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Circulating insulin-like growth factor axis and the risk of pancreatic cancer in four prospective cohorts

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Insulin-like growth factor (IGF)-I induces growth in pancreatic cancer cells and blockade of the IGF-I receptor has antitumour activity. The association of plasma IGF-I and IGF binding protein-3 (IGFBP-3) with pancreatic cancer risk has been investigated in two small studies, with conflicting results. We conducted a nested case–control study within four large, prospective cohorts to investigate whether prediagnostic plasma levels of IGF-I, IGF-II, and IGFBP-3 were associated with pancreatic cancer risk. Plasma levels in 212 cases and 635 matched controls were compared by conditional logistic regression, with adjustment for other known pancreatic cancer risk factors. No association was observed between plasma levels of IGF-I, IGF-II, or IGFBP-3 and incident diagnosis of pancreatic cancer. Relative risks for the highest vs the lowest quartile of IGF-I, IGF-II, and IGFBP-3 were 0.94 (95% confidence interval (CI), 0.60–1.48), 0.96 (95% CI, 0.61–1.52), and 1.21 (95% CI, 0.75–1.92), respectively. The relative risk for the molar ratio of IGF-I and IGFBP-3, a surrogate measure for free IGF-I, was 0.84 (95% CI, 0.54–1.31). Additionally, no association was noted in stratified analyses or when requiring longer follow-up. In four prospective cohorts, we found no association between the risk of pancreatic cancer and prediagnostic plasma levels of IGF-I, IGF-II, or IGFBP-3.

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The insulin-like growth factor (IGF) axis has been implicated in the development of several malignancies (Renehan et al, 2004). Insulin-like growth factor-I is a hormone and growth factor produced predominantly in the liver under the regulation of growth hormone, but also produced locally in multiple tissue types. Insulin-like growth factor-II is structurally similar to IGF-I, primarily produced in the liver, and maternally imprinted (Khandwala et al, 2000). More than 80% of circulating IGF-I and IGF-II are bound to IGF binding protein-3 (IGFBP-3), in a protein complex that is confined to the vascular compartment (Firth and Baxter, 2002). Tissue IGF bioactivity is thought to be determined by free IGF, the component of IGF not bound to IGF binding proteins, which binds to the IGF-I receptor (IGF-IR) on the target cell surface (Jones and Clemons, 1995). Insulin-like growth factor-I and IGF-1R are highly expressed in pancreatic cancer cell lines, where initiation of intracellular signalling through IGF-IR leads to decreased apoptosis and increased proliferation, invasion, and expression of mediators of angiogenesis (Ohmura et al, 1990; Bergmann et al, 1995; Stoeltzing et al, 2003; Zeng et al, 2003; Neid et al, 2004).

High plasma levels of IGF-I and low levels of IGFBP-3 are associated with the development of prostate (Chan et al, 1998), colorectal (Ma et al, 1999), and premenopausal breast (Hankinson et al, 1998) cancer. In addition, loss of imprinting at the IGF-II locus leads to increased expression of IGF-II and higher rates of malignancy (Cui et al, 2003; Feinberg, 2004; Sakatani et al, 2005). Two small, nested case–control studies of IGF-I, IGFBP-3, and pancreatic cancer risk have yielded conflicting results (Lin et al, 2004; Stolzenberg-Solomon et al, 2004).

To further investigate whether plasma IGF-I, IGF-II, and IGFBP-3 levels are associated with the risk of pancreatic cancer, we performed a nested case–control study using the combined resources of four large prospective cohort studies, with blood samples collected before cancer diagnosis. We hypothesized that elevated levels of IGF-I and IGF-II and/or depressed levels of IGFBP-3 would predict an increased risk of pancreatic cancer.
MATERIALS AND METHODS

Subjects

Pancreatic cancer cases and matched controls through 2003 were drawn from four prospective cohort studies: the Nurses’ Health Study (NHS), Health Professionals Follow-up Study (HPFS), Physicians’ Health Study (PHS), and Women’s Health Initiative (WHI). The NHS was initiated in 1976 when 121,701 US female registered nurses aged 30–55 responded to a mailed questionnaire regarding individual characteristics, habits, and medical history. The HPFS began in 1986 when 51,529 male health professionals aged 40–76 years responded to a similarly mailed questionnaire. The PHS was initiated in 1982 as a randomized clinical trial evaluating aspirin and β-carotene among 22,071 male physicians aged 40–84 years. The WHI observational component is a multicentre cohort study of 93,676 postmenopausal women aged 50–79 years, enrolled between 1994 and 1998. In each of these cohort studies, regular follow-up questionnaires were mailed to participants every 1–2 years to update exposure data and medical history. Deaths among non-respondents were actively ascertained. All participants provided consent upon enrollment. The current study was approved by the Human Research Committee at Brigham and Women’s Hospital, Boston, MA, USA.

If a participant (or next of kin for decedents) reported a diagnosis of pancreatic cancer, the diagnosis was confirmed by medical record and pathology report review. If the primary cause of death on a death certificate was a previously unreported or unconfirmed case of pancreatic cancer, family members were contacted for permission to retrieve medical records and confirm the diagnosis. Most deaths in these cohorts were reported by family members or by the postal service in response to follow-up questionnaires. In addition, searches of the National Death Index were conducted for non-responders; this method has a sensitivity of 98% or greater in identifying decedents (Rich-Edwards et al., 1994).

In each cohort study, blood samples drawn from participants were kept chilled until processing, separated into plasma, erythrocytes, and buffy coat, and stored as multiple aliquots in liquid nitrogen freezers. During storage, precautions were taken to ensure that no specimens thawed or warmed substantially. Blood was drawn 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.

Eligibility criteria for potential cases included no prior history of malignancy (other than non-melanoma skin cancer), available plasma sample, and two or more years between plasma collection and pancreatic cancer diagnosis. At the time of data set creation, the diagnosis of pancreatic cancer was confirmed by medical record review for all but four reported cases. Controls were required to have an available plasma sample and no cancer diagnosis (other than non-melanoma skin cancer). Three controls were matched to each case based on year of birth, smoking status (current, past, never), prospective cohort, month of blood draw, and fasting status at time of blood draw.

Plasma assays of IGF-I, IGF-II, and IGFBP-3

Plasma levels of IGF-I, IGF-II, and IGFBP-3 were assayed in the laboratory of Dr Michael N Pollak (Jewish General Hospital and McGill University) by enzyme-linked immunosorbent assay with reagents from Diagnostic Systems Laboratory (Webster, TX, USA). Plasma samples from cases and matched control subjects were assayed in the same batch to minimize interassay variability, and quality control samples were inserted randomly. Laboratory personnel were unable to distinguish among case, control, and quality control samples. The mean intra-assay coefficients of variation for IGF-I, IGF-II, and IGFBP-3 from the blinded quality control samples were <11% for IGF-I, <6% for IGF-II, and <5% for IGFBP-3.

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 χ2 tests, respectively. For the plasma biomarkers, all quartile cut-points were generated among the controls only and were determined separately for each prospective cohort. Spearman’s correlation coefficients were calculated to examine the relationships among IGF-I, IGF-II, IGFBP-3, and selected covariates.

We computed odds ratios to estimate relative risks for the association of IGF-I, IGF-II, and IGFBP-3 and pancreatic cancer risk using conditional logistic regression. We also examined the molar ratio of IGF-I to IGFBP-3, as a possible surrogate for free IGF-I (for IGF-I, 1 ng ml−1 = 0.130 nm; and for IGFBP-3, 1 ng ml−1 = 0.036 nm). Tests for trend using two-sided P-values were calculated by entering the quartile-specific median values for IGF-I, IGF-II, IGFBP-3, and molar ratio of IGF-I and IGFBP-3 as continuous variables in logistic regression models. To confirm that data from the four cohorts could be combined, we utilized Cochran’s Q test for heterogeneity between cohorts.

We adjusted for covariates that were associated with pancreatic 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. Body mass index and level of physical activity were included in models after division into quartiles. Other covariates, such as height, intake of vitamin D, intake of calcium, and total energy intake, were not included, as they were not consistently associated with pancreatic cancer risk across the cohorts.

Stratified analyses were conducted using unconditional logistic regression. We sequentially excluding cases and matched controls, with less than 4, 6, or 8 years between plasma collection and cancer diagnosis to evaluate whether the influence of IGF-I, IGF-II, or IGFBP-3 would change with longer follow-up. All statistical analyses were performed using the SAS 8.2 statistical package (SAS Institute, Cary, NC, USA) and all P-values are two sided.

RESULTS

From the four cohorts, 212 cases of pancreatic cancer were identified in participants who had provided blood two or more years before cancer diagnosis. Based on the matching factors of year of birth, smoking status, prospective cohort, month of blood draw, and fasting status, 636 control participants were chosen. One control developed pancreatic cancer and was removed from the study, resulting in 212 cases and 635 controls available for analysis. No samples fell below the lowest concentration on the standard curves for the IGF-I, IGF-II, or IGFBP-3 assays. The comparison of IGF-I, IGF-II, and IGFBP-3 data from the four cohorts using Cochran’s Q test for heterogeneity resulted in P-values of 0.58, 0.91, and 0.48, respectively, supporting the combined analysis of plasma marker data.

Baseline characteristics of the cases and matched controls are shown in Table 1. Participants who developed pancreatic cancer had a slightly higher BMI and were less likely to perform regular physical activity. No statistically significant differences were noted in other covariates or the plasma biomarkers. Spearman’s correlation coefficients demonstrated a significant positive correlation of IGF-I with IGFBP-3, IGF-1:IGFBP-3 molar ratio, and height, and a significant inverse correlation with age. IGF-II was positively correlated with IGF-I and IGFBP-3, while little
correlation was noted with the other covariates (correlation coefficients available in Table 1 of Supplementary Material).

Covariates related to the risk of pancreatic cancer with a P-value of less than 0.20 were included in multivariate analyses. Before and after adjustment for these covariates (BMI, level of physical activity, history of diabetes mellitus and regular multivitamin use), IGF-I, IGFBP-3, the IGF-I:IGFBP-3 molar ratio, and IGF-II were not associated with risk of pancreatic cancer (Table 2). The adjusted relative risk for the highest quartile of IGF-I compared with the lowest quartile was 0.94 (95% confidence interval (CI), 0.60–1.48). When the model was also adjusted for IGFBP-3, little change was noted in this relative risk. The adjusted relative risk for the highest quartile of IGFBP-3 compared with the lowest quartile was 1.21 (95% CI, 0.75–1.92), which changed minimally after inclusion of IGF-I in the multivariate model. In addition, the adjusted relative risks for the top vs the bottom quartiles of IGF-I:IGFBP-3 molar ratio and IGF-II were 0.84 (95% CI, 0.54–1.31) and 0.96 (95% CI, 0.61–1.52), respectively.

To evaluate more extreme levels of IGF-I, IGF-II, and IGFBP-3, we repeated the analyses after categorizing these plasma markers into deciles. As compared with participants in the lowest decile, participants in the highest decile of IGF-I, IGFBP-3, IGF-I:IGFBP-3 molar ratio, and IGF-II had adjusted relative risks of pancreatic cancer of 0.98 (95% CI, 0.50–1.93), 1.28 (95% CI, 0.65–2.52), 0.93 (95% CI, 0.46–1.89), and 1.14 (95% CI, 0.58–2.24), respectively. Additionally, we explored the combined effect of IGF-I and IGFBP-3 on pancreatic cancer risk by categorizing the plasma markers into tertiles and constructing a 3 x 3 table. The adjusted relative risk in the highest tertile of IGF-I and the lowest tertile of IGFBP-3 was 1.77 (95% CI, 0.25–12.70) compared with those participants in the lowest tertile of IGF-I and highest tertile of IGFBP-3. Only 3 cases and 14 controls were located in this extreme category of simultaneously high IGF-I and low IGFBP-3.

We found no evidence of an association between IGF-I and risk of pancreatic cancer in subgroups defined by categories of age, gender, BMI, smoking status, level of physical activity (Table 3), or regular multivitamin use. Similarly, no associations were noted in these subgroups for stratified analyses of IGFBP-3, IGF-I:IGFBP-3 molar ratio, and IGF-II (data not shown). Moreover, our results remained unchanged after excluding participants with a history of diabetes mellitus (data not shown).

To assess for a possible influence of the IGF axis after longer periods of follow-up and to rule out an effect of preclinical disease on IGF levels, we sequentially excluded cases and matched controls, requiring longer periods of time between plasma collection and pancreatic cancer diagnosis. No association was noted between IGF-I, IGFBP-3, IGF-I:IGFBP-3 molar ratio, or IGF-II and risk of pancreatic cancer when 2, 4, 6, or 8 years were required between plasma collection and cancer diagnosis. No association was noted between IGF-I and IGFBP-3 molar ratio, or IGF-II and risk of pancreatic cancer when 2, 4, 6, or 8 years were required between plasma collection and cancer diagnosis (Table 4).

### DISCUSSION

In this prospective, nested case–control study, we found no evidence that the risk of pancreatic cancer was influenced by prediagnostic plasma levels of IGF-I, IGF-II, or IGFBP-3. No association was observed when these serum markers were analysed by comparing the top vs the bottom quartiles or when more extreme values were analysed by comparing the top vs the bottom deciles. In addition, no association was noted within selected subgroups or when longer follow-up was required between plasma collection and cancer diagnosis. The molar ratio of IGF-I and IGFBP-3 also was not associated with the development of pancreatic cancer.

Two smaller studies have evaluated the association of IGF-I and IGFBP-3 with pancreatic cancer risk (Lin et al, 2004; Stolzenberg-Solomon et al, 2004). A study of 93 pancreatic cancer cases from the Alpha-Tocopherol, β-Carotene (ATBC) Cancer Prevention Study of Finnish, male smokers found no association between IGF-I, IGFBP-3, or IGF-I:IGFBP-3 molar ratio and the risk of pancreatic cancer (Stolzenberg-Solomon et al, 2004). 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 vs the bottom quartile of IGF-I and IGFBP-3 (RR 2.31, 95% CI 0.70–7.64, and RR 2.53, 95% CI 0.93–6.85, respectively), which was attenuated when both plasma biomarkers were included in multivariate models (Lin et al, 2004). Thus, as in the current study, prior analyses of different patient populations have not supported a significant association between prediagnostic
Table 2  Relative risk (95% CI) of pancreatic cancer according to quartile of IGF-I, IGFBP-3, IGF-I:IGFBP-3 molar ratio, and IGF-II

| Covariate                  | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P-value, trend |
|----------------------------|------------|------------|------------|------------|---------------|
| IGF-I                      | Median (ng·ml⁻¹) | 97.1       | 142.0      | 177.2      | 242.2         |
| RR⁵                        | 1.0        | 0.63 (0.41–0.99) | 0.78 (0.51–1.19) | 0.83 (0.54–1.28) | 0.57          |
| RR⁶                        | 1.0        | 0.67 (0.42–1.06) | 0.84 (0.54–1.30) | 0.94 (0.60–1.48) | 0.97          |
| RR⁷                        | 1.0        | 0.62 (0.38–1.00) | 0.73 (0.44–1.21) | 0.78 (0.44–1.38) | 0.56          |
| IGFBP-3                    | Median (ng·ml⁻¹) | 3345.3     | 4043.6     | 4539.4     | 5290.2        |
| RR⁸                        | 1.0        | 1.03 (0.66–1.62) | 0.98 (0.63–1.54) | 1.13 (0.72–1.77) | 0.66          |
| RR⁹                        | 1.0        | 1.06 (0.67–1.69) | 1.11 (0.70–1.76) | 1.21 (0.75–1.92) | 0.42          |
| RR¹⁰                       | 1.0        | 1.19 (0.73–1.95) | 1.29 (0.76–2.19) | 1.38 (0.76–2.51) | 0.28          |
| IGF-I:IGFBP-3 molar ratio  | Median      | 0.09       | 0.11       | 0.13       | 0.19          |
| RR¹¹                       | 1.0        | 0.60 (0.38–0.93) | 0.74 (0.48–1.12) | 0.77 (0.50–1.19) | 0.49          |
| RR¹²                       | 1.0        | 0.62 (0.39–0.97) | 0.79 (0.51–1.22) | 0.84 (0.54–1.31) | 0.80          |
| IGF-II                     | Median (ng·ml⁻¹) | 802.8      | 986.2      | 1116.7     | 1335.0        |
| RR¹³                       | 1.0        | 0.86 (0.55–1.33) | 1.06 (0.70–1.62) | 0.91 (0.59–1.42) | 0.88          |
| CI = confidence interval; IGF-I = insulin-like growth factor-I; IGFBP-3 = insulin-like growth factor binding protein-3; IGF-II = insulin-like growth factor-II. ⁵Matched for year of birth, smoking status, fasting status, month of blood draw, and prospective cohort. ⁶Matched for year of birth, smoking status, fasting status, month of blood draw and prospective cohort, and adjusted for BMI, regular multivitamin use, level of physical activity, and history of diabetes. ⁷Matched for year of birth, smoking status, fasting status, month of blood draw and prospective cohort, and adjusted for BMI, regular multivitamin use, level of physical activity, history of diabetes, and IGFBP-3. ⁸Matched for year of birth, smoking status, fasting status, month of blood draw and prospective cohort, and adjusted for BMI, regular multivitamin use, level of physical activity, history of diabetes, and IGF-II.

Table 3  Relative risk of pancreatic cancer according to quartile of insulin-like growth factor-I (IGF-I) in subgroups defined by selected variables

| Covariate                  | Cases/controls | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | 95% CI* of Quartile 4 | P-value, trend |
|----------------------------|----------------|------------|------------|------------|------------|-----------------------|---------------|
| Age (years)⁶               | 102/233        | 1.0        | 0.74       | 0.86       | 0.92       | 0.48–1.78             | 0.98          |
| > 62                       | 110/300        | 1.0        | 0.59       | 0.87       | 1.00       | 0.54–1.88             | 0.83          |
| Gender                     |                |            |            |            |            |                       |               |
| Male                       | 89/267         | 1.0        | 0.75       | 0.80       | 1.40       | 0.69–2.84             | 0.29          |
| Female                     | 123/368        | 1.0        | 0.63       | 0.86       | 0.76       | 0.42–1.38             | 0.53          |
| BMI (kg·m⁻²)⁷              |                |            |            |            |            |                       |               |
| < 25                       | 88/306         | 1.0        | 0.88       | 0.87       | 0.75       | 0.37–1.51             | 0.43          |
| > 25                       | 124/329        | 1.0        | 0.59       | 0.81       | 1.17       | 0.65–2.11             | 0.42          |
| Smoking status             |                |            |            |            |            |                       |               |
| Never                      | 81/243         | 1.0        | 0.78       | 0.77       | 1.00       | 0.47–2.13             | 0.97          |
| Past                       | 92/283         | 1.0        | 0.75       | 0.83       | 1.06       | 0.54–2.10             | 0.81          |
| Current                    | 39/107         | 1.0        | 0.38       | 0.85       | 0.69       | 0.22–2.16             | 0.79          |
| Level of activity⁸         |                |            |            |            |            |                       |               |
| Low                        | 128/334        | 1.0        | 0.62       | 0.86       | 0.96       | 0.52–1.76             | 0.89          |
| High                       | 84/301         | 1.0        | 0.71       | 0.63       | 0.86       | 0.44–1.69             | 0.73          |
| Multivitamin use           |                |            |            |            |            |                       |               |
| No                         | 122/408        | 1.0        | 0.84       | 0.88       | 0.88       | 0.49–1.59             | 0.74          |
| Yes                        | 90/227         | 1.0        | 0.53       | 0.86       | 1.08       | 0.53–2.21             | 0.62          |
| IGFBP-3³                   |                |            |            |            |            |                       |               |
| Low                        | 104/316        | 1.0        | 0.44       | 0.82       | 0.91       | 0.36–2.28             | 0.43          |
| High                       | 108/319        | 1.0        | 1.26       | 0.95       | 1.19       | 0.48–2.97             | 0.74          |

CI = confidence interval; BMI = body mass index; IGFBP-3 = insulin-like growth factor binding protein-3. Multivariate relative risks adjusted for year of birth, smoking status, fasting status, prospective cohort, BMI, level of physical activity, regular multivitamin use, and history of diabetes mellitus. In each stratified analysis, the stratification variable was excluded from the model. * Ninety-five percent confidence interval. ⁵Sixty-two years of age is the median age for controls. ⁶High is above the median level, while low is below the median level of physical activity. ⁷High is above the median level, while low is below the median level of IGFBP-3.
Table 4  Relative risk of pancreatic cancer according to time from plasma collection to pancreatic cancer diagnosis by quartiles of IGF-I, IGFBP-3, IGF-I:IGFBP-3 molar ratio, and IGF-II a

| Quartile  | Quartile 2 | Quartile 3 | Quartile 4 | 95% CI* for Quartile 4 | P-value, trend |
|-----------|------------|------------|------------|------------------------|---------------|
| IGF-I (years) |           |            |            |                        |               |
| ≥2        | 1.0        | 0.67       | 0.82       | 0.95                   | 0.61–1.46     | 0.96          |
| ≥4        | 1.0        | 0.68       | 1.03       | 0.73                   | 0.43–1.25     | 0.45          |
| ≥6        | 1.0        | 0.73       | 1.02       | 0.69                   | 0.35–1.37     | 0.42          |
| ≥8        | 1.0        | 0.74       | 1.12       | 0.79                   | 0.35–1.81     | 0.75          |
| IGFBP-3 (years) |          |            |            |                        |               |
| ≥2        | 1.0        | 1.08       | 1.08       | 1.27                   | 0.82–1.98     | 0.29          |
| ≥4        | 1.0        | 0.67       | 0.92       | 1.06                   | 0.64–1.74     | 0.64          |
| ≥6        | 1.0        | 0.53       | 1.05       | 0.88                   | 0.47–1.67     | 0.96          |
| ≥8        | 1.0        | 0.46       | 0.83       | 0.86                   | 0.40–1.86     | 0.94          |
| IGF-I:IGFBP-3 molar ratio (years) |          |            |            |                        |               |
| ≥2        | 1.0        | 0.64       | 0.77       | 0.85                   | 0.55–1.32     | 0.82          |
| ≥4        | 1.0        | 0.73       | 0.83       | 0.73                   | 0.43–1.23     | 0.34          |
| ≥6        | 1.0        | 0.67       | 0.70       | 0.83                   | 0.44–1.58     | 0.78          |
| ≥8        | 1.0        | 0.80       | 0.62       | 1.03                   | 0.47–2.22     | 0.82          |
| IGF-II (years) |          |            |            |                        |               |
| ≥2        | 1.0        | 0.86       | 1.07       | 1.00                   | 0.64–1.57     | 0.81          |
| ≥4        | 1.0        | 0.65       | 0.75       | 0.94                   | 0.57–1.55     | 0.90          |
| ≥6        | 1.0        | 0.62       | 0.74       | 0.85                   | 0.45–1.60     | 0.68          |
| ≥8        | 1.0        | 0.58       | 0.76       | 0.71                   | 0.33–1.55     | 0.46          |

Cl = confidence interval; IGF-I = insulin-like growth factor-I, IGFBP-3 = insulin-like growth factor binding protein-3, IGF-II = insulin-like growth factor-II. Multivariate relative risks are adjusted for year of birth, smoking status, fasting status, prospective cohort, regular multivitamin use, level of physical activity, history of diabetes mellitus, and BMI. Ninety-five percent CI.
mechanisms by which multiple anthropometric factors lead to an increased risk for this highly lethal malignancy.

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