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Insulin-like Growth Factor-I Concentration and Risk of Prostate Cancer: Results from the European Prospective Investigation into Cancer and Nutrition

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Abstract

Background—High circulating insulin-like growth factor-I (IGF-I) concentrations have been associated with increased risk for prostate cancer in several prospective epidemiological studies. In this study, we investigate the association between circulating IGF-I concentration and risk of prostate cancer over the long term in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Methods—In a nested case–control design, 1,542 incident prostate cancer cases from eight European countries were individually matched to 1,542 controls by study center, age at recruitment, duration of follow-up, time of day, and duration of fasting at blood collection. Conditional logistic regression models were used to calculate risk for prostate cancer associated with IGF-I concentration, overall and by various subgroups.

Results—Circulating IGF-I concentration was associated with a significant increased risk for prostate cancer [OR for highest vs. lowest quartile, 1.69; 95% confidence interval (CI), 1.35–2.13; P_{trend} = 0.0002]. This positive association did not differ according to duration of follow-up [ORs for highest vs. lowest quartile were 2.01 (1.35–2.99), 1.37 (0.94–2.00), and 1.80 (1.17–2.77) for cancers diagnosed <4, 4—7, and >7 years after blood collection, respectively ($P_{heterogeneity}$ = 0.77)] or by stage, grade, and age at diagnosis or age at blood collection (all subgroups $P_{heterogeneity}$ >0.05).

Conclusion—In this European population, high circulating IGF-I concentration is positively associated with risk for prostate cancer over the short and long term.

Impact—As IGF-I is the only potentially modifiable risk factor so far identified, research into the effects of reducing circulating IGF-I levels on subsequent prostate cancer risk is warranted.

Introduction

Insulin-like growth factor (IGF-I), a polypeptide with mitotic and antiapoptotic effects (1), is associated with an increased risk for prostate cancer, as shown in a pooled reanalysis of worldwide prospective data based on 3,700 men with prostate cancer and 5,200 controls (2). However, most of the cases in this collaborative reanalysis were diagnosed within 6 years of blood collection, limiting the ability to investigate heterogeneity in risk by length of follow-up and leaving open the possibility of reverse causality (whereby, before diagnosis, a developing prostate cancer causes alterations in circulating IGF-I concentration).

In the European Prospective Investigation into Cancer and Nutrition (EPIC), we previously reported a marginally significant increased prostate cancer risk for men in the highest versus lowest third of IGF-I concentration [OR 1.35; 95% confidence interval (CI) 0.99–1.82; P_{trend} = 0.08]. These results were on the basis of 630 cases (and 630 controls), with a median time from blood collection to diagnosis of 3.4 years (range, 0.1–8.5 years; ref. 3). We report here

results from an extension of this work, including a total of 1,542 prostate cancer cases (matched to 1,542 control men) diagnosed a median of 5.8 years after blood collection, with approximately 35% of cases diagnosed more than 7 years after blood collection.

Materials and Methods

Study population

The methods of recruitment used in the EPIC study have been described previously (4). In brief, between 1992 and 2000, approximately 360,500 women and 153,400 men were recruited from 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). All participants completed either a standardized food-frequency questionnaire or an interview-based dietary questionnaire, and a detailed lifestyle questionnaire. Approximately 385,700 participants (of which 139,600 were men) provided a blood sample. All participants provided written informed consent and local ethics committees in the participating countries and the Internal Review Board of the International Agency for Cancer Research (IARC) approved the study.

The standardized blood collection protocol involved transportation of whole blood in the collection syringe to a local laboratory where samples were processed and separated into serum, plasma, red cells, and buffy coat fractions within 24 hours of collection, before placement in 0.5-mL straws for storage at −196°C in liquid nitrogen tanks. Variation to the standardized procedure occurred in the following centers: in the Oxford cohort (UK), samples were sent in the post at ambient temperature to a laboratory in Norfolk (UK), with an average transit time of 1.5 days; in the Copenhagen cohort (Denmark), samples were stored in 1 mL tubes in nitrogen vapor at −150°C, and in the Umeå cohort (Sweden), EDTA plasma (rather than serum) samples were archived and stored at −80°C in electric freezers.

Follow-up for cancer incidence and vital status

Follow-up and case identification was provided through record linkage with population-based cancer registries in Denmark, Italy, the Netherlands, Spain, Sweden, and the United Kingdom. In Germany and Greece, active follow-up was achieved through contact with study participants and their next of kin and verified through health insurance or medical records and cancer and pathology registries or reports. The subcohorts of France and Norway were not included as these countries only recruited women. Prostate cancer cases were defined as code C61 of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). For each EPIC center, closure dates of the study period were defined as the latest date of complete follow-up for both cancer incidence and vital status: December 2003 for Denmark and the Netherlands, December 2004 for Italy and the United Kingdom, December 2005 for Spain and Sweden, and December 2006 for Germany and Greece.

Selection of case and control participants from the study cohort

Cases were defined as men who developed prostate cancer after the date of blood collection and before the end of the study period, as determined by the latest date of follow-up in each study center. Among participants who had completed a lifestyle and dietary questionnaire,

provided a blood sample at recruitment, and had no previous cancer diagnosis, 1,874 were diagnosed with incident prostate cancer during the follow-up period. An incidence density sampling protocol was used to select control participants at random from the cohort of men who were alive and free of cancer (except nonmelanoma skin cancer) at the time of diagnosis of the index case and who were matched on study center, length of follow-up, age at blood collection (+/− 6 months), time of blood collection (+/− 1 hour) and duration of fasting at blood collection (< 3, 3–6, >6 hours). Blood samples were available for 1,711 of the 1,874 identified cases, and after exclusion of incomplete case–control sets, 1,542 prostate cancer cases, and 1,542 matched controls were available for analysis. This number includes 630 prostate cancer cases from an earlier study (phase I) and an additional 912 cases with a later diagnosis (phase II).

Tumor stage information [tumor-node-metastasis (TNM) staging code], derived from pathology reports and cancer registry data, was used to define the following categories: localized (T0 or T1 or T2 and N0 or NX and M0, or stage coded in the recruitment center as localized; $N = 745$), advanced (T3 or T4 and/or N1+ and/or M1, or stage coded in the recruitment center as metastatic; $N = 309$), and unknown stage ($N = 488$). Information on Gleason score or the World Health Organization (WHO) grading system was used to generate categories of low grade (Gleason score ≤7, or cases coded as well differentiated or moderately differentiated; $N = 848$), high grade (Gleason score >7, or cases coded as poorly differentiated or undifferentiated; $N = 159$), and unknown grade ($N = 535$).

Laboratory analysis

Serum samples from phase I of the study were assayed in singleton at IARC, Lyon (France) using the DSL-10-5600 ACTIVE ELISA from Diagnostic Systems Laboratories (DSL) as previously reported (3). Serum samples from phase II were assayed in duplicate at the Cancer Epidemiology Unit (CEU) laboratory in Oxford (UK) using the DSL-10-5600 ACTIVE ELISA from DSL, with the exception of plasma samples from Sweden, which were analyzed in singleton by using the automated IDS-iSYS immunoassay system from Immunodiagnostic Systems (IDS) Ltd. Both assays included a step to dissociate IGF-I from IGF-I–binding proteins before measurement. A comparison of 20 samples measured using both the DSL-10-5600 ACTIVE ELISA and the IDS-iSYS showed relative agreement ($r = 0.99$), although IGF-I concentrations were on average 23% lower in the IDS-iSYS assay than the DSL-10-5600 ACTIVE ELISA. The lower limit of detection was <1 nmol/L for the DSL-10-5600 ACTIVE ELISA and 1.3 nmol/L for the IDS-iSYS immunoassay, adequate to detect the lowest concentration in all study samples.

Laboratory personnel were blind to the case–control status of the samples and each case–control set was analyzed in the same batch, together with duplicate quality control samples. For the DSL-10-5600 ACTIVE ELISA assay, the mean intra- and interbatch coefficients of variation were 3% and 13% for phase I samples and 4.4% and 12.4% for phase II samples, respectively; for the IDS-iSYS immunoassay the mean intra- and interbatch coefficients of variation were 2.3% and 3.2% for phase II samples (from Sweden only).

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Statistical analysis

Differences in baseline characteristics of case and control participants in matched sets were compared using paired-sample *t* tests for continuous variables and conditional logistic regression for categorical variables. Logarithmic transformation of IGF-I values was conducted to approximate a normal distribution and box and whisker plots and letter-value displays were used to examine the distribution and to identify possible outliers. Exclusion of observations identified as severe outliers on the logarithmic scale (>3 times the inter-quartile range; $N = 4$) made no material difference to the risk estimates and therefore all observations were included in the final models.

Analysis of variance was used to examine heterogeneity in the geometric mean IGF-I concentration amongst controls by the following variables: phase of study (phase I, phase II), country (8), age at blood collection (≤54, 55–59, 60–64, ≥65 years), height (quintiles), weight (quintiles), body mass index (BMI; <24.4, 24.4–26.3, 26.4–28.6, ≥28.7 kg/m^2), smoking (never, past, current, unknown), alcohol consumption (<8, 8–15, 16–39, ≥40 g/d, unknown), physical activity (inactive, moderately inactive, active, unknown), marital status (married/cohabitating, not married/cohabitating, unknown), and educational attainment (primary or equivalent, secondary, degree level, unknown). Where appropriate, adjustment was made for center, age at blood collection, alcohol consumption, educational attainment, BMI, and assay batch.

Conditional logistic regression models were used to calculate the ORs for prostate cancer risk by fourths of IGF-I concentration and for a doubling (log2 scale) in IGF-I concentration. Quartile cutoff points were defined by the distribution of values among the controls for all cohorts combined with the exception of Sweden, where country-specific cutoff points were used to account for the differences in absolute concentrations attributable to the IDS-iSYS immunoassay. Likelihood ratio χ^2 tests for linear trend were obtained by replacing the quartiles with the logarithm of IGF-I as a continuous variable in the model.

The effects of potential confounding variables (other than those accounted for in the matched design) were examined by including additional regression terms in the conditional logistic regression model. Adjustment for height, weight, smoking, alcohol consumption, physical activity, marital status, and educational attainment made little difference to the risk estimates or their 95% confidence intervals (<10% change). However, all final models included adjustment for age at blood collection to ensure close comparability within matched sets. Separate sensitivity analyses were conducted that excluded the Umeå (Sweden) cohort (because of the different assay used for these samples), and that excluded the first 4 years of follow-up.

Likelihood ratio χ^2 tests (on the basis of the difference between the χ^2 values from models with and without an interaction term between the linear trend variable and the factor of interest, e.g., stage of disease) were used to examine heterogeneity of linear-trend relative risk estimates for prostate cancer associated with the logarithm of IGF-I concentration by prostate cancer stage (localized, advanced), grade (low, high), time between blood collection and diagnosis (<4, 4–7, >7 years), age at diagnosis (<65, ≥65 years), age at blood collection (<60, ≥60 years), laboratory assay (DSL-10-5600 ACTIVE ELISA, IDS-iSYS), country

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(including countries grouped according to a North/South latitude (i.e., Northern countries defined as Denmark, Germany, the Netherlands, Sweden, and the UK, and Southern countries defined as Greece, Italy, and Spain)], and BMI (<25, ≥25 kg/m^2).

Owing to the use of incidence density sampling for the selection of controls, the ORs presented approximate the incidence rate ratios for IGF-I in relation to prostate cancer in the study cohort (5). All statistical analyses were conducted using Stata Statistical Software: Release 12 (StataCorp LP) and 2-tailed tests of statistical significance with *P* values below 0.05 were considered significant.

Results

IGF-I measurements were available for 1,542 matched case–control sets: 630 from phase I and 912 from phase II. Of these, 152 were from Denmark, 383 from Germany, 40 from Greece, 145 from Italy, 50 from the Netherlands, 200 from Spain, 192 from Sweden, and 380 from the United Kingdom. The mean age at diagnosis was 65.3 years (SD, 6.5) and the median time between blood collection and diagnosis was 5.8 years (range, 1 month–12.8 years). As shown in Table 1, there were no significant differences between cases and controls according to height, BMI, smoking status, alcohol consumption, physical activity, marital status, and educational attainment. However, cases were on average slightly older at blood collection (60.12 vs. 60.10 years; $P = 0.03$) and lighter (79.8 vs. 80.6 kg; $P = 0.04$) than controls. The geometric mean IGF-I concentration was 3.8% higher in cases than in controls (20.5 vs. 19.8 nmol/L; $P = 0.001$). Amongst the cases with information on stage and grade of disease, there was no evidence of heterogeneity by phase of study in the proportion of cases diagnosed with localized or advanced stage disease or in the proportion of cases classified as low- or high-grade disease (Table 1).

The geometric mean IGF-I concentrations according to baseline characteristics amongst the controls, with adjustment for center, age at blood collection, alcohol intake, educational attainment, BMI and batch, are shown in Table 2. IGF-I concentration was lower in older men (P_{trend} <0.0001) and higher in taller (P_{trend} = 0.01) and more educated men (P_{trend} = 0.01). There was significant heterogeneity in IGF-I concentration by assay for the IDS-iSYS assay used for Umeå (Sweden) and DSL-10-5600 ACTIVE ELISA assay used for all other centers ($P_{heterogeneity}$ <0.0001), and by country (among those assayed using the DSL-10-5600 ACTIVE ELISA), being lowest in Greece (19.5 nmol/L), and highest in the Netherlands (22.8 nmol/L; $P_{heterogeneity}$ = 0.002). There was also evidence of heterogeneity in IGF-I concentration by alcohol consumption ($P_{heterogeneity}$ = 0.01), weight ($P_{heterogeneity}$ = 0.01), and BMI ($P_{heterogeneity}$ = 0.003), although there was no evidence of a trend for these variables (P_{trend} = 0.08, P_{trend} = 0.40, and P_{trend} = 0.34, respectively). IGF-I concentration did not vary according to smoking status or physical activity.

Table 3 shows that IGF-I concentration was significantly associated with an increased risk of prostate cancer overall. In comparison to the lowest fourth, the risk of prostate cancer in the highest fourth of IGF-I concentration was 1.69 (95% CI: 1.35, 2.13; P_{trend} = 0.0002) after adjusting for age at blood collection. Further adjustment for height, weight, smoking, alcohol intake, marital status, physical activity, and educational attainment made little

difference to the risk estimate (OR 1.72; 95% CI: 1.36, 2.17; P_{trend} = 0.0001; results not shown in table). The OR associated with a doubling of IGF-I concentration was 1.38 (95% CI: 1.17, 1.64; P_{trend} = 0.0002).

The associations between IGF-I concentration and risk for prostate cancer subdivided by case participant characteristics are also shown in Table 3. Higher IGF-I was associated with increased risk for prostate cancer in all subgroups, with the exception of high-grade disease. Nonetheless, there was no significant heterogeneity between low- and high-grade diseases in the estimates of linear trends in relative risks. Furthermore, the positive association of higher circulating IGF-I with prostate cancer risk did not differ according to duration of follow-up [ORs for highest vs. lowest quartile for cancer diagnosis <4, 4—7, and >7 years after blood collection were 2.01 (1.35–2.99), 1.37 (0.94–2.00), and 1.80 (1.17–2.77), respectively ($P_{heterogeneity}$ = 0.77)] or by any other subgroup examined, including stage of disease, age at diagnosis, age at blood collection, assay type, country (including countries grouped according to a North/South latitude), or BMI ($P_{heterogeneity} \geq 0.05$).

There was no evidence of heterogeneity in the trend for the association of IGF-I and risk for prostate cancer between the Umeå cohort (Sweden) and the other centers ($P_{heterogeneity}$ = 0.46) and exclusion of case–control sets from Umeå changed the risk estimate by less than 10%.

Discussion

Our finding that a relatively high concentration of IGF-I is associated with an increased risk for prostate cancer is consistent with results from a pooled reanalysis of individual participant data from 12 prospective studies (which includes phase I of this study; ref. 2). This association is evident for both localized and advanced disease and exists over the short and long term. While it is likely that some men with subclinical disease at recruitment were included in our study [because of the long lag time between disease onset and clinical symptoms (6)], the positive association observed among men diagnosed with advanced stage disease (for whom nearly 65% were diagnosed more than 4 years after recruitment) and among men diagnosed more than 7 years after blood collection, supports the hypothesis that IGF-I is associated with prostate cancer many years before diagnosis.

IGF-I concentration was also associated with an increased risk of localized prostate cancer. This finding contrasts with those from ProtecT, a large case–control study of approximately 3,000 cases and 3,000 controls in the United Kingdom, which found no association between total IGF-I concentration and the risk for PSA (prostate specific antigen)-detected prostate cancer (7). As there is no formal screening program for prostate cancer in the countries included in the EPIC study, our cases comprise a mixture of PSA-detected and clinically detected disease, and it is possible that the differences between our results and those from ProtecT [and other studies of PSA-detected prostate cancer (7)] reflect biological differences in the association of IGF-I with PSA-detected and clinically relevant disease.

Our finding that the association between higher IGF-I concentration and prostate cancer risk did not differ significantly by cancer stage is consistent with results from the pooled

reanalysis (2) and supports a role for IGF-I in the development of prostate cancer, conceivably via established mitogenic and antiapoptotic mechanisms (1). There was no significant difference in the association of IGF-I with prostate cancer by grade of disease, although the risk appeared to be restricted to low-grade disease, with no association for high-grade disease, which is also consistent with the pooled reanalysis (2) and more recent findings from a large prospective study (8). However, these results should be interpreted with caution because of small numbers of cases in the high-grade subgroup and the potential for misclassification error because of changes in grading practices over time (9–11) that may obscure the distinction between low- and high-grade diseases.

Strengths of this study are the prospective nature of the design, the moderately long length of follow-up and large sample size that meant that the subgroup investigations were, in most instances, adequately powered to detect modest risk estimates. The association between IGF-I and risk for prostate cancer remained significant after excluding the first 4 years of follow-up (thereby reducing the possibility of reverse causality) and the subcohort with deviations from the standardized assay method. There was minimal laboratory measurement error and the distribution of our IGF-I values amongst controls is comparable with that from other studies in healthy male adults (7, 12). Previous studies have shown relatively high within-individual reproducibility for IGF-I measured in 2 samples collected up to 5 years apart [Spearman rank correlations of 0.7 (13), 0.66 (14), and 0.87 (15)]; however, measurement error and attenuation of risk estimates associated with a single sample would suggest that the true association per increment increase in IGF-I concentration with prostate cancer risk may be substantially stronger than that observed in our study.

Comparisons of these findings on the basis of men of white European origin with those in other ethnic groups are difficult to interpret as studies in Asian and African–American populations have been too small to detect modest risk estimates (16, 17). We did not measure IGF-I–binding proteins (IGFBP) in our extended study and although they are known to influence the bioavailability of IGF-I (18), there is evidence to suggest that the association between IGF-I concentration and risk for prostate cancer is not materially affected by adjustment for IGFBP-3, the major IGF-I–binding protein in the circulation (2). The extent to which circulating IGF-I concentrations [influenced by anthropometric, diet, and lifestyle factors (19–22)] reflect activity at the tissue level is difficult to determine, as the bioavailability of IGF-I is modulated by interactions between growth hormone, insulin, IGFBPs, and IGF-I receptors (18, 23). In future, investigation of the association between circulating IGF-I concentrations and expression of biomarkers at the tissue level may determine further the nature of the association of IGF-I with prostate cancer risk. Moreover, information from studies in a younger population is needed to determine the impact of long-term exposure to IGF-I levels and to elucidate the most important time period of IGF-I exposure in relation to prostate cancer development.

In conclusion, our results suggest that circulating concentrations of IGF-I in middle to late adulthood are strongly associated with subsequent prostate cancer risk over the relatively long term.

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Footnotes

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Table 1

Characteristics of 1,542 prostate cancer cases and 1,542 control subjects in EPIC overall and subdivided into study phase

	Overall			Phase I			Phase II		
	Cases *N* = 1,542	Controls *N* = 1,542	*P* [b]	Cases *N* = 630	Controls *N* = 630	*P* [b]	Cases *N* = 912	Controls *N* = 912	*P* [b]
Age at blood collection, mean (SD), y	60.12 (6.5)	60.10 (6.5)	0.03	61.5 (6.2)	61.4 (6.2)	0.07	59.2 (6.5)	59.2 (6.5)	0.23
Anthropometry: mean (SD)									
Height, cm	173.0 (6.9)	173.2 (6.9)	0.29	172.2 (6.7)	172.5 (7.0)	0.43	173.5 (7.0)	173.9 (6.9)	0.46
Weight (kg)	79.8 (11.4)	80.6 (12.1)	0.04	79.3 (11.2)	80.6 (12.2)	0.05	80.1 (11.5)	80.7 (12.1)	0.30
BMI (kg/m^2)	26.7 (3.5)	26.9 (3.6)	0.10	26.8 (3.5)	27.1 (3.7)	0.09	26.6 (3.4)	26.7 (3.6)	0.45
Smoking, *N*(%)[a]									
Never	518 (34.2)	489 (32.2)		197 (31.5)	168 (27.0)		321 (36.3)	321 (35.8)	
Former	662 (43.7)	640 (42.2)		282 (45.1)	281 (45.2)		380 (42.8)	359 (40.1)	
Current	334 (22.1)	389 (25.6)	0.06	147 (23.5)	173 (27.8)	0.12	187 (21.1)	216 (24.1)	0.27
Alcohol consumption, g/d (%)[a]									
<8	621 (40.3)	623 (40.5)		223 (35.5)	223 (35.5)		398 (43.6)	400 (43.9)	
8–15	301 (19.6)	311 (20.2)		121 (19.3)	134 (21.3)		180 (19.7)	177 (19.4)	
16–39	354 (23.0)	370 (24.0)		169 (26.9)	155 (24.7)		185 (20.3)	215 (23.6)	
≥40	264 (17.1)	236 (15.3)	0.57	115 (18.3)	116 (18.5)	0.72	149 (16.3)	120 (13.2)	0.13
Physical activity, *N*(%)[a]									
Inactive	245 (18.4)	221 (16.6)		124 (20.0)	107 (17.3)		121 (17.1)	114 (16.1)	
Moderately inactive	425 (32.0)	415 (31.2)		218 (35.1)	199 (32.1)		207 (29.2)	216 (30.5)	
Active	660 (49.6)	693 (52.1)	0.25	279 (44.9)	314 (50.7)	0.06	381 (53.7)	379 (53.5)	0.86
Marital status, *N*(%)[a]									
Married or cohabitating	1,023 (88.0)	1,030 (88.7)		391 (87.5)	396 (89.2)		632 (88.4)	634 (88.4)	
Not married or cohabitating	139 (12.0)	131 (11.3)	0.60	56 (12.5)	48 (10.8)	0.39	83 (11.6)	83 (11.6)	1.00
Educational level, *N*(%)[a]									
Primary or equivalent	561 (38.1)	579 (39.3)		232 (38.7)	231 (39.0)		329 (37.7)	348 (39.5)	
Secondary	552 (37.5)	556 (37.7)		215 (35.8)	224 (37.8)		337 (38.6)	332 (37.6)	
Degree	360 (24.4)	339 (23.0)	0.55	153 (25.5)	137 (23.1)	0.54	207 (23.7)	202 (22.9)	0.49
IGF-I concentration, nmol/L geometric mean (95% CI)[c]	20.5 (20.2, 20.9)	19.8 (19.5, 20.1)	0.001	21.9 (21.2, 22.5)	21.3 (20.7, 21.9)	0.23	19.7 (19.4, 12.0)	18.8 (18.5, 19.1)	<0.0001
Country, *N*(%)									
Denmark	152 (9.9)	152 (9.9)		79 (12.5)	79 (12.5)		73 (8.0)	73 (8.0)	
Germany	383 (24.8)	383 (24.8)		186 (29.5)	186 (29.5)		197 (21.6)	197 (21.6)	
Greece	40 (2.6)	40 (2.6)		9 (1.4)	9 (1.4)		31 (3.4)	31 (3.4)	
Italy	145 (9.4)	145 (9.4)		60 (9.5)	60 (9.5)		85 (9.3)	85 (9.3)	
Netherlands	50 (3.2)	50 (3.2)		25 (4.0)	25 (4.0)		25 (2.7)	25 (2.7)	
Spain	200 (13.0)	200 (13.0)		93 (14.8)	93 (14.8)		107 (11.7)	107 (11.7)	
Sweden	192 (12.5)	192 (12.5)		—	—		192 (21.1)	192 (21.1)	
United Kingdom	380 (24.6)	380 (24.6)		178 (28.3)	178 (28.3)		202 (22.2)	202 (22.2)	
Cases only, N(%)									
Time to diagnosis, y									

	Overall			Phase I			Phase II		
	Cases *N* = 1,542	Controls *N* = 1,542	*P* [b]	Cases *N* = 630	Controls *N* = 630	*P* [b]	Cases *N* = 912	Controls *N* = 912	*P* [b]
<4	457 (29.6)			374 (59.4)			83 (9.1)		
4–7	560 (36.3)			228 (36.2)			332 (36.4)		
>7	525 (34.1)			28 (4.4)			497 (54.5)		
Age at diagnosis, mean (SD), y	65.3 (6.5)			64.4 (6.2)			65.9 (6.6)		
Stage, *N*(%) [a,d]									
Localized	745 (71.7)			303 (68.7)			442 (72.1)		
Advanced	309 (29.3)			138 (31.3)			171 (27.9)		
Grade, *N*(%) [a,e]									
Low	848 (84.2)			385 (84.6)			463 (83.9)		
High	159 (15.8)			70 (15.4)			89 (16.1)		

[a] Unknown for some participants; percentages exclude unknown values.

[b] *P* values relate to likelihood ratio χ^2 tests of association for categorical variables, and paired differences tests for continuous variables.

[c] Adjusted for age (<50, 50–54, 55–59, 60–64, 65–69, ≥70 years), center (1–18), batch (1–78), alcohol intake (<8, 8–15, 16–39, ≥40g/d, unknown), educational attainment (primary school, secondary school, higher education/degree, unknown), and body mass index (quartile cutoff points: <24.4, 24.4, 26.4, 28.7 kg/m^2); with 95% CI in parenthesis.

[d] Localized stage includes T0 or T1 or T2 and N0 or NX and M0, or stage coded in the recruitment center as localized and advanced stage includes T3 or T4 and/or N1+ and/or M1, or stage coded in the recruitment center as metastatic.

[e] Low grade includes Gleason score ≤7, or cases coded as well differentiated or moderately differentiated according to the WHO grading system and high grade includes Gleason score >7, or cases coded as poorly differentiated or undifferentiated according to the WHO grading system.

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Table 2

Adjusted geometric mean IGF-I concentrations and 95% CI among 1,542 control participants

	N	Adjusted geometric mean IGF-I (nmol/L)[a] (95% CI)	$P_{heterogeneity}$ [c]	P_{trend} [d]
Characteristics				
Phase I	630	20.1 (18.3–22.0)		
Phase II	912	19.6 (18.4–20.8)	0.74	
Assay type				
DSL-10-5600 ACTIVE ELISA	1,350	20.9 (20.3–21.5)		
IDS-iSYS immunoassay	192	13.3 (11.1–15.9)	<0.0001	
Age at blood collection, y				
≤54	308	21.6 (20.8–22.4)		
55–59	446	20.5 (19.8–21.1)		
60–64	520	19.3 (18.7–19.8)		
≥65	268	17.7 (16.8–18.7)	<0.0001	<0.0001
Height, cm				
<167.1	309	19.2 (18.5–20.0)		
167.1	310	19.3 (18.6–20.0)		
171.5	332	19.9 (19.2–20.6)		
175.0	311	19.9 (19.1–20.6)		
≥179.0	280	20.7 (19.9–21.5)	0.07	0.01
Weight, kg				
<71.0	312	18.7 (18.1–19.4)		
71.0	308	20.6 (19.9–21.4)		
76.5	312	20.0 (19.3–20.8)		
82.5	303	20.0 (19.3–20.8)		
≥89.5	307	19.5 (18.8–20.2)	0.01	0.40
BMI, kg/m^2				
≤24.9	485	19.6 (19.0–20.1)		
25–29.9	793	20.3 (19.8–20.7)		
≥30	264	18.7 (18.0–19.5)	0.003	0.34
Smoking[b]				
Never	489	20.1 (19.6–20.8)		
Former	640	19.7 (19.2–20.2)		
Current	389	19.5 (18.8–20.1)	0.32	
Alcohol consumption, g/d[b]				
<8	623	19.8 (19.3–20.4)		
8–15	311	20.4 (19.6–21.1)		
16–39	370	20.0 (19.3–20.7)		
≥40	236	18.5 (17.7-19.3)	0.01	0.08
Physical activity[b]				

	N	Adjusted geometric mean IGF-I (nmol/L)[a] (95% CI)	$P_{heterogeneity}$ [c]	P_{trend} [d]
Inactive	221	20.7 (19.7–21.7)		
Moderately inactive	415	20.2 (19.6–20.9)		
Active	693	20.4 (19.9–20.9)	0.75	0.46
Educational level[b]				
Primary or equivalent	579	19.2 (18.7–19.7)		
Secondary	556	19.9 (19.4–20.5)		
Degree	339	20.5 (19.7–21.2)	0.03	0.01
Country				
Denmark	152	19.9 (18.4–21.4)		
Germany	383	19.8 (19.0–20.6)		
Greece	40	19.5 (17.5–21.7)		
Italy	145	20.6 (19.3–22.1)		
Netherlands	50	22.8 (20.8–25.1)		
Spain	200	20.5 (19.5–21.7)		
Sweden	192	13.9 (12.2–15.8)		
United Kingdom	380	22.3 (21.2–23.5)	0.002 [e]	

[a] Adjusted for age (<50, 50–54, 55–59, 60–64, 65–69, ≥70 years), center (1–18), batch (1–78), alcohol consumption (<8, 8–15, 16–39, ≥40 g/d, unknown), educational attainment (primary school, secondary school, higher education/degree, unknown), and body mass index (quartile cutoff points: <24.4, 24.4, 26.4, 28.7 kg/m^2), where the adjustment variable is not the variable of interest; with 95% CI in parenthesis.

[b] Unknown for some participants; number of unknowns calculated by subtracting the known total number in each group from 1,542.

[c] *P* value refers to tests of heterogeneity between the logarithm of the geometric means in the separate categories (excluding unknowns) calculated by using analysis of variance.

[d] *P* value refers to the test for trend obtained by treating the categorical variable as a continuous variable in the model.

[e] *P* value refers to tests of heterogeneity between the logarithmof the geometric means amongst countries assayed using the DSL-10-5600 ACTIVE ELISA (i.e., excluding Umeaå , Sweden, assayed using the IDS-iSYS immunoassay).

Table 3

OR (and 95% CI) for prostate cancer associated with quartile concentrations of IGF-I or a doubling in IGF-I concentration in the European Prospective Investigation into Cancer and Nutrition

		Fourth of circulating IGF-I concentration[a]						
		Q1	Q2	Q3	Q4	$OR_{doubling}$[b]	P_{trend}[c]	$P_{heterogeneity}$[d]
Overall prostate cancer[b]	Cases/ controls (*N*)	297/386	375/385	419/386	451/385	1,542/1,542		
	OR (95% CI)	1 (ref)	1.31 (1.05, 1.62)	1.51 (1.21, 1.88)	1.69 (1.35, 2.13)	1.38 (1.17, 1.64)	0.0002	
Prostate cancer stage[b,e]								
Localized stage	Cases/ controls (*N*)	146/196	186/195	208/174	205/180	745/745		
	OR (95% CI)	1 (ref)	1.29 (0.95, 1.76)	1.69 (1.24, 2.30)	1.65 (1.19, 2.27)	1.40 (1.10, 1.78)	0.01	
Advanced stage	Cases/ controls (*N*)	57/83	84/68	71/77	97/81	309/309		0.84
	OR (95% CI)	1 (ref)	2.05 (1.22, 3.44)	1.58 (0.95, 2.63)	2.15 (1.26, 3.68)	1.46 (1.01, 2.12)	0.04	
Histological grade[b,f]								
Low grade	Cases/ controls (*N*)	165/208	197/212	218/196	268/232	848/848		
	OR (95% CI)	1 (ref)	1.19 (0.89, 1.59)	1.46 (1.09, 1.96)	1.57 (1.17, 2.10)	1.36 (1.09, 1.69)	0.01	
High grade	Cases/ controls (*N*)	37/45	46/34	40/36	36/44	159/159		0.19
	OR (95% CI)	1 (ref)	1.79 (0.90, 3.56)	1.48 (0.75, 2.94)	1.05 (0.52, 2.10)	0.95 (0.58, 1.55)	0.84	
Time to diagnosis[b]								
<4 y	Cases/ controls (*N*)	93/136	88/90	107/90	169/141	457/457		
	OR (95% CI)	1 (ref)	1.57 (1.03, 2.39)	1.96 (1.29, 2.99)	2.01 (1.35, 2.99)	1.39 (1.08, 1.80)	0.01	
4–7 y	Cases/ controls (*N*)	122/145	135/139	154/139	149/137	560/560		
	OR (95% CI)	1 (ref)	1.13 (0.80, 1.61)	1.33 (0.94, 1.90)	1.37 (0.94, 2.00)	1.29 (0.96, 1.71)	0.08	0.77
>7 y	Cases/ controls (*N*)	82/105	152/156	158/157	133/107	525/525		
	OR (95% CI)	1 (ref)	1.30 (0.89, 1.89)	1.39 (0.95, 2.05)	1.80 (1.17, 2.77)	1.50 (1.04, 2.16)	0.03	
Age at diagnosis[b]								
<65 y	Cases/ controls (*N*)	106/139	166/165	176/185	255/214	703/703		
	OR (95% CI)	1 (ref)	1.33 (0.95, 1.86)	1.29 (0.92, 1.81)	1.67 (1.19, 2.34)	1.26 (0.99, 1.60)	0.06	
≥65 y	Cases/ controls (*N*)	191/247	209/220	243/201	196/171	839/839		0.33
	OR (95% CI)	1 (ref)	1.28 (0.96, 1.70)	1.67 (1.25, 2.22)	1.67 (1.22, 2.28)	1.50 (1.18, 1.92)	0.001	
Age at blood collection[b]								
<60 y	Cases/ controls (*N*)	113/144	185/184	194/215	262/211	754/754		
	OR (95% CI)	1 (ref)	1.29 (0.93, 1.79)	1.18 (0.86, 1.64)	1.67 (1.21, 2.32)	1.34 (1.05, 1.70)	0.02	
≥60 y	Cases/ controls (*N*)	184/242	190/201	225/171	189/174	788/788		0.73

		Fourth of circulating IGF-I concentration[a]						
		Q1	Q2	Q3	Q4	$OR_{doubling}$[b]	P_{trend}[c]	$P_{heterogeneity}$[d]
	OR (95% CI)	1 (ref)	1.28 (0.96, 1.72)	1.87 (1.38, 2.53)	1.65 (1.19, 2.28)	1.43 (1.12, 1.81)	0.003	
Assay type[b]								
IDS-iSYS immunoassay	Cases/ controls (*N*)	35/48	47/48	36/48	74/48	192/192		
(Umeaå, Sweden only)	OR (95% CI)	1 (ref)	1.35 (0.75, 2.42)	1.01 (0.54, 1.88)	2.19 (1.21, 3.97)	1.64 (0.97, 2.76)	0.06	
DSL-10-5600 ACTIVE ELISA	Cases/ controls (*N*)	262/338	328/337	383/338	377/337	1,350/1,350		0.46
(All centers except Umeaå)	OR (95% CI)	1 (ref)	1.30 (1.03, 1.65)	1.57 (1.24, 1.98)	1.61 (1.26, 2.07)	1.35 (1.13, 1.62)	0.001	

[a] Quartile cutoff points (16.5, 20.6, and 25.3 nmol/L) were defined among control participants for all cohorts combined except Umeaå , Sweden where country specific cutoff points (13.2,16.0, and 18.8 nmol/L) were used to account for variation in IGF-I concentrations attributable to the assay method.

[b] Conditioned by matching factors: study center, age at recruitment, time of blood collection, and duration of fasting at blood collection and adjusted for age at blood collection.

[c] *P* values for trend were obtained by replacing the categorical variable with the logarithm of IGF-I concentration; with adjustment for age at blood collection.

[d] *P* for heterogeneity values relate to likelihood ratio χ^2 tests of heterogeneity between trends (using the logarithm of IGF-I); with adjustment for age at blood collection.

[e] Localized stage includes T0 or T1 or T2 and N0 or NX and M0, or stage coded in the recruitment center as localized and advanced stage includes T3 or T4 and/or N1+ and/or M1, or stage coded in the recruitment center as metastatic.

[f] Low grade includes Gleason score ≤7, or cases coded as well differentiated or moderately differentiated according to the WHO grading system and high grade includes Gleason score >7, or cases coded as poorly differentiated or undifferentiated according to the WHO grading system.