# Serum IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 Molar Ratio and Risk of Pancreatic Cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

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## Abstract

**Background:** Experimental evidence suggests that an overexpression of insulin-like growth factor (IGF)-I is implicated in human pancreatic tumors. Increased IGF-II and decreased IGF binding protein (IGFBP)-3 serum concentrations have been linked to a number of other cancers.

**Methods:** We conducted a nested case-control study in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort of men and women 55 to 74 years of age at baseline to test whether prediagnostic circulating IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio concentrations were associated with exocrine pancreatic cancer risk. Between 1994 and 2006, 187 incident cases of pancreatic adenocarcinoma occurred (follow-up of up to 11.7 years). Two controls ($n$ = 374), who were alive at the time the case was diagnosed, were selected for each case and matched by age, race, sex, and date of blood draw. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) with the use of conditional logistic regression, adjusting for smoking.

**Results:** IGF-I, IGF-II, and IGFBP-3 concentrations were not significantly associated with pancreatic cancer (highest compared with lowest quartile: OR, 1.58; 95% CI, 0.91-2.76; and $P$-trend = 0.25; OR, 0.86; 95% CI, 0.49-1.50; and $P$-trend = 0.31; and OR, 0.88; 95% CI, 0.51-1.51; and $P$-trend = 0.47, respectively). However, a significant positive trend was observed with high IGF-I/IGFBP-3 molar ratio levels (highest compared with lowest quartile: OR, 1.54; 95% CI, 0.89-2.66; $P$-trend = 0.04).

**Conclusion:** A higher IGF-I/IGFBP-3 molar ratio represents increased free IGF-I, which may be a risk factor for pancreatic cancer.

**Impact:** Our results highlight the importance of this biomarker for further investigation in large prospective cohort studies and pooled analysis with other prospective cohorts.

## Introduction

Insulin-like growth factors (IGF) are peptide hormones that constitute a system important in regulating proliferation and apoptosis in many cell types, including epithelial cells *in vitro*. IGFs delay apoptosis through either an intrinsic or extrinsic pathway. Intrinsically, it is through the Ras/Raf/mitogen-activated protein kinase or phosphoinositide 3-kinase pathways. Extrinsically, IGFs antagonize cytokine signaling activation (1-5). The IGF axis includes IGF-I and IGF-II, their receptors, and six binding proteins (4). IGF-I is principally synthesized in the liver and regulated by growth hormone, although it can be produced locally (6). Moreover, IGF-II is primarily synthesized by the liver (7, 8). Approximately 80% of IGF-I binds to IGF binding protein (IGFBP)-3, which forms a complex and limits the bioavailability of IGF-I to bind to the IGF-I receptor (9). IGF-I signaling is important in both cellular mutagenesis and human malignancies, and an overexpression of IGF-I is implicated in human pancreatic tumors (5, 10). Moreover, increased IGF-II and decreased IGFBP-3 concentrations are found in a number of cancers (10-13). Thus far, results from past prospective studies pertaining to the association between IGF-I, IGFBP-3, and IGF-I/IGFBP-3 molar ratio and risk of pancreatic cancer have been inconsistent (8, 14, 15). Moreover, one past study has found no association for IGF-II and pancreatic cancer (8).

Given the conflicting results from recent epidemiologic studies examining the IGF axis and pancreatic cancer, we conducted a nested case-control study in the Prostate,

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Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) to test whether prediagnostic serum IGF-I, IGF-II, and IGFBP-3 concentrations, and IGF-I/IGFBP-3 molar ratio are associated with pancreatic cancer. We hypothesized that a higher IGF-I and IGF-II, and a lower IGFBP-3 concentration will be associated with increased pancreatic cancer risk. We also hypothesized that higher molar ratios of IGF-I/IGFBP-3, an estimator of bioactive IGF-I (16), would be found in pancreatic cancer cases in comparison with the controls.

## Materials and Methods

### Study design and population

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial is a randomized multicenter trial in the United States (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St. Louis, MO; and Washington, DC) that has been previously described in detail (17). Briefly, it aimed to test the effectiveness of early detection procedures for prostate, lung, colorectal, and ovarian cancer on disease-specific mortality. The study recruitment and randomization began in November 1993 and was completed in July 2001. The cohort comprised 152,810 men and women ages 55 to 74 years old at baseline. Exclusion criteria included subjects that had a personal history of prostate, lung, colorectal, or ovarian cancer, or those currently undergoing treatment for any cancer, except for nonmelanoma of the skin, as well as those who had been screened for prostate or colorectal cancer during the past 3 years. Participants were randomized to an intervention arm or the control arm. The intervention arm participants had periodic cancer screening tests, which included prostate-specific antigen and digital rectal exams (men), chest X-ray, flexible sigmoidoscopy, or cancer antigen 125 and transvaginal ultrasound (women). Those in the control arm followed their usual medical care. Informed consent was obtained from all participants. The study was approved by the Institutional Review Boards of all 10 screening centers as well as that of the U.S. National Cancer Institute.

### Case and control selection

The vital status of cohort participants and pancreatic cancer cases were identified by self-report in the annual mail-in survey, state cancer registries, death certificates, physician referrals, and reports from next of kin for deceased individuals. All medical and pathologic records related to pancreatic cancer diagnosis, and supporting documentation were obtained and abstracted by trained medical record specialists for cancer confirmation. Incident primary adenocarcinoma of the exocrine pancreas (International Classification of Disease for Oncology, 3rd edition code C250-C259) was included in the statistical analysis. Endocrine pancreatic tumors (histology types 8150, 8151, 8153, 8155, and 8240) were rare and excluded because the etiology of these cancers is thought to be different from that of exocrine pancreas. There were 187 incident cases of pancreatic adenocarcinomas between 1994 and 2006 (follow-up of up to 11.7 y; median, 5.4 y). One hundred seventy-three pancreatic cancer cases (92.5%) were confirmed through medical review. In sensitivity analyses, the results were similar when the nonconfirmed cases were excluded; therefore, all cases were included to increase statistical power.

Controls, alive at the time the case was diagnosed, were randomly selected from all Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial participants. Two controls were matched to each case by age (±5 y), race, sex, and calendar date of blood draw in 2-month blocks.

### Biomarkers

Nonfasting blood samples were collected in 10-mL red top blood tube at study year $T_0$ from the intervention arm subjects and processed within 2 hours of collection, either on-site or at a central processing laboratory, into fractions stored at –70°C. We sent our samples to Michael Pollak's laboratory at the Lady Davis Institute for Medical Research in Montreal, Canada. At the laboratory, serum concentrations of IGF-I, IGF-II, and IGFBP-3 were assayed by enzyme-linked immunosorbent assay with reagents from Diagnostic Systems Laboratory, a part of Beckman Coulter. Case and control samples were treated identically and were laboratory-blinded to case-control status. Matched serum case and control samples were analyzed consecutively as triplets within batches, and blinded replicate "phantom" samples from two pooled samples were placed in triplicate toward the beginning and end of each batch; these comprised 10% of each batch. With the use of a variance components estimation procedure with logarithmically transformed quality control measurements across all batches (18), the estimated overall (intrabatch and interbatch) percent coefficient of variation of the IGF-I, IGF-II, and IGFBP-3 assays were 10.3%, 5.1%, and 5.1%, respectively.

### Assessment of diet and baseline characteristics

Study subjects completed a self-administered baseline questionnaire that included medical history, family history of cancer, reproductive history, hormone and oral contraceptive use, tobacco use, use of selected drugs, height, weight, physical activity, and exposure to other risk factors at the initial screening exam. We assessed dietary intake with the use of a self-administered food frequency questionnaire, which used a grid format to determine the frequency of 137 food items over the past 12 months, 77 of which inquired about usual portion size (19).

### Statistical analysis

The distribution of selected characteristics of cases and controls were compared with the use of the Wilcoxon rank sum test for the continuous variables and $\chi^2$ tests for categorical variables (Table 1). Potential confounders were also identified by calculating the means and proportions of baseline characteristics among the controls across IGF-I,

**Table 1.** Selected baseline characteristics of case and cohort control subjects (median and interdecile range or number, and proportion)

| Characteristics | Cases ($n$ = 187) | Controls ($n$ = 374) | $P$* |
|---|---|---|---|
| Age (y) | 66 (59.0-72.0) | 66 (58.0-72.0) | 0.82 |
| Sex, male, $n$ (%) | 121 (64.7) | 242 (64.7) | 0.96 |
| Serum IGF-I (ng/mL) | 184.7 (105.4-274.0) | 175.8 (95.2-271.4) | 0.50 |
| Serum IGF-II (ng/mL) | 1,618.8 (1,151.0-2,228.0) | 1,641.9 (1,154.7-2,179.9) | 0.43 |
| Serum IGFBP-3 (ng/mL) | 3,564.3 (2,644.4-4,993.4) | 3,700.0 (2,544.8-4,883.5) | 0.43 |
| Race, $n$ (%) | | | |
| White | 169 (90.4) | 338 (90.4) | 0.99 |
| Black | 6 (3.2) | 12 (3.2) | |
| Hispanic | 3 (1.6) | 6 (1.6) | |
| Asian | 9 (4.8) | 18 (4.8) | |
| Smoking status, $n$ (%) | | | |
| Never | 72 (38.5) | 174 (46.5) | 0.0002 |
| Former | 79 (42.3) | 174 (46.5) | |
| Former quit ≥15 y | 48 (25.7) | 112 (29.9) | |
| Former quit <15 y | 31 (16.6) | 62 (16.6) | |
| Current | 36 (19.3) | 26 (7.0) | |
| Height (cm) | | | |
| Male | 177.8 (167.6-185.4) | 177.8 (170.2-185.4) | 0.74 |
| Female | 162.6 (152.4-170.2) | 162.6 (154.9-170.2) | 0.69 |
| BMI (kg/m$^2$) | 26.7 (22.3-32.7) | 26.5 (22.0-32.9) | 0.18 |
| WHO cut points, $n$ (%) | | | |
| <25.0 | 57 (30.5) | 133 (35.6) | 0.29 |
| >25.0 to <30 | 84 (44.9) | 168 (44.9) | |
| ≥30 | 46 (24.6) | 73 (19.5) | |
| Medical history, $n$ (%) | | | |
| Self-reported diabetes mellitus | 22 (12.2) | 36 (9.9) | 0.41 |
| Family history of pancreatic cancer, $n$ (%) | 7 (3.76) | 8 (2.15) | 0.27 |
| Education, $n$ (%) | | | |
| Less than high school | 14 (7.5) | 39 (10.4) | 0.64 |
| High school graduate | 48 (25.7) | 86 (23.0) | |
| Post–high school, vocational training | 22 (11.8) | 41 (11.0) | |
| Some college | 38 (20.3) | 67 (17.9) | |
| College graduate | 37 (19.8) | 65 (17.4) | |
| Post-college graduate | 28 (15.0) | 76 (20.3) | |
| Dietary intake per day† | | | |
| Red meat (g) | 55.8 (16.3-149.2) | 61.3 (19.4-165.7) | 0.79 |
| Alcohol (g) | | | |
| 0-2 drinks | 163 (90.1) | 326 (91.0) | 0.87 |
| 3-5 drinks | 14 (7.7) | 25 (7.0) | |
| ≥6 drinks | 4 (2.2) | 7 (2.0) | |
| Nutrients | | | |
| Energy (kcal) | 1,819 (1,074-2,957) | 1,976 (1,130-3,298) | 0.16 |
| Total fat (g) | 61.3 (28.1-100.3) | 73.1 (33.1-116.2) | 0.22 |
| Saturated fat (g) | 20.4 (9.8-33.8) | 21.0 (10.8-40.9) | 0.20 |
| Carbohydrate (g) | 247.5 (131.2-389.4) | 265.8 (157.4-423.6) | 0.07 |
| Protein (g) | 72.9 (42.0-126.4) | 77.3 (45.0-128.9) | 0.16 |
| Vigorous physical activity, h/wk,‡ $n$ (%) | | | |
| None or <1 h | 66 (38.2) | 113 (32.1) | |
| 1-3 h | 70 (40.5) | 146 (41.5) | |
| >4 h | 37 (21.4) | 93 (26.4) | 0.18 |

Abbreviation: BMI, Body mass index.

*$P$-values for categorical variables based on $\chi^2$ or Fisher's exact test, and $P$-values for continuous variables based on Wilcoxon rank sum test.

†All foods and nutrients were energy adjusted, except for supplements and alcohol, and based on $n$ = 181 cases and 358 controls.

‡Vigorous activity variables based on $n$ = 173 cases and $n$ = 352 controls.

IGF-II, and IGFBP-3 quartiles (Table 2). The potential confounders that were examined in the analyses included age; smoking status (never, former, current) and history (number of cigarettes smoked per day, years smoked, pack-years, smoking cessation); education; baseline height, weight, and body mass index; history of diabetes; dietary nutrients from foods (energy, carbohydrate, fat, saturated fat, protein); red meat intake; alcohol intake; and physical activity. Body mass index was categorized to be consistent with WHO obesity classifications as <25 (normal), 25 to <30 (overweight), and >30 kg/$m^2$ (obese; ref. 20). Foods highly correlated with energy and dietary nutrients were energy adjusted with the use of the residual method described by Willett and Stampfer (21).

Because the distribution for IGF-I was observed to be different for men and women in our data and that of others (9), we used sex-specific cut points in sex-stratified analyses and in the models combining both sexes (Tables 2 and 3). Conditional logistic regression was used to calculate odds ratios (OR) for pancreatic cancer, with subjects in the lowest quartile as the reference. Linear trends were tested with the use of the *P*-value based on treating the median values within each quartile of the controls as a continuous variable. Continuous ORs were determined by standardizing to the average size of the two central quartiles. We also examined the molar ratio of IGF-I to IGFBP-3, a surrogate estimate of free IGF-I (1 ng/mL IGF-I = 0.130 nmol/L; 1 ng/mL IGFBP-3 = 0.036 nmol/L). We individually added or subtracted covariates to the model to develop multivariate models with the use of forward and backward approaches. Variables were retained in the model if they were associated with both the disease and the IGF-axis biomarker, and changed the ORs by >10%. Although no covariates changed the point estimate of the ORs by >10%, smoking (never, former quit ≥15 y ago, former quit <15 y ago, current), an established risk factor for pancreatic cancer in our study, was included in our final model (22). To evaluate whether preclinical disease influenced the association between the IGF-I/IGFBP-3 molar ratio and pancreatic cancer, we conducted an analysis to compare risk for cases that occurred during the first 5 years and after ≥5 years of follow-up.

All statistical analyses were done with the use of the Statistical Analytic Systems software (SAS Institute Inc.), and the statistical tests were two-tailed.

## Results

Cases and controls had similar baseline characteristics (Table 1), although more cases than controls reported being a current smoker ($P = 0.0002$). There was no significant difference between serum IGF-I, IGF-II, and IGFBP-3 concentrations between cases and controls ($P > 0.4$). Spearman's correlation coefficients showed a significant positive correlation of IGF-I with IGF-II ($r = 0.52$; $P < 0.0001$), IGFBP-3 ($r = 0.63$; $P < 0.0001$), and IGF-I/IGFBP-3 molar ratio ($r = 0.74$; $P < 0.0001$). IGF-II was significantly positively correlated to IGFBP-3 ($r = 0.93$; $P < 0.0001$) but significantly inversely correlated to IGF-I/IGFBP-3 molar ratio ($r = -0.10$; $P = 0.02$).

Table 2 shows the sex-specific means and proportions of selected characteristics among control participants according to the quartile of serum IGF-I concentration. Compared with that of women, the distribution of IGF-I was higher for men; however, the distribution of IGF-II and IGFBP-3 was higher among women. For both men and women, increasing IGF-I concentration was directly related to higher IGF-II and IGFBP-3 concentrations, and higher IGF-I/IGFBP-3 molar ratios. Higher IGF-I concentrations corresponded to less alcohol use ($P < 0.05$) in men, whereas no significant associations were apparent in women (Table 2). In addition, higher IGF-I/IGFBP-3 molar ratios were directly associated with being overweight (body mass index, ≥25 to <30) and less alcohol use (*P*-trend < 0.05) among men, and did not significantly correspond to any characteristic among women. Although not significant in either sex, a higher IGF-I/IGFBP-3 molar ratio tended to be inversely associated with obesity.

Higher IGF-I concentrations tended to be positively but not significantly associated with pancreatic cancer in sex-stratified or combined models (Table 3), whereas higher levels of IGFBP-3 were not associated with pancreatic cancer; however, higher compared with lower IGF-I/IGFBP-3 molar ratio concentrations tended to be positively associated with pancreatic cancer for both men (OR, 1.39; 95% CI, 0.69-2.80) and women (OR, 1.47; 95% CI, 0.58-3.75) in the smoking-adjusted model, with the combined-sex models showing a significant trend across quartiles in both the crude and smoking-adjusted models (*P*-trend = 0.04 and *P*-trend = 0.04, respectively). IGF-II was not associated with pancreatic cancer in any models.

The association between IGF-I/IGFBP-3 molar ratio and pancreatic cancer was similar in time-stratified analysis (i.e., first 5 y: continuous OR, 1.40; 95% CI, 0.49-3.99; $P = 0.10$; and ≥5 y: OR, 1.43; 95% CI, 0.59-3.44; $P = 0.66$). Moreover, the association of IGF-II and IGFBP-3 with pancreatic cancer had no clear difference between short and long follow-up (first 5 y: continuous OR, 1.03; 95% CI, 0.38-2.82; $P = 0.95$; and OR, 0.79; 95% CI, 0.29-2.15; $P = 0.64$, respectively; and ≥5 y: OR, 1.00; 95% CI, 0.39-2.57; $P = 0.99$; and OR, 1.14; 95% CI, 0.44-2.95; $P = 0.78$, respectively). In contrast, the association between IGF-I and pancreatic cancer was stronger among cases with shorter follow-up (first 5 y: continuous OR, 2.28; 95% CI, 0.71-7.30; $P = 0.17$; and ≥5 y: OR, 1.51; 95% CI, 0.65-3.54; $P = 0.34$), although none of these risk estimates reached statistical significance. There was no significant interaction by sex for IGF-I, IGFBP-3, IGF-II, and IGF-I/IGFBP-3 molar ratio ($P = 0.94$, $P = 0.84$, $P = 0.72$, and $P = 0.84$, respectively).

## Discussion

We observed a significant trend across quartiles in the association between IGF-I/IGFBP-3 molar ratio and risk of pancreatic cancer. The highest compared with lowest

**Table 2.** Selected characteristics of control subjects (means or proportions) by quartile of serum IGF-I concentration

| Characteristics | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| Age (y) | 66.8 | 64.6 | 65.3 | 64.8 | 64.7 | 64.3 | 65.2 | 64.7 |
| Serum IGF-I (ng/mL) | 115.8 | 174.1 | 215.8 | 286 | 83.4 | 128.4 | 164.8 | 236.7 |
| Serum IGF-II (ng/mL) | 1,248.6 | 1,627.6 | 1,725.8 | 1,884.8 | 1,409.8 | 1,637.4 | 1,866.9 | 2,180.2 |
| Serum IGFBP-3 (ng/mL) | 2,647.8 | 3,530.8 | 3,890.3 | 4,408.3 | 2,994.7 | 3,657.6 | 4,185.9 | 4,974.5 |
| Serum IGF-I/IGFBP-3 molar ratio | 0.16 | 0.18 | 0.21 | 0.24 | 0.1 | 0.13 | 0.14 | 0.18 |
| Race (%) | | | | | | | | |
| White | 89.2 | 86.7 | 91.4 | 89.8 | 82.9 | 100 | 94.4 | 93.6 |
| Smoking status (%) | | | | | | | | |
| Never | 47.7 | 36.7 | 37.9 | 39 | 54.3 | 60 | 66.7 | 48.4 |
| Former | 46.1 | 56.6 | 48.3 | 57.6 | 40 | 33.3 | 27.8 | 45.1 |
| Former quit ≥15 y | 29.2 | 31.6 | 27.6 | 45.7 | 28.6 | 16.7 | 19.5 | 29 |
| Former quit <15 y | 16.9 | 25 | 20.7 | 11.9 | 11.4 | 16.6 | 8.3 | 16.1 |
| Current | 6.2 | 6.7 | 13.8 | 3.4 | 5.7 | 6.7 | 5.5 | 6.5 |
| Height (cm) | 178.2 | 176.3 | 178.2 | 178.4 | 161.7 | 164.2 | 162.3 | 162.2 |
| BMI (kg/m$^2$) | 26.3 | 27.5 | 26.9 | 27.5 | 27.3 | 26.7 | 27.1 | 26.4 |
| WHO cut points (%) | | | | | | | | |
| <25.0 | 38.5 | 28.3 | 34.5 | 23.7 | 37.2 | 50 | 41.7 | 45.2 |
| ≥25.0 to <30 | 46.1 | 48.3 | 43.1 | 61 | 37.1 | 30 | 41.7 | 35.5 |
| ≥30 | 15.4 | 23.4 | 22.4 | 15.3 | 25.7 | 20 | 16.6 | 19.3 |
| Medical history (%) | | | | | | | | |
| Self-reported diabetes mellitus | 14.8 | 11.9 | 8.6 | 6.9 | 6.1 | 3.3 | 11.1 | 13.3 |
| Education (%) | | | | | | | | |
| Less than high school | 9.2 | 11.7 | 10.3 | 18.6 | 0 | 13.3 | 11.1 | 3.3 |
| High school graduate | 15.4 | 16.7 | 13.8 | 25.4 | 31.4 | 23.4 | 44.4 | 29 |
| Post–high school, vocational training | 7.7 | 10 | 6.9 | 10.2 | 17.1 | 13.3 | 13.9 | 16.1 |
| Some college | 23.1 | 18.3 | 19 | 11.9 | 20 | 20 | 16.7 | 12.9 |
| College graduate | 23.1 | 23.3 | 15.5 | 16.9 | 14.3 | 16.7 | 5.6 | 16.1 |
| Post-college graduate | 21.5 | 20 | 34.5 | 17 | 17.1 | 13.3 | 8.3 | 22.6 |
| Dietary intake per day* | | | | | | | | |
| Red meat (g) | 95.5 | 103.3 | 92.2 | 89.6 | 52.8 | 56.3 | 58.1 | 52 |
| Alcohol (g) | | | | | | | | |
| 0-2 drinks | 80.7 | 76.3 | 89.7 | 94.8 | 97 | 96.6 | 100 | 100 |
| 3-5 drinks | 16.1 | 13.5 | 8.6 | 5.2 | 3 | 3.4 | 0 | 0 |
| ≥6 drinks | 3.2 | 10.2 | 1.7 | 0 | 0 | 0 | 0 | 0 |
| Nutrients | | | | | | | | |
| Energy (kcal) | 2,277 | 2,583 | 2,266 | 2,202 | 1,722 | 1,673 | 1,844 | 1,677 |
| Total fat (g) | 78.2 | 86.2 | 75.7 | 77.6 | 53.1 | 50.9 | 59.5 | 52.6 |
| Saturated fat (g) | 27.2 | 30.1 | 25.6 | 27 | 18 | 16.8 | 19.8 | 17.4 |
| Carbohydrate (g) | 287.9 | 329 | 301.6 | 287.1 | 243.8 | 236.3 | 265.7 | 238.7 |
| Protein (g) | 89 | 96.6 | 88.8 | 89.3 | 71 | 67.8 | 71.8 | 68.1 |
| Vigorous physical activity, h/wk (%) | | | | | | | | |
| None or <1 h | 27.9 | 33.9 | 29.8 | 37.5 | 21.9 | 51.8 | 21.9 | 34.6 |
| 1-3 h | 31.1 | 23.7 | 22.8 | 26.8 | 37.5 | 24.1 | 34.4 | 26.9 |
| >4 h | 41 | 42.4 | 47.4 | 35.7 | 40.6 | 24.1 | 43.7 | 38.5 |

NOTE: Sex-specific quartiles based on IGF-I concentration cut points observed separately for men and women in the study population at baseline.

*All dietary variables were energy adjusted, except for alcohol, and based on 348 controls with complete diet data.

**Table 3.** Age-adjusted and variable-adjusted ORs and 95% CIs of baseline serum IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio concentrations and pancreatic cancer among 187 cases and 374 matched control samples

| | Quartile of serum IGF-I concentration, ng/mL*† | | | | | |
|---|---|---|---|---|---|---|
| | **Q1** | **Q2** | **Q3** | **Q4** | **$P_{trend}$** | **Continuous** |
| Men | <151.4 | >151.4 to <191.9 | >191.9 to <237.8 | >237.8 | | |
| Case/Controls (*n*) | 25/65 | 31/60 | 33/58 | 32/59 | | |
| Crude OR (95% CI)‡ | 1.00 (reference) | 1.41 (0.73-2.74) | 1.59 (0.81-3.12) | 1.51 (0.77-2.97) | 0.24 | 1.09 (0.94-1.26) |
| Smoking-adjusted OR (95% CI)§ | 1.00 (reference) | 1.34 (0.68-2.65) | 1.39 (0.69-2.82) | 1.56 (0.78-3.14) | 0.22 | 1.09 (0.94-1.27) |
| Women | <106.4 | >106.4 to <144.1 | >144.1 to <186.8 | >186.8 | | |
| Case/Controls (*n*) | 14/35 | 20/30 | 14/36 | 18/31 | | |
| Crude OR (95% CI)‡ | 1.00 (reference) | 1.82 (0.74-4.49) | 0.99 (0.41-2.36) | 1.58 (0.64-3.92) | 0.66 | 1.04 (0.84-1.27) |
| Smoking-adjusted OR (95% CI)§ | 1.00 (reference) | 2.12 (0.82-5.45) | 0.95 (0.39-2.34) | 1.74 (0.67-4.51) | 0.68 | 1.03 (0.83-1.27) |
| Combined Characteristics | | | | | | |
| Case/Controls (*n*) | 39/100 | 51/89 | 46/95 | 51/90 | | |
| Crude OR (95% CI)‡ | 1.00 (reference) | 1.53 (0.90-2.60) | 1.29 (0.76-2.19) | 1.53 (0.89-2.62) | 0.23 | |
| Smoking-adjusted OR (95% CI)§ | 1.00 (reference) | 1.57 (0.91-2.71) | 1.19 (0.69-2.06) | 1.58 (0.91-2.76) | 0.25 | |
| | **Quartile of serum IGFBP-3 concentration, ng/mL†** | | | | | |
| | **Q1** | **Q2** | **Q3** | **Q4** | **$P_{trend}$** | **Continuous** |
| Men | <2,977.6 | >2,977.6 to <3,526.6 | >3,526.6 to <4,181.2 | >4,181.2 | | |
| Case/Controls (*n*) | 28/62 | 36/55 | 29/62 | 28/63 | | |
| Crude OR (95% CI)‡ | 1.00 (reference) | 1.44 (0.77-2.69) | 1.04 (0.55-1.96) | 0.98 (0.50-1.95) | 0.70 | 1.01 (0.86-1.18) |
| Smoking-adjusted OR (95% CI)§ | 1.00 (reference) | 1.55 (0.81-2.96) | 0.96 (0.50-1.86) | 1.03 (0.51-2.09) | 0.73 | 1.01 (0.86-1.19) |
| Women | <3,236.8 | >3,236.8 to <3,922.7 | >3,922.7 to <4,481.0 | >4,481.0 | | |
| Case/Controls (*n*) | 17/32 | 16/34 | 17/33 | 16/33 | | |
| Crude OR (95% CI)‡ | 1.00 (reference) | 0.89 (0.38-2.08) | 0.97 (0.41-2.31) | 0.92 (0.41-2.07) | 0.88 | 0.96 (0.79-1.17) |
| Smoking-adjusted OR (95% CI)§ | 1.00 (reference) | 0.78 (0.33-1.87) | 0.92 (0.38-2.28) | 0.77 (0.32-1.83) | 0.63 | 0.94 (0.76-1.15) |
| Combined Characteristics | | | | | | |
| Case/Controls (*n*) | 45/92 | 52/91 | 46/94 | 44/97 | | |
| Crude OR (95% CI)‡ | 1.00 (reference) | 1.17 (0.71-1.93) | 1.00 (0.60-1.68) | 0.92 (0.55-1.56) | 0.62 | |
| Smoking-adjusted OR (95% CI)§ | 1.00 (reference) | 1.16 (0.69-1.95) | 0.95 (0.55-1.61) | 0.88 (0.51-1.51) | 0.47 | |
| | **Quartile of serum IGF-II concentration, ng/mL†** | | | | | |
| | **Q1** | **Q2** | **Q3** | **Q4** | **$P_{trend}$** | **Continuous** |
| Men | <1,339.3 | >1,339.3 to <1,576.6 | >1,576.6 to <1,831.8 | >1,831.8 | | |
| Case/Controls (*n*) | 29/61 | 37/54 | 31/60 | 24/67 | | |
| Crude OR (95% CI)‡ | 1.00 (reference) | 1.40 (0.76-2.60) | 1.07 (0.56-2.06) | 0.70 (0.34-1.42) | 0.20 | 0.99 (0.85-1.15) |
| Smoking-adjusted OR (95% CI)§ | 1.00 (reference) | 1.40 (0.74-2.65) | 1.01 (0.51-1.99) | 0.75 (0.36-1.56) | 0.29 | 0.99 (0.86-1.15) |
| Women | <1,452.5 | >1,452.5 to <1,741.8 | >1,741.8 to <1,999.7 | >1,999.7 | | |
| Case/Controls (*n*) | 14/35 | 21/29 | 15/35 | 16/33 | | |
| Crude OR (95% CI)‡ | 1.00 (reference) | 1.79 (0.77-4.16) | 1.08 (0.44-2.63) | 1.21 (0.51-2.86) | 0.96 | 0.95 (0.78-1.15) |
| Smoking-adjusted OR (95% CI)§ | 1.00 (reference) | 1.75 (0.73-4.17) | 1.05 (0.43-2.60) | 1.12 (0.45-2.77) | 0.91 | 0.93 (0.76-1.14) |

(*Continued on the following page*)

**Table 3.** Age-adjusted and variable-adjusted ORs and 95% CIs of baseline serum IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio concentrations and pancreatic cancer among 187 cases and 374 matched control samples (Cont'd)

| | Quartile of serum IGF-II concentration, ng/mL[†] | | | | | |
|---|---|---|---|---|---|---|
| | **Q1** | **Q2** | **Q3** | **Q4** | $P_{trend}$ | **Continuous** |
| Combined Characteristics | | | | | | |
| Case/Controls (*n*) | 43/95 | 58/83 | 46/96 | 40/100 | | |
| Crude OR (95% CI) | 1.00 (reference) | 1.52 (0.92-2.51) | 1.05 (0.62-1.77) | 0.87 (0.50-1.49) | 0.32 | |
| Smoking-adjusted OR (95% CI)[§] | 1.00 (reference) | 1.49 (0.89-2.49) | 1.01 (0.59-1.72) | 0.86 (0.49-1.50) | 0.31 | |
| | **Quartile of serum IGF-I/IGFBP-3 concentration, ng/mL[†]** | | | | | |
| | **Q1** | **Q2** | **Q3** | **Q4** | $P_{trend}$ | **Continuous** |
| Men | ≤0.17 | >0.17 to ≤0.20 | >0.20 to ≤0.23 | >0.23 | | |
| Case/Controls (*n*) | 27/63 | 23/68 | 38/53 | 33/58 | | |
| Crude OR (95% CI)[‡] | 1.00 (reference) | 0.79 (0.39-1.58) | 1.68 (0.89-3.19) | 1.41 (0.72-2.77) | 0.10 | 1.16 (0.98-1.36) |
| Smoking-adjusted OR (95% CI)[§] | 1.00 (reference) | 0.66 (0.32-1.36) | 1.52 (0.78-2.96) | 1.39 (0.69-2.80) | 0.10 | 1.16 (0.98-1.38) |
| Women | ≤0.12 | >0.12 to ≤0.13 | >0.13 to ≤0.16 | >0.16 | | |
| Case/Controls (*n*) | 16/33 | 13/37 | 18/32 | 19/30 | | |
| Crude OR (95% CI)[‡] | 1.00 (reference) | 0.72 (0.29-1.79) | 1.23 (0.49-3.11) | 1.42 (0.57-3.53) | 0.33 | 1.03 (0.98-1.09) |
| Smoking-adjusted OR (95% CI)[§] | 1.00 (reference) | 0.60 (0.23-1.52) | 1.15 (0.45-2.94) | 1.47 (0.58-3.75) | 0.29 | 1.04 (0.98-1.10) |
| Combined Characteristics | | | | | | |
| Case/Controls (*n*) | 44/106 | 30/82 | 61/97 | 52/89 | | |
| Crude OR (95% CI)[‡] | 1.00 (reference) | 0.89 (0.50-1.59) | 1.56 (0.50-1.59) | 1.51 (0.88-2.57) | 0.04 | |
| Smoking-adjusted OR (95% CI)[§] | 1.00 (reference) | 0.79 (0.43-1.44) | 1.44 (0.86-2.41) | 1.54 (0.89-2.66) | 0.04 | |

*Sex-specific quartiles based on IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio concentration cut points observed separately for men and women in the study population at baseline.
[†]There was no interaction by sex for IGF-I, IGFBP-3, IGF-II, and IGF-I/IGFBP-3 molar ratio ($P$ = 0.94, $P$ = 0.84, $P$ = 0.72, and $P$ = 0.84, respectively).
[‡]Crude OR adjusted for matching variables (age, race, sex, and date of blood draw based on 2-month blocks).
[§]Adjusted for smoking (never, former quit ≥15 y ago, former quit <15 y ago, current).

quartile IGF-I/IGFBP-3 molar ratio concentrations yielded a nonsignificant 54% increase in pancreatic cancer risk. We observed a nonsignificant positive association for IGF-I concentrations but did not observe associations for IGF-II or IGFBP-3 concentrations and pancreatic cancer in this nested case-control study of men and women.

Three previous epidemiologic studies have investigated IGF-axis analytes measured in peripheral blood and risk of pancreatic cancer, with inconsistent study results. Consistent with our study, another smaller nested case-control study ($n$ = 69 cases) within the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (14) showed a nonsignificant 131% increased pancreatic cancer risk with IGF-I. In addition, the said study found an increased pancreatic cancer risk with increasing levels of serum IGFBP-3, which differs from the nonsignificant results from our study. One other small prospective case-control study ($n$ = 93 cases) from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study with follow-up of up to 12.7 years examined the incidence of pancreatic cancer among male smokers (15). All participants in the study were alive and free of cancer after 5 years of follow-up. Although the authors found no association between IGF-I, IGFBP-3, and IGF-I/IGFBP-3 molar ratio and risk of pancreatic cancer, IGF-I and IGFBP-3 showed nonsignificant protective associations, but the confounding effect of smoking could not be taken into account. Finally, a meta-analysis of four combined nested case-control studies from the Nurses' Health Study, the

Health Professionals Follow-up Study, the Physicians' Health Study, and the Women's Health Initiative showed no association between IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio and risk of pancreatic cancer (8). This study had a similar number of cases ($n = 212$); however, in contrast to our study, the authors found a nonsignificant protective association between both IGF-I and IGF-I/IGFBP-3 molar ratio and risk of pancreatic cancer.

The possible mechanism surrounding IGF-I and IGFBP-3 and risk of pancreatic cancer has been reviewed in detail (23). Increases in IGF-I levels enhance IGF-I bioactivity, whereas higher IGFBP-3 levels decrease it. Growth hormone stimulates total IGF-I but also total IGFBP-3, although the IGF-I/IGFBP-3 molar ratio increases. Growth hormone stimulation, in turn, is regulated by insulin, which itself is influenced by other exogenous factors (24-26). For example, obesity as a result of chronic high energy intake is a determinant of insulin resistance and hyperinsulinemia. IGF-I and its receptor are abundant in pancreatic cancer cell lines, and signaling through the IGF-I receptor leads to diminished apoptosis and increased proliferation (13, 27-30).

The strength of this study is that it is prospective, with serum IGF-I, IGF-II, and IGFBP-3 being measured in blood samples of participants collected before cancer diagnosis, which decreases the likelihood of reverse causation. In addition, risks seemed to be similar in the analyses stratified by time. Our study is larger than two of the previous studies and has internal validity because cases and controls are taken from the same cohort. Residual confounding by smoking is not likely because there were few current smokers in our study. In addition, we found a weak association between former smoking and pancreatic cancer in our study (former compared with never smoker: OR, 1.26; 95% CI, 0.52-3.08). Our results may be considered generalizable to men and women, as well as never, former, and current smokers that are similar to the population that participated in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

A weakness of this study is that the follow-up of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort is relatively short (up to 11.7 y; median, 5.4 y). Moreover, IGF concentrations change during a lifetime (31), and a single measurement of serum IGF-I, IGF-II, and IGFBP-3 may not reflect lifetime IGF status (32). As in the previous studies, our study had relatively small sample sizes, limiting the power to observe an association if one exists. There is also the possibility that unknown correlates to serum IGF status may exist and could explain the association between IGFs and risk of pancreatic cancer.

In conclusion, we observed a positive significant trend among those with higher levels of IGF-I/IGFBP-3 molar ratio and risk of pancreatic cancer, and confirmed the nonsignificant associations for IGF-I, IGF-II, and IGFBP-3 and risk of pancreatic cancer from previous studies. Larger prospective studies, as well as pooled analysis with other prospective cohorts, are necessary to foster more conclusive evidence for the IGF-axis analytes and pancreatic cancer development.


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