref)	0.70 (0.42–1.15)	0.59 (0.35–0.97)	0.10	
IGF-I/IGFBP-3 molar ratio					
Female					
Number of cases					
Model 1	1.00 (ref)	0.88 (0.45–1.72)	1.17 (0.59–2.33)	0.46	
Model 2	1.00 (ref)	0.94 (0.47–1.87)	1.20 (0.57–2.54)	0.50	
Male					0.52
Number of cases					
Model 1	1.00 (ref)	1.44 (0.89–2.32)	1.40 (0.88–2.24)	0.46	
Model 2	1.00 (ref)	1.26 (0.76–2.10)	1.38 (0.86–2.21)	0.35	

178 cases, 62 females, and 116 males

[a] Model 1: adjusted for stage

[b] Model 2: adjusted for stage, age, body mass index, history of diabetes, and smoking status

[c] Model 3: mutually adjusted for IGF-I (IGFII analyses), or IGF-II (IGF-I analyses) in addition to variables in model 2

TABLE 3 Hazard ratios and 95% confidence intervals (HR, 95% CI) of pancreatic cancer survival by tertiles of IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio, stratified by time between blood draw and diagnosis among all participants in the intervention arm of PLCO

	HR (95% CI) Tertile 1 (<152)	HR (95% CI) Tertile 2 (152–205)	HR (95% CI) Tertile 3 (>205)	*p* trend	*p*-int
IGF-I(ng/ml)					
<5 years $N = 78$	$N = 26$	$N = 23$	$N = 29$	0.90	0.34
	1.00 (ref)	1.00 (0.5–2.01)	0.89 (0.45–1.76)		
≥5 years $N = 100$	N = 33	$N = 37$	$N = 30$	0.26	
	1.00 (ref)	1.6 (0.86–2.96)	1.15 (0.6–2.22)		
	(<1456)	(1456–1726)	(>1726)		
IGF-II ng/ml					
<5 years $N = 78$	$N = 29$	$N = 22$	$N = 27$	0.95	0.07
	1.00 (ref)	0.92 (0.49–1.74)	0.92 (0.5–1.7)		
≥5 years $N = 100$	$N = 30$	$N = 38$	$N = 32$	0.24	
	1.00 (ref)	0.83 (0.47–1.47)	0.58 (0.3–1.11)		
	(<3225)	(3225–3945)	(>3945)		
IGFBP-3 ng/ml					
<5 years $N = 78$	$N = 27$	$N = 23$	$N = 28$	0.82	0.54
	1.00 (ref)	1.21 (0.65–2.27)	1.15 (0.65–2.05)		
≥5 years $N = 100$	$N = 32$	$N = 37$	$N = 31$	0.55	
	1.00 (ref)	0.78 (0.45–1.35)	0.75 (0.43–1.31)		
IGF-I/IGBO-3 molar ratio					
<5 years $N = 78$	$N = 25$	$N = 24$	$N = 29$	0.22	0.12
	1.00 (ref)	0.60 (0.3–1.21)	0.98 (0.52–1.83)		
≥5 years $N = 100$	$N = 34$	$N = 36$	$N = 30$	0.12	
	1.00 (ref)	1.27 (0.74–2.19)	1.86 (1.03–3.35)		

Models adjusted for stage, age, body mass index, history of diabetes, and smoking status. IGF-I and IGF-II analyses mutually adjusted for each other

IGF-I did not alter the results. The HR for death comparing extreme tertiles of IGF-I in males was 0.83 (95% CI 0.52–1.32, $p = 0.65$). Elevated IGF-I was associated with nonstatistically significant reduced survival among women; HR 1.84 (95% CI 0.92–3.71, $p = 0.07$), but adjustment for IGF-II attenuated the association (HR 1.46, 95% CI 0.57–3.78, $p = 0.29$). For IGF-II and IGFBP-3, the corresponding HRs were 1.60 (95% CI 0.79–3.23, $p = 0.73$) and 1.58 (95% CI 0.76–3.27, $p = 0.72$), respectively. IGF-I/IGFBP-3 molar ratio was not associated with survival among males (HR 1.38, 95% CI 0.86–2.21, $p = 0.35$) and females (HR 1.20, 95% CI 0.57–2.54, $p = 0.50$). Findings were similar when participants diagnosed with pancreatic cancer within 2 years of study enrollment, and those who had diabetes before study enrollment were excluded from the analyses (data not shown). The associations of IGF-II with pancreatic cancer survival appeared stronger among those who provided blood samples ≥5 years before diagnosis (HR 0.58, 95% CI 0.3–1.11, $p = 0.24$) than those who provided blood samples <5 years before diagnosis (HR 0.92, 95% CI 0.5–1.7, $p = 0.95$). The test for interaction was, however, not statistically significant (p-interaction = 0.07; Table 3). No statistically significant interactions were observed by smoking status (data not shown).

DISCUSSION

To the best of our knowledge, this is the first prospective study to evaluate associations of prediagnosis IGF-axis biomarkers with pancreatic cancer survival. We observed better survival for men with higher IGF-II IGFBP-3 concentrations. The inverse association of IGF-II with survival was still evident after adjustment for IGF-I. IGF biomarkers were not associated with pancreatic cancer survival in females; however, the smaller sample size needs to be taken into consideration.

The inverse association between prediagnosis IGF-II and pancreatic cancer survival is novel and extends knowledge on IGF biomarkers in relation to cancer, as the

few available studies focus on prediagnosis IGF-I and IGFBP-3. Although, to our knowledge, there appears to be no published prospective studies on prediagnosis IGF-II and cancer-specific survival, similar inverse associations have been reported between postdiagnostic IGF-II levels and colorectal cancer survival in clinical studies.[23,24]

The underlying mechanisms that may explain our observed association for IGF-II concentrations with increased cancer survival are not well known. IGF-II promotes cell survival and stimulates glucose and amino acid uptake.[25] IGF-IIR overexpression, however, is associated with decreased multiple tumor growth in nude mice.[26] It is possible that IGF-II is a downstream biological proxy for lifestyle-related activities that are associated with pancreatic cancer survival. Cigarette smoking is associated with lower IGF-II levels, especially in males, as well as higher pancreatic cancer mortality.[1,27] Thus, the association of higher IGF-II with longer pancreatic cancer survival could be secondary to the effect of smoking. Nevertheless, we adjusted for smoking in our analyses, and the majority of our cases were either never or former smokers at baseline, suggesting that its effect is independent of smoking. In addition, men, but not women, with high levels of physical activity have higher IGF-II levels.[27] We did not have detailed data on physical activity to allow for adequate adjustment; hence, this will need to be explored in future studies with detailed physical activity data. Diet does not appear to have any impact on circulating IGF-II levels in men.[28] In addition to its effect on cell proliferation, the influence of IGF-II on muscle mass may provide some explanation for the observed results. IGF-II is an embryonic regulator of skeletal muscle formation; hence, low IGF-II levels may indicate early stage muscle wasting from occult pancreatic cancer.[29] In a small, clinical study among pancreatic cancer patients, anti-IGF-1R therapy, although it had clinical benefit, was associated with muscle loss, and muscle mass loss correlated with death.[30] Although blood samples were collected from all participants before cancer diagnosis, participants might have developed pancreatic cancer at the time of baseline examination, because pancreatic cancer has a very long latency period. In a recent study, it was established that metabolic abnormalities may be detectable in the circulation of pancreatic cancer patients years before the development of clinical disease, especially 2–5 years before diagnosis.[31] The associations of IGFBP-3 with survival is biologically plausible, because IGFBP-3 independently inhibits cancer progression, in addition to its IGF-I modulating activities.[7]

The gender-specific differences we observed are also notable. Gender-specific differences in the associations of IGF biomarkers with outcomes, including cardiovascular disease and all-cause mortality have been documented previously.[17–20] The underlying mechanisms are poorly understood, although hormonal mechanisms have been hypothesized to play a role. Growth hormone (GH) is a major stimulus for hepatic IGF production, and estrogens and androgens have divergent effects on the action of GH.[32] Estrogen impairs GH function, resulting in a reduction in circulating IGF-I levels, whereas testosterone enhances the metabolic effect of GH.[33] Furthermore, women are less sensitive to the effects of GH than men.[33]

Before our study, only one other study had investigated associations of circulating IGF-I and IGFBP-3 with pancreatic cancer mortality. The authors reported nonsignificant increased risks of death associated with high IGF-I and IGFBP-3 levels.[34] The study is different from ours in terms of methodology, because it was a nested case–control study of 69 pancreatic cancer cases and 207 matched controls. In addition, we conducted analyses stratified by gender, whereas this study did not. The association of prediagnosis IGF biomarkers with mortality from other cancer types has been evaluated in a few other studies. In a combined analyses within the Nurses' Health Study and Health Professionals Follow-Up Study, elevated IGFBP-1 levels prior to colorectal cancer diagnosis was associated with reduced mortality, but no associations were reported for IGF-I and IGFBP-3.[35] In another prospective cohort study, inverse associations were reported between IGFBP-3 and colorectal cancer mortality among people who were physically active but not among those who were inactive.[36] Other prospective studies have investigated associations of IGF biomarkers with all-cause cancer mortality, with conflicting results.[19,37–40] Among older men, high IGF-I levels were associated with increased all-cause cancer mortality in one small study but a U-shaped association in another.[37,38] Another study conducted in Germany reported inverse associations between IGF-I, IGFBP-3, and cancer mortality. Two other studies observed null associations.[19,39,40] These discrepancies could result from the heterogeneity arising from the use of all-cause cancer mortality as the outcome, because the underlying biological mechanisms driving deaths will differ according to cancer types. Because deaths from some cancer types may be driven by disruptions in circulating IGF biomarkers, while others will not, more studies evaluating associations of these biomarkers, especially IGF-II, with cancer-specific deaths are needed.

The following limitations need to be considered. We had single measurements of circulating IGF biomarkers. Although the biomarkers are stable over time and one single measurement captures circulating levels over a period of time, we could not evaluate how changes in biomarker levels might influence survival. Metformin and statin use may be associated with pancreatic cancer survival, but we had no such data. Therefore, we could not adjust for these in our analyses. Despite these limitations, the prospective nature with samples collected before

documented pancreatic cancer diagnosis, availability of data on variables associated with pancreatic cancer survival, and adequate follow-up for outcome ascertainment are strengths of our study. Furthermore, our findings that the association with IGF-II appeared stronger among those who provided blood samples $\geq$5 years before diagnosis suggesting that reverse causality is not likely to be a consideration.

Although based on small numbers, our findings suggest that the metabolic environment, as evidenced by prediagnosis IGF-II and IGFBP-3 levels are associated with survival in men diagnosed with pancreatic cancer but not women. In view of the very poor survival associated with pancreatic cancer, these results require confirmation in other prospective studies, as well as larger studies to explore other important subgroup interactions.

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