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 (MCCS) (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 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 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/m^2, 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 IGFP-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 log$_2$ transformation was used such that a unit increase would represent a doubling in IGF concentration (24) (other transformations, such as log$_{10}$ 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/m^2), 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.

References

1. Woodson K, Tangrea JA, Pollak M, Copeland TD, Taylor PR, Virtamo J, et al. Serum insulin-like growth factor I: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. Cancer Research 2003;63(14):3991-3994.

2. Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Serum levels of insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-3, and prostate-specific antigen as predictors of clinical prostate cancer. The Journal of Clinical Endocrinology and Metabolism 2000;85(11):4258-4265.

3. Morris JK, George LM, Wu T, Wald NJ. Insulin-like growth factors and cancer: no role in screening. Evidence from the BUPA study and meta-analysis of prospective epidemiological studies. British Journal of Cancer 2006;95(1):112-117.

4. Chen C, Lewis SK, Voigt L, Fitzpatrick A, Plymate SR, Weiss NS. Prostate carcinoma incidence in relation to prediagnostic circulating levels of insulin-like growth factor I, insulin-like growth factor binding protein 3, and insulin. Cancer 2005;103(1):76-84.

5. Lacey JV, Jr., Hsing AW, Fillmore CM, Hoffman S, Helzlsouer KJ, Comstock GW. Null association between insulin-like growth factors, insulin-like growth factor-binding proteins, and prostate cancer in a prospective study. Cancer Epidemiology, Biomarkers & Prevention 2001;10(10):1101-1102.

6. Price AJ, Allen NE, Appleby PN, Crowe FL, Travis RC, Tipper SJ, et al. Insulin-like growth factor-I concentration and risk of prostate cancer: results from the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiology, Biomarkers & Prevention 2012;21(9):1531-1541.

7. Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Rinaldi S, et al. Serum insulin-like growth factor (IGF)-I and IGF-binding protein-3 concentrations and prostate cancer risk: results from the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiology, Biomarkers & Prevention 2007;16(6):1121-1127.

8. Janssen JA, Wildhagen MF, Ito K, Blijenberg BG, Van Schaik RH, Roobol MJ, et al. Circulating free insulin-like growth factor (IGF)-I, total IGF-I, and IGF binding protein-3 levels do not predict the future risk to develop prostate cancer: results of a case-control study involving 201 patients within a population-based screening with a 4-year interval. The Journal of Clinical Endocrinology and Metabolism 2004;89(9):4391-4396.

9. Platz EA, Pollak MN, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E. Plasma insulin-like growth factor-1 and binding protein-3 and subsequent risk of prostate cancer in the PSA era. Cancer Causes & Control 2005;16(3):255-262.

10. Nimptsch K, Platz EA, Pollak MN, Kenfield SA, Stampfer MJ, Willett WC, et al. Plasma insulin-like growth factor 1 is positively associated with low-grade prostate cancer in the Health Professionals Follow-up Study 1993-2004. International Journal of Cancer 2011;128(3):660-667.

11. Pham TM, Fujino Y, Nakachi K, Suzuki K, Ito Y, Watanabe Y, et al. Relationship between serum levels of insulin-like growth factors and subsequent risk of cancer mortality: findings from a nested case-control study within the Japan Collaborative Cohort Study. Cancer Epidemiology 2010;34(3):279-284.

12. Schaefer C, Friedman GD, Quesenberry CP, Jr., Orentreich N, Vogelman JH. IGF-I and Prostate Cancer. Science 1998;282:199a.

13. Severi G, Morris HA, MacInnis RJ, English DR, Tilley WD, Hopper JL, et al. Circulating insulin-like growth factor-I and binding protein-3 and risk of prostate cancer. Cancer Epidemiology, Biomarkers & Prevention 2006;15(6):1137-1141.

14. Gill JK, Wilkens LR, Pollak MN, Stanczyk FZ, Kolonel LN. Androgens, growth factors, and risk of prostate cancer: the Multiethnic Cohort. The Prostate 2010;70(8):906-915.

15. Stattin P, Bylund A, Rinaldi S, Biessy C, Dechaud H, Stenman UH, et al. Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. Journal of the National Cancer Institute 2000;92(23):1910-1917.

16. Stattin P, Rinaldi S, Biessy C, Stenman UH, Hallmans G, Kaaks R. High levels of circulating insulin-like growth factor-I increase prostate cancer risk: a prospective study in a population-based nonscreened cohort. Journal of Clinical Oncology 2004;22(15):3104-3112.

17. Neuhouser ML, Platz EA, Till C, Tangen CM, Goodman PJ, Kristal A, et al. Insulin-like growth factors and insulin-like growth factor-binding proteins and prostate cancer risk: results from the prostate cancer prevention trial. Cancer Prev Res 2013;6(2):91-99.

18. Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 1998;279(5350):563-566.

19. Chan JM, Stampfer MJ, Ma J, Gann P, Gaziano JM, Pollak M, et al. Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. Journal of the National Cancer Institute 2002;94(14):1099-1106.

20. Mucci LA, Stark JR, Pollak MN, Li H, Kurth T, Stampfer MJ, et al. Plasma levels of acid-labile subunit, free insulin-like growth factor-I, and prostate cancer risk: a prospective study. Cancer Epidemiology, Biomarkers & Prevention 2010;19(2):484-491.

21. Weiss JM, Huang WY, Rinaldi S, Fears TR, Chatterjee N, Chia D, et al. IGF-1 and IGFBP-3: Risk of prostate cancer among men in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. International Journal of Cancer 2007;121(10):2267-2273.

22. Meyer F, Galan P, Douville P, Bairati I, Kegle P, Bertrais S, et al. A prospective study of the insulin-like growth factor axis in relation with prostate cancer in the SU.VI.MAX trial. Cancer Epidemiology, Biomarkers & Prevention 2005;14(9):2269-2272.

23. Oliver SE, Gunnell D, Donovan J, Peters TJ, Persad R, Gillatt D, et al. Screen-detected prostate cancer and the insulin-like growth factor axis: results of a population-based case-control study. International Journal of Cancer 2004;108(6):887-892.

24. Rowlands MA, Holly JM, Gunnell D, Donovan J, Lane JA, Hamdy F, et al. Circulating insulin-like growth factors and IGF-binding proteins in PSA-detected prostate cancer: the large case-control study ProtecT. Cancer Research 2012;72(2):503-515.