Supplementary Materials and Methods

A meta-analysis of individual participant data reveals an association between circulating levels of IGF-I and prostate cancer risk

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Supplementary Methods

Data collection
In 2004, the principal investigators who had published studies on prostate cancer risk and endogenous sex hormones and growth factors measured in blood samples collected before the diagnosis of prostate cancer and which included at least 50 cases were invited to join the collaboration. In 2010, collaborators were invited to update their data on endogenous sex hormones and growth factors and to include any data on nutritional biomarkers and prostate cancer. Additional studies with data on these analytes in relation to prostate cancer risk were also invited to join the collaboration.

Individual participant data were available from 19 studies by the closure of the dataset for these analyses on November 8th, 2012: In total, these 19 studies included data on IGF-I and IGFBP-3 from up to 10554 prostate cancer cases and 13618 control participants, representing more than 98% of the worldwide data. Of these studies, 11 also provided data on circulating IGF-II and 6 provided data on IGFBP-1 and IGFBP-2.

In total in 2010 18 eligible prospective studies with data on IGFs were identified: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) (1), Baltimore Longitudinal Study of Aging (BLSA) (2), British United Provident Association Study (BUPA) (3), the Cardiovascular Health Study (CHS) (4), the CLUE 1 Study (named after the campaign slogan “Give Us a Clue to Cancer”) (5), European Prospective Investigation into Cancer and Nutrition (EPIC) (6, 7), European Randomized Study of Screening for Prostate Cancer (ERSPC) (8), Health Professionals Follow-up Study (HPFS) (9, 10), Japan Collaborative Cohort Study (JACC) (11), Kaiser Permanente Medical Care Programme (KPMCP) (12), Melbourne Collaborative Cohort Study (MC3S) (13), Multiethnic Cohort (MEC) (14), Northern Sweden Health and Disease Cohort (NSHDC) (15, 16), Prostate Cancer Prevention Trial (PCPT) (17), Physicians’ Health Study (PHS) (18-20), Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) (21), and the Supplémentation en Vitamines et Minéraux AntioXydants (SU.VI.MAX) trial (22). The data from all but one of these studies were available for these epidemiological analyses by the closure of the dataset for these analyses on November 8th, 2012: data on IGFs (IGF-I and IGFBP-3) from the prospective multiethnic cohort from the USA with 96 cases and 416 controls were unavailable for analysis. Data were also available for the collaborative analyses from two stages of a large cross-sectional case-control study nested within the Prostate Testing for Cancer and Treatment (ProtecT) study, a trial of PSA-screening in the UK, the feasibility phase (23) and main study (24). IGF-I, IGF-II and IGFBP-3 values from the main ProtecT study were pre-adjusted for assay kit and storage time.

The characteristics of these studies in the collaborative analyses are shown in Supplementary Table S1. Most of the studies are case-control studies nested within traditional prospective cohort studies, with some variation in the case mix of these studies according to the prevalence of PSA testing within that population during follow-up. For example, there is a generally higher proportion of early stage and low grade cases in studies from the USA, where there has been relatively high levels of PSA-testing since the mid-1990s, than in studies in European populations where PSA-testing has only more recently started to become common. Four of the studies (ERSPC, PCPT, PLCO and ProtecT) are observational investigations using data from trials that included organized screening for prostate cancer, and these four studies have distinct characteristics. In three of these trials, men with a raised PSA or abnormal digital rectal examination at recruitment-screening were excluded, and the eligible cases were diagnosed during subsequent follow-up (for ERSPC and PCPT the majority being diagnosed at the end of the study, 4 and 7 years after recruitment, respectively), with the majority of cases being detected either through PSA-screening (ERSPC and PLCO) or by routine end of study biopsy (PCPT). The ProtecT studies include participants from a trial of different prostate cancer treatments, in which (mostly asymptomatic) men were screened with PSA and those with PSA ≥3 ng/mL were offered a diagnostic biopsy; men diagnosed at this time were included as cases for the observational study of biomarkers and prostate cancer. The data from ProtecT are reported here because on average the blood was collected several years before the cancer would have been diagnosed in an unscreened population, although the study is cross-sectional rather than prospective.

Collaborators were asked to provide data on concentrations of IGF-I, IGF-II, IGFBP-1, IGFBP-2 and IGFBP-3, and on a number of other selected hormones and nutritional biomarkers. 18 of the original studies contributing to the collaborative analyses used a matched case-control design nested within a prospective cohort study (BLSA, CHS, CLUE I, EPIC, HPFS, JACC, MCCS), a health plan (BUPA, KPMCP) or a randomized trial (ATBC, ERSPC, NSHDC, PCPT, PHS, PLCO, ProtecT feasibility study, ProtecT, SU.VI.MAX) and we retained the original matched case-control sets. MMCS had a case-cohort design and was converted into a matched case-control design; up to 4 controls, each at least as old as at censoring as their case was at diagnosis, were matched with each case, matching on assay batch, country of birth group (Australia, New Zealand, Other, UK, Malta or Italy/Greece), age at blood collection (plus or minus 60 months) and date of blood collection (plus or minus 24 months). Some studies used density sample, meaning that an individual could appear more than once in a data file. Individual participant data were also contributed for age, height, weight, smoking status, alcohol consumption, marital status, socioeconomic status (accessed by educational achievement), ethnicity and PSA level. Information sought about prostate cancer included date of diagnosis and stage and grade of disease. Men were excluded from the analyses if data were missing for dates of birth, blood collection, or diagnosis (for cases).
Statistical analyses
To explore the relationships between analytes, partial correlation coefficients between IGFs and other selected analytes were calculated using standardised log-transformed concentrations among controls from each study (calculated by subtracting the mean log concentration and dividing by the standard deviation), adjusting for age at blood collection and, in a second analysis, also for BMI.

Multivariable conditional logistic regression analyses
To examine the effects of potential confounders (other than the matching criteria, controlled for by design), the logistic regression analyses were repeated including additional variables that have been associated with prostate cancer risk in previous studies. These variables included age at blood collection (exact), body mass index (BMI; <25, 25-27.4, 27.5-29.9, ≥30 kg/m², or not known), height (≤170, 171-175, 176-180, >180 cm, or not known), marital status (married or cohabiting, not married or cohabiting, or not known), educational status (did not graduate from high school/secondary school/college, high school/secondary school/college graduates, university graduates, or not known), and cigarette smoking (never smoker, past smoker, current, or not known), all of which were associated with prostate cancer risk in these analyses (P<0.05). The potential confounding effect of family history of prostate cancer was also examined in the subset of 10 studies for which family history data were available. The associations of IGFs with prostate cancer risk were also examined after mutual adjustment for concentrations of other IGFs, testosterone and sex-hormone binding globulin (SHBG), where available, and the joint association of IGF-I and IGF-P-3 on prostate cancer risk was examined.

For comparability with previous publications, we also calculated a linear trend on prostate cancer risk in relation to the logarithm of the IGF (see Supplementary Table S5). A log₂ transformation was used such that a unit increase would represent a doubling in IGF concentration (24) (other transformations, such as log₁₀ and ln, would have produced identical P values but different and less easily interpretable risk estimates). However, pooling the risk estimates from separate cohorts does assume that a doubling in IGF concentration has the same effect on the risk estimate in each cohort.

Tests for heterogeneity in the linear-trend odds ratio estimates
To test whether the linear-trend OR estimates for each analyte varied according to certain case participant characteristics, ORs were estimated within a series of subsets for the following characteristics; age at diagnosis (<60, 60–69, or ≥70 years), years from blood collection to diagnosis (<3, 3–6, or ≥7 years), year of diagnosis (pre-1990, 1990–1994, 1995-1999 or 2000 onwards), stage of disease (early stage, other localized or advanced), aggressive disease (no or yes), and grade of disease (low or high). Controls in each matched set were assigned the value of their matched case for the case-defined factors (e.g. age at diagnosis and years from blood collection to diagnosis). For the multi-case matched sets in NSHDC, PLCO and ProtecT in which the case characteristics varied (e.g. some low-intermediate grade, some high grade), controls were randomly allocated to cases in the same proportions. Tests for heterogeneity for the case-defined factors were obtained by fitting separate models for each subgroup and assuming independence of the ORs using a method analogous to a meta-analysis. Subgroup analyses were also conducted according to the following participant characteristics; age at blood draw (<55, 55–59, 60–64 or ≥65 years), PSA at blood draw (<2 or ≥2 ng/mL), university or higher education (no or yes), BMI (<25 or ≥25 kg/m²), cigarette smoking (never, past smoker or current smoker), usual alcohol consumption (<10 or ≥10 g/day), and family history of prostate cancer (no or yes). For age at blood draw and age at diagnosis, a test for heterogeneity in the trends was also conducted (based on one degree of freedom), taking into account the ordering of the age-group variables.

Presentation of results in the figures
Results in the figures are presented as squares and lines, representing the odds ratios and corresponding 95% confidence intervals (CIs), respectively. The position of the square indicates the value of the odds ratio where the size is inversely proportional to the variance of the logarithm of the odds ratio and indicates the amount of statistical information available for that particular estimate. The open diamonds (the lateral points of which are the 95% CIs) represent the overall odds ratio for an 80 percentile increase in the individual IGF analyte.

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References


