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Accessibility
Concentrations of IGF-I and IGFBP-3 and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition

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BACKGROUND: Insulin-like growth factors (IGFs) and their binding proteins (BPs) regulate cell differentiation, proliferation and apoptosis, and may have a role in the aetiology of various cancers. Information on their role in pancreatic cancer is limited and was examined here in a case–control study nested within the European Prospective Investigation into Cancer and Nutrition.

METHODS: Serum concentrations of IGF-I and IGFBP-3 were measured using enzyme-linked immunosorbent assays in 422 cases and 422 controls matched on age, sex, study centre, recruitment date, and time since last meal. Conditional logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI) adjusted for confounding variables.

RESULTS: Neither circulating levels of IGF-I (OR = 1.21, 95% CI 0.75–1.93 for top vs bottom quartile, P-trend 0.30), IGFBP-3 (OR = 1.00, 95% CI 0.66–1.51, P-trend 0.79), nor the molar IGF-I/IGFBP-3 ratio, an indicator of free IGF-I level (OR = 1.22, 95% CI 0.75–1.97, P-trend 0.27), were statistically significantly associated with the risk of pancreatic cancer. In a cross-classification, however, a high concentration of IGF-I with concurrently low levels of IGFBP-3 was related to an increased risk of pancreatic cancer (OR = 1.22, 95% CI 0.75–1.97, P-trend 0.27). When adjusted for potential confounding factors, this association was statistically significant (OR = 1.21, 95% CI 0.75–1.93, P-trend 0.30). However, on the basis of the results of a subanalysis, it cannot be excluded that a relatively large amount of IGF-1 together with very low levels of IGFBP-3 might still be associated with an increase in pancreatic cancer risk.

CONCLUSION: On the basis of these results, circulating levels of components of the IGF axis do not appear to be the risk factors for pancreatic cancer. However, on the basis of the results of a subanalysis, it cannot be excluded that a relatively large amount of IGF-1 together with very low levels of IGFBP-3 might still be associated with an increase in pancreatic cancer risk.

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Pancreatic cancer is one of the most common causes of cancer deaths in the western world. In Europe, 48,300 deaths in men and 46,900 deaths in women due to pancreatic cancer were estimated for 2008 (Ferlay et al., 2010). So far, only few risk factors for pancreatic cancer have been clearly identified. Smoking is the major established lifestyle factor known to cause pancreatic cancer, accounting for up to 25 – 30% of all pancreatic cancer cases (Lowenfels and Maisonneuve, 2004). Some nutrition-related factors have also been found to be associated with pancreatic cancer risk, including excess body weight (Berrington de González et al., 2003; Jiao et al., 2010), history of type-2 diabetes mellitus (Huxley et al., 2005), elevated blood levels of glucose (Gapskar et al., 2001; Watts et al., 2007; Jiao et al., 2002; Stattin and Solomom et al., 2006). However, the number of studies conducted with pancreatic cancer (The Endogenous Hormones and Breast Cancer Collaborative Group, 2010). However, the number of studies conducted with pancreatic cancer is limited, as is the number of cases in these studies. The results of the prospective studies are rather inconsistent, however, with most studies showing no association of circulating IGF-I or IGFBP-3 levels with pancreatic cancer risk (Lin et al., 2011). IGFBP-3 has growth-inhibiting properties by competitively binding IGF-I, but it also has independent growth inhibiting effects, for example, via induction of apoptosis (Rahaj et al., 1997). IGFBP activities are, among others, regulated by IGFBP proteases, which may cleave IGFBPs into fragments with lower affinity to IGFs (Nunn et al., 1997).

Ohmura et al. (1990) have shown that IGF-I can stimulate pancreatic cancer cell growth in vitro, and that this effect is mediated by the IGF-I receptor (Bergmann et al., 1995). The analysis of pancreatic cancer tissue revealed increased IGF-I mRNA and IGFI receptor mRNA levels, compared with tissue of healthy individuals (Bergmann et al., 1995). Similarly, increased levels of IGF-I and increased IGF-I receptor expression were observed in pancreatic cancer tissue compared with normal pancreatic tissue (Karna et al., 2002). It appears that IGF-I stimulation and subsequent suppression of tumour suppressor chromosome 10 (PTEN) activity enhance invasiveness and proliferation of the pancreatic cancer cells (Ma et al., 2010).

Circulating levels of IGF-1- and IGF-binding proteins have been found to be associated with several types of cancers, including colon (Rinaldi et al., 2010), prostate (Roddam et al., 2008), and breast cancer (The Endogenous Hormones and Breast Cancer Collaborative Group, 2010). However, the number of studies conducted with respect to pancreatic cancer is limited, as is the number of cases in these studies. The results of the prospective studies are rather inconsistent, however, with most studies showing no association of circulating IGF-I or IGFBP-3 levels with pancreatic cancer risk (Lin et al., 2011). Stattin and Solomom et al. (2006). Because of the inconsistencies of previous studies, we examined the association between IGF-I, IGFBP-3, and pancreatic cancer in the prospective European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, including more than 400 incident cases of pancreatic cancer.

### MATERIAL AND METHODS

**Study description**

European Prospective Investigation into Cancer and Nutrition is a prospective cohort study that includes more than 500,000 male and female participants recruited in 23 centres in 10 European countries between 1992 and 2000. Most centres recruited subjects from the general population, but in Utrecht and Florence, only women from breast cancer screening programs were recruited; the Spanish and Italian centres include blood donors, and the French cohort consists of members of a health insurance for state school employees. A high proportion of participants of the Oxford cohort are vegetarians or health-conscious volunteers. The cohorts of France, Utrecht, Florence, and Norway include women only.

Information on lifestyle and diet was collected during baseline examination. Diet was assessed using country-specific, validated dietary assessment instruments (Kaaks et al., 1997; Riboli and Kaaks, 1997). Information on smoking, alcohol consumption, physical activity, education, occupation, and medical and reproductive history was collected using questionnaires and personal interviews. Anthropometric measurements were conducted during the baseline examination (Haftenberger et al., 2002).

Following a standardized protocol, a blood sample of 30 ml was collected in all participating EPIC countries. In all centres except Oxford, blood samples were stored protected from light at 5 – 10°C until further processing and aliquoting. In the Oxford centre, blood samples were collected throughout the United Kingdom and transported to the laboratory in Norfolk by mail at an ambient temperature. In all centres except Denmark and Sweden, 0.5 – 1.5 ml aliquots of serum, plasma, red blood cells, anduffycoat were filled into plastic straws and stored in liquid nitrogen at −190°C. In the Danish centres, 1 ml aliquots were filled into tubes and stored in the vapour phase of liquid nitrogen containers (−150°C). In Sweden, the samples were stored at −80°C.

**Selection of case and control subjects**

Pancreatic cancer incidence data were coded according to ICD-10, and included all invasive exocrine pancreatic cancers that were coded as C25 (25.0 – 25.3, 25.7 – 25.9). Cases were those EPIC participants who developed pancreatic cancer after their recruitment into the cohort and before the end of the study period. Individuals were excluded when diagnosed with another malignant tumour before the diagnosis of pancreatic cancer, except for non-melanoma skin cancer, and when no blood specimens were available for analysis. A total of 638 incident cases of pancreatic cancer occurred until December 2006. 578 of them were primary exocrine pancreatic tumours. Blood specimens were available for 422 of these cases. The included 422 pancreatic cancer cases were similar in their characteristics to the overall 578 cases with pancreatic adenocarcinoma (data not shown). Of the 422 cases, 307 (76%) were microscopically confirmed. The remaining 24% were diagnosed by clinical symptoms, imaging results, or physical examination. Forty-one percent of the tumours occurred in the head of the pancreas, followed by body (76%) and tail (5%), the rest of the tumours were of unknown localization. One control, alive and free of cancer at time of diagnosis of the index case, was selected for each case using incidence density sampling, that is, controls may include subjects who became a case later in time, and free of cancer at time of diagnosis of the index case, was selected for each case using incidence density sampling, that is, controls may include subjects who became a case later in time, and for each control, one control was matched by study centre, sex, age at enrollment (+6 months), date of entry in the cohort, time between blood sampling and time of last consumption of foods and drinks (<3h, 3–6h, >6h).

**Laboratory assays**

Serum IGF-I and IGFBP-3 concentrations were measured in the immunoassay laboratory at the German Cancer Research Center (DKFZ), Heidelberg, Germany. Both peptides were analysed by enzyme-linked immunosorbent assays purchased from Beckman Coulter (Wyester, TX, USA). Before the total IGF-I analysis, IGF-I was separated from IGF-I–binding proteins by an acid–ethanol extraction step. Cases and matched controls were measured in...
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(0.82)), whereas the ratio showed no correlation with IGFBP-3 (0.59)) and the molar IGF-1/IGFBP-3 ratio (0.26). Circulating C-peptide level (0.12) showed correlations with body mass index (0.14) and length of follow-up (0.06). Age at recruitment (0.10) showed significant correlation with IGF-1 (0.03) and IGFBP-3 (0.03) and the molar IGF-1/IGFBP-3 ratio (0.04). Statistical tests for heterogeneity were based on χ2-tests, calculated as the deviations of logistic beta-coefficients observed in each of the subgroups, relative to the overall beta-coefficient. All analyses were conducted with SAS version 9.2 (Cary, NC, USA).

RESULTS

Of the 422 cases in this analysis, 46% were men (Table 1). Mean age at baseline was 58 years; mean age at diagnosis was 63 years. Female cases had a higher body mass index and waist circumference than female controls, but no difference was observed among men. Cases were more often smokers at baseline than controls, and they more often reported a diagnosis of diabetes at baseline (0.02) or had elevated baseline blood levels of HbA1c. IGF-1 was calculated as the deviations of logistic beta-coefficients observed into sex-specific quartiles, based on the distribution among all controls. Crude models took into account matching criteria; multivariate models were additionally adjusted for body mass index (continuous), smoking history (never, former, quitting smoking less than 10 years ago, more than 10 years ago, current, with 1–9, 10–19, or ≥20 cigarettes per day, missing), and history of diabetes (self-reported or high glycated haemoglobin (HbA1c) concentration (≥6.5%).). These covariates were added in the multivariable adjusted models, because they were associated with pancreatic cancer, correlated with IGF-1 or IGFBP-3, or changed the logistic β-estimate by more than 10%. Further adjustment was made for circulating C-peptide concentration, which has been measured previously on the same subjects (Grote et al, 2011). Further analyses were conducted with mutual adjustments between IGF-1 and IGFBP-3 concentrations.

Sub-analyses were performed, stratified by sex, smoking status at baseline (smoker/non-smoker), diabetes (defined by self-report or HbA1c concentrations (≥6.5%)), waist circumference (<73 cm for men and 80 cm for women), length of follow-up (<16 years or ≥20 years of follow-up time in cases), concentration of C-peptide (<8 mg/l), median, 5.57 ng ml1), and microscopical verification of cases. Odds ratios (OR) were estimated for quartiles of IGF-1 and IGFBP-3 concentrations, as well as IGF-1/IGFBP-3 ratio. Additionally, we examined the interaction between IGF-1 and IGFBP-3 levels (both variables were dichotomized by median concentration) in a cross-classification. Statistical tests for heterogeneity were based on χ2-statistics, calculated as the deviations of logistic beta-coefficients observed in each of the subgroups, relative to the overall beta-coefficient. All analyses were conducted with SAS version 9.2 (Cary, NC, USA).

| Variable                        | Cases (n = 422) | Controls (n = 422) |
|---------------------------------|-----------------|--------------------|
| Male subjects, n (%)           | 195 (46)        | 195 (46)           |
| Age at recruitment (y), mean (range) | 58 (30–76)  | 58 (30–76)          |
| Age at diagnosis (y), mean (range) | 63 (37–82)   | —                  |
| Follow-up (y), mean (range)    | 5.4 (0–13)      | —                  |
| BMI (kg m2), mean ± s.d.       |                 |                    |
| Male                            | 26.8 ± 3.6      | 26.7 ± 3.7         |
| Female                          | 26.5 ± 4.9      | 25.2 ± 4.2         |
| Height (cm), mean ± s.d.       |                 |                    |
| Male                            | 174.6 ± 7.4     | 175.1 ± 7.7        |
| Female                          | 162.3 ± 6.6     | 161.5 ± 7.2        |
| Waist circumference (cm), mean ± s.d. |            |                    |
| Male                            | 96.2 ± 10.1     | 96.6 ± 10.3        |
| Female                          | 84.3 ± 12.3     | 81.1 ± 10.6        |
| Smoking status, n (%)*         |                 |                    |
| Never                           | 155 (37)        | 189 (45)           |
| Former                          | 130 (31)        | 137 (32)           |
| Current                         | 132 (31)        | 91 (22)            |
| Education, n (%)*              |                 |                    |
| Primary school or less          | 165 (40)        | 158 (39)           |
| University                      | 82 (20)         | 86 (21)            |
| Physical activity, n (%)*       |                 |                    |
| Active                          | 62 (16)         | 60 (16)            |
| Inactive                        | 103 (27)        | 119 (31)           |
| Alcohol intake at recruitment (g per day), mean ± s.d. |            |                    |
| Male                            | 19.7 ± 24.4     | 20.4 ± 26.2        |
| Female                          | 9.1 ± 13.1      | 7.4 ± 10.6         |
| Fasting status, n (%)           |                 |                    |
| Fasting (>6 h)                  | 117 (28)        | 113 (27)           |
| In between (3–6 h)              | 158 (37)        | 163 (39)           |
| Non-fasting (<3 h)              | 66 (16)         | 66 (15)            |
| Unknown                         | 81 (19)         | 80 (19)            |
| Self-reported diabetes at recruitment, n (%) | 30 (7)       | 17 (4)             |
| Subjects HbA1c ≥6.5%, n (%)     | 50 (12)         | 28 (7)             |
| C-peptide (ng ml-1), mean ± s.d. | 6.9 ± 4.6  | 6.66 ± 4.5         |
| IGF-1 (ng ml-1), mean ± s.d.    | 181.8 ± 713     | 182.5 ± 685        |
| Male                            | 187.1 ± 74.1    | 185.7 ± 86.3       |
| Female                          | 182.9 ± 68.9    | 179.7 ± 68.7       |
| IGFBP-3 (ng ml-1), mean ± s.d.  | 4668 ± 1209     | 4665 ± 1085        |
| Male                            | 4411 ± 1267     | 4484 ± 1042        |
| Female                          | 4890 ± 1114     | 4821 ± 1100        |
| IGF-1/IGFBP-3 ratio             | 0.19 ± 0.06     | 0.18 ± 0.06        |

Abbreviations: BMI = body mass index; IGF = insulin-like growth factor; IGFBP = IGF-binding protein; IQR = interquartile range; y = years. *Percentages do not add up to 100%, because not all subgroups are shown.

Circulating levels of IGF-1 or IGFBP-3 were not related to the risk of pancreatic cancer (Table 2). Using molar IGF-1/IGFBP-3 ratio as an indicator of free IGF-I concentration, we also observed no association with pancreatic cancer risk. The results were only slightly affected by different types of adjustment. Additional mutual adjustment of IGF-1 and IGFBP-3 also did not strongly change the observed associations with pancreatic cancer. There were no associations of IGF-1, IGFBP-3, or the ratio of these two with pancreatic cancer, when using only microscopically confirmed cases (Table 3).

In sub-analyses, we examined whether the association of IGF-1, IGFBP-3, or IGF-I/IGFBP-3 with pancreatic cancer was modified...
Table 2  Relative risk (OR (95% CI)) of pancreatic cancer by quartiles of IGF-I, IGFBP-3, and its ratio in EPIC.

| Quartiles* | OR P-trendb | Continuous OR P-trendb |
|-----------|-------------|------------------------|
|           | 1           | 2                     | 3                        | 4                     |
| IGF-I men (ng ml⁻¹) | 33–138 | 139–176 | 177–226 | 227–437 | — | Per 10 ng ml⁻¹ | — |
| IGF-I women (ng ml⁻¹) | 40–128 | 129–168 | 169–220 | 221–433 | — | — | — |
| Number of cases/controls | 103/104 | 88/105 | 115/106 | 114/105 | — | — | — |
| Model 1d  | 1.0 | 0.85 (0.55–1.34) | 1.21 (0.77–1.90) | 1.13 (0.67–1.92) | 0.472 | 1.01 (0.98–1.04) | 0.721 |
| Model 2e  | 1.0 | 0.88 (0.58–1.35) | 1.23 (0.78–1.94) | 1.13 (0.67–1.92) | 0.469 | 1.01 (0.98–1.04) | 0.460 |
| Model 3f  | 1.0 | 0.87 (0.57–1.33) | 1.21 (0.78–1.91) | 1.13 (0.67–1.92) | 0.469 | 1.01 (0.98–1.04) | 0.460 |
| Model 4g  | 1.0 | 0.89 (0.56–1.42) | 1.27 (0.75–2.14) | 1.21 (0.66–2.25) | 0.439 | 1.01 (0.97–1.06) | 0.597 |
| Model 5h  | 1.0 | 0.85 (0.56–1.35) | 1.21 (0.75–1.98) | 1.13 (0.67–1.92) | 0.469 | 1.01 (0.98–1.04) | 0.460 |

IGFBP-3 men (ng ml⁻¹)  

| Quartiles* | OR P-trendb | Continuous OR P-trendb |
|-----------|-------------|------------------------|
|           | 1           | 2                     | 3                        | 4                     |
| IGF-I men (ng ml⁻¹) | 33–138 | 139–176 | 177–226 | 227–437 | — | Per 10 ng ml⁻¹ | — |
| IGF-I women (ng ml⁻¹) | 40–128 | 129–168 | 169–220 | 221–433 | — | — | — |
| Number of cases/controls | 103/104 | 88/105 | 115/106 | 114/105 | — | — | — |
| Model 1d  | 1.0 | 0.85 (0.55–1.34) | 1.21 (0.77–1.90) | 1.13 (0.67–1.92) | 0.472 | 1.01 (0.98–1.04) | 0.721 |
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| Model 5h  | 1.0 | 0.85 (0.56–1.35) | 1.21 (0.75–1.98) | 1.13 (0.67–1.92) | 0.469 | 1.01 (0.98–1.04) | 0.460 |

IGFBP-3 women (ng ml⁻¹)  

| Quartiles* | OR P-trendb | Continuous OR P-trendb |
|-----------|-------------|------------------------|
|           | 1           | 2                     | 3                        | 4                     |
| IGF-I men (ng ml⁻¹) | 33–138 | 139–176 | 177–226 | 227–437 | — | Per 10 ng ml⁻¹ | — |
| IGF-I women (ng ml⁻¹) | 40–128 | 129–168 | 169–220 | 221–433 | — | — | — |
| Number of cases/controls | 103/104 | 88/105 | 115/106 | 114/105 | — | — | — |
| Model 1d  | 1.0 | 0.85 (0.55–1.34) | 1.21 (0.77–1.90) | 1.13 (0.67–1.92) | 0.472 | 1.01 (0.98–1.04) | 0.721 |
| Model 2e  | 1.0 | 0.88 (0.58–1.35) | 1.23 (0.78–1.94) | 1.13 (0.67–1.92) | 0.469 | 1.01 (0.98–1.04) | 0.460 |
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| Model 5h  | 1.0 | 0.85 (0.56–1.35) | 1.21 (0.75–1.98) | 1.13 (0.67–1.92) | 0.469 | 1.01 (0.98–1.04) | 0.460 |

Abbreviations: BMI = body mass index; CI = confidence interval; EPIC = European Prospective Investigation into Cancer and Nutrition; IGF = insulin-like growth factor; IGF-I = IGF-binding protein; OR = odds ratio. *Quartile cut points were based on the distribution of controls. **P-trend test was based on median values of each quartile. ***P-trend test was based on continuous values.  

Discussion

We examined the association of components of the IGF axis in association with the risk of pancreatic cancer in the largest prospective study, so far without finding any indication for an association with the circulating levels of IGF-I and IGFBP-3. There was, however, an increased risk among those with high IGF-I and concurrently low IGFBP-3 concentrations, although the interaction was not statistically significant. Evans et al (1997) found no elevated serum levels of IGF-I and IGFBP-3 in pancreatic cancer compared with controls. In contrast, Karna et al (2002) showed significant increases in serum IGF-I and IGFBP-3 levels in patients with pancreatic cancer compared with control subjects. Among prospective studies, a case–control study nested within the ATBC trial did not observe associations of serum concentrations of IGF-1, IGFBP-3, or IGF-1/IGFBP-3 ratio with the risk of pancreatic cancer (Stolzenberg-Solomon et al, 2004); however, this result is based on a cohort of male smokers only. This null association, though, is similar to the results seen in the four US cohorts that were analysed together (Wolpin et al, 2007). Only a nested case–control study conducted in Japan reported that individuals in the highest quartile of IGF-I concentration had an OR of 2.31 (95% CI 0.70–7.64) compared with participants in the lowest quartile (Lin et al, 2004). A recently published study nested in the PLCO cohort observed an increased risk of pancreatic cancer with increasing IGF-I/IGFBP-3 molar ratio, which was interpreted as an indicator of the concentration of free IGF-I (Douglas et al, 2010). We did not observe an increased risk in conference with increasing IGF-I/IGFBP-3 molar ratio, but did observe that those participants with high IGF-I levels above the median and low IGFBP-3 concentrations had an increased risk of pancreatic cancer.

IGFBP-3 is supposed to have growth-inhibiting properties and one would, thus, expect that high IGFBP-3 concentrations are inversely associated with cancer risk. On the other hand, IGFBP-3 and IGF-I are highly correlated in our cohort. In the Japanese nested case–control study, IGFBP-3 concentration was positively associated with pancreatic cancer risk; the risk of death from pancreatic cancer was increased with increasing levels of serum IGFBP-3, with the OR for the highest quartile being 2.53 (95% CI 0.93–6.85; Lin et al, 2004). However, the results of previous studies on different types of cancer have been inconsistent with some studies indeed showing inverse associations, but some also showing no or even a positive association (Renehan et al, 2004).

Cleavage of IGFBPs by proteases results in IGFBP fragments with affinity to IGFs and additionally influences IGF-I bioavailability by reducing the amount of functional IGFBPs. It has been
suggested that the maintenance of normal IGFBP levels is critical to normal rates of cell growth and cell death (Nunn et al, 1997; Firth and Baxter, 2002). It has also been discussed that different assays measuring concentrations of total or intact IGFBP-3 could cause differences between studies (Kaaks et al, 2001; Renehan et al, 2004; Rinaldi et al, 2005). We measured intact IGFBP-3, not total IGFBP-3, which also includes IGFBP-3 fragments that are less biologically active.

Most IGF-1 in the circulation is produced by the liver (Pollak et al, 2004). A major factor stimulating the hepatic production of IGF-1 and IGFBP-3 is growth hormone (Jones and Clemmons, 1995), but insulin also has a central role in regulating levels of

Abbreviations: BMI = body mass index; CI = confidence interval; EPIC = European Prospective Investigation into Cancer and Nutrition; IGF = insulin-like growth factor; IGFBP = IGF-binding protein; OR = odds ratio. *Logistic regression conditioned on matching factors (EPIC recruitment centre, sex, age at recruitment, date at entry in the cohort, time between blood sampling and last consumption of foods and drinks) and adjusted for smoking (never, former, quitting smoking less than 10 years ago, more than 10 years ago, current, with 1–9, 10–19, or ≥ 20 cigarettes per day, missing), BMI (continuous) and diabetes (defined by self-report or HbA1c concentrations ≥ 6.5%). 1P-trend test was based on median values of each quartile.
Spearman’s rank correlations between repeat measurements in serum concentrations over longer time periods. In a study IGFBP-3 generally have been found to be quite representative of baseline. It might be that repeated measurements of IGF-I and IGF-I/IGFBP-3 ratio, but the associations in the respective subgroups were not consistently statistically significant. or IGF-II/IGFBP-3 ratio are associated with the risk of pancreatic cancer, which confirms the results of most previous prospective studies. However, it is noteworthy that individuals with high circulating IGF-I and low IGFBP-3 levels have an increased risk of pancreatic cancer, compared with those with low IGF-I and high IGFBP-3 concentrations.

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Table 4 Joint effect of IGF-1 and IGFBP-3 concentrations on risk of pancreatic cancer (OR (95% CI))

| Median IGF-1 | Median IGFBP-3 | IGF-1 | IGFBP-3 |
|--------------|---------------|-------|---------|
| < Median IGF-1 | > Median IGFBP-3 | 1.0   | 1.48 (0.97–2.22) |
| < Median IGFBP-3 | > Median IGF-1 | 1.47 (0.97–2.22) | 1.72 (1.65–2.83) |

Abbreviations: BMI = body mass index; CI = confidence interval; EPIC = European Prospective Investigation into Cancer and Nutrition; IGF = insulin-like growth factor; IGFBP = IGF-binding protein; OR = odds ratio. Logistic regression conditioned on matching factors (EPIC recruitment centre, sex, age at recruitment, date at entry in the cohort, time between blood sampling and last consumption of foods and drinks) and adjusted for smoking (never, former, quitting smoking less than 10 years ago, more than 10 years ago, current, with 1–9, 10–19, or ≥20 cigarettes per day, missing), BMI (continuous) and diabetes (defined by self-report or HbA1c concentrations ≥6.5%). 1°-interaction = 0.154.

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