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# Plasma insulin-like growth factor 1 is positively associated with low-grade prostate cancer in the Health Professionals Follow-up Study 1993–2004

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## Abstract

The insulin-like growth factor (IGF) axis plays a role in growth and progression of prostate cancer. High circulating IGF-1 levels have been associated with an increased risk of prostate cancer. Results for IGF binding protein 3 (IGFBP-3) are inconclusive. Some studies have indicated that the positive association with IGF-1 is observed only for low-grade prostate cancer (Gleason sum <7). We previously reported in the Health Professionals Follow-up Study (HPFS) a direct positive association between ELISA-measured plasma IGF-1 and IGFBP-3 and risk of prostate cancer (462 cases diagnosed after providing a blood specimen (between 1993 and 1995), but before February 1998). With additional follow-up through January 31st 2004, and 1331 case-control pairs in total, we were now able to investigate low-grade (Gleason sum <7, n=635) and high-grade (Gleason sum ≥7, n=515) prostate cancer separately. Matched odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. ORs of total prostate cancer comparing top to bottom quartiles were 1.41 (95% CI 1.12–1.78, p-trend=0.001) for IGF-1 and 1.58 (95% CI 1.24–2.01, p-trend=0.003) for IGFBP-3. IGF-1 was more strongly associated with low-grade (OR=1.61 top versus bottom quartile, 95% CI 1.16–2.25, p-trend=0.01), than with high-grade (OR=1.29, 95% CI 0.89–1.88, p-trend-0.12) prostate cancer (p-heterogeneity=0.08). We hypothesize that these findings reflect that high-grade prostate cancers are more autonomous, and, thus, less sensitive to the action of IGF-1 than low-grade cancers.

## Introduction

Two recent meta-analyses of circulating insulin-like growth factor (IGF-1) in relation to prostate cancer risk consistently report moderately increased risks of prostate cancer with higher circulating IGF-1 concentrations[1, 2]. Results for IGFBP-3, its major binding protein, are less consistent, possibly reflecting complexities in the immunoassays regarding whether intact or digested IGFBP-3 is being assessed, each with perhaps quite different effects on IGF physiology and cancer risk. Moreover, IGFBP-3 is typically highly correlated with

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IGF-1. One meta-analysis that used individual participant data from 12 prospective studies (Roddam et al. 2008) found higher IGFBP-3 levels to be associated with an overall moderately increased risk of prostate cancer[1], while the more recent meta-analysis (Rowlands et al. 2008), which included retrospective studies as well as two prospective studies not included in the aforementioned analysis, observed a significantly decreased overall pooled odds ratio (OR) and a non-significantly decreased pooled OR among prospective studies[2].

Whether IGF-1 acts differentially on subtypes of prostate cancer as defined by stage and grade has not been studied sufficiently. Only some of the prospective studies report risk estimates stratified by cancer stage or some study-specific definition of aggressiveness of disease[3–10], and two of them showed stronger positive associations between IGF-1 and advanced versus non-advanced prostate cancer[4, 9]. Even less studies show estimates by Gleason grade[3, 5, 7, 11], and stronger associations of IGF-1 with low-grade prostate cancer were observed in two of these[3, 4]. In several studies, the number of low-grade or advanced cases was very low (e.g. below 100) so that the statistical power to detect differential effects in subgroups of prostate cancer was limited. In the Physicians' Health Study, a particularly strong association with IGF-1 was observed for the small group of low-grade but advanced stage prostate cancers (OR of advanced stage prostate cancer in an analysis restricted to cases with a Gleason score of 2 to 7 was 9.6 comparing highest versus lowest quartile, 95% CI 2.0–45.6).

We previously examined circulating IGF-1 and IGFBP-3 in relation to prostate cancer in the Health Professionals Follow-up Study based on follow-up from 1993 to 1998 including 462 matched case-control pairs. Both IGF-1 (OR comparing highest versus lowest quartile 1.37, 95% CI 0.92–2.03, p-trend=0.05) and IGFBP-3 (OR 1.62, 95% CI 1.07–2.46, p-trend=0.08) were positively associated with the risk of prostate cancer in models where IGF-1 and IGFBP-3 were not mutually adjusted for each other. At that time, our study had insufficient power to detect differential effects by tumor stage or grade. Therefore, with extended follow-up to 2004 and including 1331 case-control pairs, we evaluated the hypotheses that plasma IGF-1 is differentially associated with advanced versus organ-confined or high-grade versus low-grade prostate cancer. We also provide an updated analysis of the association between plasma IGF-1 and IGFBP-3 concentrations in relation to prostate cancer overall. In addition, we investigated potential effect modifying factors, including age at diagnosis, family history of prostate cancer, and lycopene intake, which has been shown to reduce IGF-1 signaling through increasing membrane associated IGFBP-3 concentrations[12–14].

## Materials and Methods

### Study population

This matched case-control study is nested within the Health Professionals Follow-up Study, an ongoing prospective cohort study of 51,529 men. The study began in 1986, and extensive and repeated exposure measurements of anthropometric variables, medical conditions, and diet and lifestyle factors are collected through biennial questionnaires. Between 1993 and 1995, 18,018 participants provided a blood specimen. Participants report a variety of diseases including prostate cancer on the biennial follow-up questionnaires. After a new report of prostate cancer, we request written permission to obtain medical and pathology reports. Using these records, study investigators, blinded to the information from the questionnaires, confirm the diagnosis and extract stage at diagnosis and Gleason grade. Prostate cancer cases with T1a disease (i.e., incidental microscopic focal tumors) were excluded. Between the date of blood collection and January 31st 2004, 1,331 incident prostate cancer cases were confirmed.

Eligible controls were participants with available blood samples, who were alive and free of diagnosed cancer at the date of the case's diagnosis, and who had had a PSA test after the date of blood draw (for opportunity for prostate cancer detection as the vast majority of cases had had a PSA test for screening or as part of their diagnostic evaluation). From among these men, one randomly selected control was matched per case on year of birth (±1 year), PSA test prior to blood draw (yes/no), and timing of blood draw – time of day (midnight to before 9 am, 9 am to before noon, noon to before 4 pm, 4 pm to before midnight), season (winter, spring, summer, fall), and year (exact). IGF-1 and IGFBP-3 are not affected by fasting status. The cases and corresponding controls were identified in four waves of follow-up resulting in four assay batches: blood-draw to 1996, 1996–1998, 1998–2000, 2000–2004. This study was approved by the Human Subjects Committee at the Harvard School of Public Health.

## Laboratory analysis

Plasma IGF-1 and IGFBP-3 concentrations were measured by ELISA (Diagnostic Systems Laboratory, Webster, TX) in the laboratory of Dr. Michael Pollak, as was described previously[11]. Case-control pairs were analyzed together and laboratory personnel were blinded to case-control status. The mean intrapair coefficients of variation calculated from blinded quality control samples were below 10% for both IGF-1 and IGFBP-3 in all batches, except for IGF-1 in the batch 1998 to 2000, where the CV was 13.1%. In a subsample comprising all cases (and their matched controls) confirmed through 2000 (700 case-control pairs), plasma lycopene was determined by reverse-phase high performance liquid chromatography[15, 16]. Depending on the analysis batch, mean intrapair coefficients of variation for plasma lycopene were between 5.2% and 11.9%.

## Statistical analysis

Plasma concentrations of IGF-1, IGFBP-3 and their molar ratio were compared between cases and matched controls by using paired t-tests for unadjusted comparison or generalized estimating equations to mutually adjust for IGF-1 and IGFBP-3. Indicator variables for quartiles of IGF-1, IGFBP-3 and their molar ratio were entered into conditional logistic regression models to estimate matched odds ratios (OR) of prostate cancer. Quartile cutpoints were defined separately for the four assay batches based on the distribution among controls. In addition, continuous estimates per standard deviation in IGF-1, IGFBP-3 or ratio of IGF-1 to IGFBP-3 are presented. For this purpose, continuous variables were adjusted by batch to account for batch-specific differences in absolute concentrations[17]. To test for trend, a single ordinal variable with values of 1 to 4 corresponding to the quartile into which an individual's concentration fell was entered into the model. We tested for confounding by including potentially confounding factors one by one in the conditional logistic regression models. These included height, BMI, vigorous physical activity, vasectomy, family history of prostate cancer, smoking, dietary intake of energy, total fat, total protein, lycopene. None of these factors changed the association between IGF-1 or IGFBP-3 and prostate cancer materially, so multivariate adjusted models are not presented.

Our primary a priori hypothesis was that IGF-1 would be more strongly associated with low-grade or advanced stage prostate cancer. We therefore assessed the association between IGF-1 and prostate cancer separately by categories of grade and stage. Using the Gleason score from diagnostic biopsy, or, if available, Gleason score on radical prostatectomy specimen, cases were defined as low-grade (Gleason score<7) or high-grade (Gleason score ≥7). Cases were classified as organ-confined, or limited extraprostatic extension (T1b to T3a and N0M0), or advanced/fatal if participant had regionally invasive or metastatic disease (≥T3b, N1, or M1) at diagnosis, or developed metastases or died from prostate cancer as underlying cause of death during follow-up. Models by grade or stage of disease were

analyzed by conditional logistic regression, using only the controls matched to the cases with the respective stage or grade classification. We tested for heterogeneity by category of grade or stage by using a chi-square statistic.

In addition, we investigated potential effect modification by exposures that in our cohort were independent risk factors for prostate cancer or appeared to be effect modifiers in previous diet-related analyses of prostate cancer: age at diagnosis (<65 years, ≥65 years), body mass index (BMI) at diagnosis (<25 kg/m$^2$, ≥25 kg/m$^2$), family history of prostate cancer (yes/no), tomato sauce intake (0–≤2 servings/week, >2 servings/week; approximately 90$^{th}$ percentile) and plasma lycopene (<1123 nmol/L, ≥ 1123 nmol/L; cutoff based on 75$^{th}$ percentile in controls). Stratum-specific ORs were obtained by either conditional logistic regression for age at diagnosis or unconditional logistic regression adjusted for matching factors to avoid loss of statistical power, for BMI, family history of prostate cancer, tomato sauce intake, and plasma lycopene. Heterogeneity in the association by age at diagnosis was assessed by comparing the stratum-specific ORs using the chi-square test. To test for statistical interaction, cross-product terms between BMI, family history of prostate cancer, tomato sauce intake and plasma lycopene and IGF-1 or IGFBP-3, respectively, were entered into the appropriate model along with the main effect terms. P-interaction corresponds to the p-value from the Wald test for the respective cross-product term. Analyses were conducted using SAS release 9.1 (SAS Institute, Cary, NC). Two-sided p-values are given for all statistical tests.

## Results

Clinical and pathological characteristics of the case subjects included in this study are shown in table 1. Based on this information, 992 cases were classified as organ-confined and 146 cases as advanced stage/fatal; 635 cases were low-grade and 515 high-grade.

Plasma IGF-1 and IGFBP-3 were strongly positively correlated (Pearson's correlation coefficient r=0.66, p <0.0001) among control subjects. Mean plasma concentrations of both IGF-1 and IGFBP-3 were statistically significantly higher in cases than in controls (table 2). After mutually adjusting for each other, both IGF-1 and IGFBP-3 were higher in cases than in controls, although a statistically significant difference persisted only for IGF-1. The molar ratio of IGF-1 to IGFBP-3 did not differ between cases and controls. Compared to their matched controls, mean IGF-1 was significantly higher in low-grade, but not in high-grade prostate cancer cases, while IGFBP-3, after adjustment for IGF-1, was not significantly different either in low-grade or high-grade prostate cancer cases.

Both plasma IGF-1 and IGFBP-3 were positively associated with risk of total prostate cancer diagnosed between 1993 and 2004 (table 3). ORs of total prostate cancer comparing top to bottom quartiles were 1.41 (95% CI 1.12–1.78, p-trend=0.001) for IGF-1 and 1.58 (95% CI 1.24–2.01, p-trend=0.003) for IGFBP-3. Considering only the cases diagnosed between 1998 and 2004 (not included in the previously published analysis[5]) ORs were very similar (OR=1.41, 95% CI 1.06–1.88, p-trend=0.01 for IGF-1 and 1.54, 95% CI 1.15–2.08, p-trend=0.01 for IGFBP3.

After mutually adjusting IGF-1 and IGFBP-3, a statistically significant positive association persisted in the top three quartiles with IGFBP-3 but not with IGF-1. The molar ratio of IGF-1 to IGFBP-3 was not clearly associated with risk of prostate cancer.

To evaluate the possibility that the presence of undiagnosed tumors may have altered levels of IGF or the binding protein (reverse causation) in cases that were diagnosed early after blood draw, in a sensitivity analysis we excluded cases diagnosed within the first two years after blood draw and found similar associations (OR for highest versus lowest quartile 1.40,

95% CI 1.07–1.82 for IGF-1 and 1.64 95% CI 1.25–2.16 for IGFBP-3). In addition, the strength of association did not materially vary within two-year strata of follow-up (<2, 2–4, 4–6, 6–8 and ≥ 8 years; data not shown).

ORs for IGF-1 and subgroups of prostate cancer as defined by Gleason grade and stage are shown in table 4. IGF-1 was significantly associated with low-grade prostate cancer (OR=1.61 comparing highest versus lowest quartile, 95% CI 1.16–2.25, p-trend=0.01), while no significant association was observed for high-grade prostate cancer (OR=1.29 highest versus lowest quartile, 95% CI 0.89–1.88, p-trend=0.12). Significant heterogeneity by Gleason grade was observed when IGF-1 was adjusted for IGFBP-3 (p-heterogeneity=0.04). For IGFBP-3, we observed significant positive associations with both low-grade and high-grade prostate cancer (p-heterogeneity=0.85 and 0.25 unadjusted and mutually adjusted, respectively, data not shown).

When comparing the associations of IGF-1 between advanced/fatal and organ-confined prostate cancer, we observed significant positive associations with organ-confined, but not with advanced or fatal prostate cancer. There was no indication of heterogeneous associations by stage. Similarly, IGFBP-3 was significantly positively associated with organ-confined, but not with advanced/fatal prostate cancer in both unadjusted and mutually adjusted models (data not shown). Although we had little power to analyze the uncommon group of low-grade (Gleason score <7) but advanced/fatal prostate cancers (27 cases), we observed a strong positive association of IGF-1 with this subgroup of prostate cancer (OR per standard deviation in IGF-1 2.56, 95% CI 1.06–6.14). In contrast, for high-grade (Gleason score ≥7) and advanced/fatal prostate cancer (93 cases) a non-significant inverse association was observed with IGF-1 (OR per standard deviation in IGF-1 0.85, 95% CI 0.59–1.24).

The association between IGF-1 and prostate cancer risk did not differ by age at diagnosis, baseline BMI, tomato sauce intake or plasma lycopene (data not shown). We observed a slightly stronger association between IGF-1 and prostate cancer risk among men who reported a family history of prostate cancer (father or brother) (OR, 95% CI per standard deviation of IGF-1 1.15, 1.01–1.31 in subjects with and 1.06, 0.99–1.13 in subjects without family history of prostate cancer, p-interaction=0.04).

## Discussion

In this study, we observed moderate positive associations between both IGF-1 and IGFBP-3 and risk of total prostate cancer, as has been reported previously in an analysis with a shorter follow-up time[5]. With extended follow-up, the strengths of the associations were similar, and the trends became stronger. The results were not changed after excluding the first two years of follow-up. In line with our hypothesis, we observed a significant positive association between IGF-1 and low-grade prostate cancer, but not for high-grade prostate cancer, but the differences in these associations were not statistically significant.

A positive association between IGF-1 and/or IGFBP-3 and prostate cancer has been observed in a number of epidemiologic studies. IGF-1 may influence the growth and progression of prostate cancer cells via mitogenic and anti-apoptotic effects mediated by activation of type 1 IGF receptor[19, 20]. IGFBP-3 may affect prostate cancer risk by either modulation of the bioavailability of IGF-1 or independent anti-apoptotic effects[20]. Our observation of a moderate positive association between circulating IGF-1 and prostate cancer is in line with a pooled analysis of 12 prospective studies[1] and a recent meta-analysis[2]. Both meta-analyses include data from the HPFS through 1998[5].

Few studies have explicitly reported on IGF-1 separately for high- and low-grade prostate cancers. The update of the Physicians' Health Study (PHS) was the first study to report a stronger association of IGF-1 with low-grade as compared to high-grade prostate cancer risks[4]. Our findings are consistent with those observations. In contrast to the PHS, we did not observe stronger associations for advanced stage/fatal prostate cancer. This discrepancy might be explained by a different case mix in the two studies. In the PHS analysis, largely based on cases diagnosed before the PSA era, 142 of 530 (27%) cases were diagnosed at an advanced stage; in contrast, 146 of 1331 (11%) cases in the HPFS follow-up during the PSA era were advanced/fatal. In the PHS, a particularly strong association was observed between IGF-1 and low-grade but advanced prostate cancer. Since almost half of the advanced cases were low-grade (66 of 144), the pronounced association between IGF-1 and advanced prostate cancer may be driven by this group. In our study, only 27 of the 146 (18%) advanced cases were low-grade. This low proportion is probably explainable by frequent PSA-screening in our cohort, since low-grade cases might take longer to become advanced and, if detected early by PSA-screening, are more likely to be diagnosed at a non-advanced stage. Although we saw a slight suggestion that there might be a particular strong association between IGF-1 and low-grade but advanced/fatal prostate cancer comparable to the PHS, the statistical power in our study was limited by the small proportion of this type of cancer. In neither of the two recent meta-analyses were heterogeneous associations by stage of disease observed[1, 2]. Apart from the PHS and our study, two other prospective studies have reported on the IGF-1 association by grade; one also found a stronger association with lower grade cancers[3], while the results of the other were equivocal due to small numbers[7]. The most recent meta-analysis on IGF and prostate cancer (Rowlands et al. 2009) reports similar grade-specific pooled estimates (per SD IGF-1) based on 4 prospective studies (OR 1.09, 95%CI 1.00–1.20 for low-grade and 1.21, 95%CI 0.90–1.62 for high-grade prostate cancer, p-heterogeneity=0.5)[2]. In contrast, the pooled analysis by Roddam et al. which included 12 prospective studies, shows stronger linear trend estimates for low-grade disease (OR for the linear trend for IGF-1 obtained by replacing the categorical variable with a variable that was scored as 0, 0.25, 0.5, 0.75, and 1: 1.57, 95% CI 1.32–1.87) than for high-grade disease (OR 1.12, 95% CI 0.87–1.43; p-heterogeneity=0.027). The conflicting results of these two meta-analyses with respect to grade-specific associations is not surprising, since the pooled estimates by Roddam et al. are based on individual participant data and includes information from 12 prospective studies, including studies that did not explicitly publish on IGF-1 associations by grade (2010 low-grade cases and 954 high-grade cases), as compared to the classical meta-analysis done by Rowlands et al. which included 869 low-grade cases and 477 high-grade cases from four studies. The recent EPIC-study[3], which was included in both meta-analyses, showed a stronger association between IGF-1 and low-grade cancers, with borderline significant heterogeneity (p-heterogeneity=0.06).

Comparable to our findings, some prospective studies[9, 10, 21] found a positive association between IGFBP-3 and prostate cancer, while no[22, 23] or non-significant inverse[6, 7, 11, 24] associations were observed in others. In the PHS IGFBP-3 was inversely associated with total[11] and advanced stage prostate cancer[4] when mutually adjusting for IGF-1. It has been suggested that the heterogeneous results may be due to differences in assay specificity and the stage of proteolytic cleavage of the measured form of IGFBP-3[25]. However, the same IGFBP-3 ELISA was applied in HPFS and PHS. Thus, the discrepant results between HPFS and PHS are more likely due to differences in case-mix as discussed for IGF-1.

Concerns in the validity of Gleason grading cannot be excluded in the present study. Grading is subject to inter- and intra-observer variability and a limitation of our study is that only in a subset of prostate cancer cases (n=180, 14% of all cases), Gleason score was re-evaluated by pathologists in tissue samples[18]. However, it seems unlikely that grading errors

would be related to IGF exposure and thus, such error probably has attenuated the associations.

Our hypothesis that some factors may act on the progression of well-differentiated (i.e. low Gleason score) but not on poorly differentiated lesions, as seen for IGF-1, is biologically plausible. The 5α-reductase inhibitor finasteride, for example, may be an agent selectively inhibiting low-grade tumors[26]. Grade-specific associations have also been observed for an IGFBP-3 polymorphism in relation to prostate cancer[27]. A possible explanation for a pattern of stronger effects on low-grade as compared to high-grade prostate cancer as seen for circulating IGF-1 is that growth in poorly differentiated cancers may be more autonomous. The IGF-1 signaling pathway, that is, the PI3k/Akt pathway, is negatively regulated by the tumor suppressor gene PTEN, which plays a role in the progression of prostate cancer. The prevalence of complete loss of PTEN increases with increasing Gleason sum[28]. Thus, it seems plausible that in high-grade prostate cancers with loss of PTEN, the PI3/Akt pathway is constitutively active and requires minimal activation by IGF-1, so that IGF-1 levels do not have a major impact on cancer progression, while in low-grade prostate cancers with regulated IGF-1 signaling, individual availability of IGF-1 is more likely to play a major role in prostate cancer development and progression.

We observed a stronger association between IGF-1 and prostate cancer in men with family history of prostate cancer, which is consistent with one other study[29]. So far, no convincing biological plausible mechanism that could explain this observation has been proposed, so this finding requires confirmation. We did not observe significant effect modification when stratifying by tomato sauce intake or plasma lycopene, suggesting that the interference of lycopene with IGF-1 signaling does not have a major influence on the association between IGF-1 and prostate cancer.

This study has several strengths, including its prospective design and large size, and the ability to investigate associations by Gleason sum and tumor stage. Controls had the same opportunity for prostate cancer detection as cases by including only participants who have had a PSA test after the date of blood draw as controls. Limitations include a single measurement of IGF-1 and IGFBP-3 to reflect usual levels, measurement errors in IGF-1 and IGFBP-3 concentrations, and potential grading errors. In addition, observed associations may be due to growth factors produced by extant cancers. However, when we excluded cases diagnosed within the first two years after blood draw, ORs did not change. In addition, the results were not attenuated with up to 12 years of follow-up, suggesting that a single measurement of IGF-1 and IGFBP-3 at baseline may be appropriate to reflect long-term exposure. We used the same IGF-1 and IGFBP-3 assays throughout the different sampling periods in our study. Nevertheless, absolute concentrations of IGF-1 and IGFBP-3 varied across analysis batches. We controlled for this by using batch-specific quartiles and adjusting continuous variables for batch-specific differences. The associations between IGF-1 or IGFBP-3, respectively, in relation to prostate cancer were stable across analysis batches.

In conclusion, this study provides further evidence that IGF-1 and IGFBP-3 may be preferentially associated with the risk of low-grade prostate cancer. We subsequently hypothesize that differences in underlying molecular lesions in prostate cancer, perhaps related to the IGF-1 signaling pathway, may explain this pattern. This hypothesis should be examined in studies linking plasma levels and tumor markers in tissue.

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**Table 1**

Characteristics of prostate cancer cases in the Health Professionals Follow-up Study, 1993–2004

| | |
|---|---|
| Total number of cases, n (%) | 1331 (100.0) |
| Sampling period, n (%) | |
| Blood draw (1993–1995) to 1996 | 208 (15.6) |
| 1996 to 1998 | 257 (19.3) |
| 1998 to 2000 | 236 (17.7) |
| 2000 to 2004 | 630 (47.3) |
| Gleason score on diagnostic biopsy, n (%) | |
| 2,3 or 4 | 75 (5.6) |
| 5 or 6 | 706 (53.0) |
| 7 | 277 (20.8) |
| 8,9 or 10 | 100 (7.5) |
| Gleason score on radical prostatectomy specimen, n (%[1]) | |
| 2,3,4 | 13 (2.3) |
| 5,6 | 243 (42.6) |
| 7 | 257 (45.0) |
| 8,9,10 | 56 (10.1) |
| TNM stage at diagnosis, n (%) | |
| T1b or T1c, N0, M0 | 167 (12.5) |
| T2 or T3a, N0, M0 | 825 (62.0) |
| T3b or T4, N0, M0 | 34 (2.6) |
| N1, M0 | 15 (1.1) |
| M1 (N0 or N1) | 11 (0.8) |
| M1 and N1 | 4 (0.3) |
| Metastases reported over follow-up, n[2] (%) | 37 (2.8) |
| Fatal prostate cancer, n (%) | 78 (5.9) |
| Year of diagnosis, median (inter-quartile range) | 2000 (1997–2002) |
| Age at diagnosis, years, median (inter-quartile range) | 65 (70–75) |
| PSA at diagnosis, ng/mL, median (inter-quartile range) | 6.8 (5.0–10.4) |

Percentage does not always sum up to 100% due to missing information

[1] % relative to all radical prostatectomy specimens

[2] Only cases who were not M1 at diagnosis

**Table 2**

Mean plasma IGF-1 and IGFBP-3 concentrations in prostate cancer cases and matched controls nested in the Health Professionals Follow-up Study, 1993–2004

| | Controls (n=1331) | All prostate cancer cases (n=1331) | | | Cases with Gleason grade <7 (n=635) | | | Cases with Gleason grade ≥7 (n=515) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | p[a] | p[b] | Mean (SD) | p[a] | p[b] | Mean (SD) | p[a] | p[b] |
| IGF-1 (ng/mL) | 197.0 (61.5) | 205.0 (62.1) | 0.0001 | 0.02 | 206.6 (62.4) | 0.0001 | 0.02 | 200.2 (59.9) | 0.26 | 0.99 |
| IGFBP-3 (ng/mL) | 3536.9 (971.3) | 3632.6 (942.2) | 0.001 | 0.44 | 3661.6 (965.3) | 0.002 | 0.51 | 3606.4 (920.9) | 0.01 | 0.09 |
| Molar ratio of IGF-1 to IGFBP-3 | 0.22 (0.05) | 0.22 (0.05) | 0.23 | | 0.22 (0.05) | 0.09 | | 0.22 (0.05) | 0.34 | |

SD=Standard deviation

[a] paired t-test comparing cases with matched controls

[b] mutually adjusted using generalized estimating equations comparing cases with matched controls

**Table 3**

Association between plasma IGF-1 and IGFBP-3 concentrations and prostate cancer among 1331 cases and 1331 matched controls nested in the Health Professionals Follow-up Study, 1993–2004

| | Cases/Controls | OR1 | 95% CI | OR2 | 95% CI |
|---|---|---|---|---|---|
| IGF-1 | | | | | |
| Quartile 1 | 289/332 | 1 | | 1 | |
| Quartile 2 | 293/333 | 1.02 | (0.82–1.28) | 0.91 | (0.72–1.16) |
| Quartile 3 | 364/336 | 1.26 | (1.02–1.57) | 1.08 | (0.84–1.39) |
| Quartile 4 | 385/330 | 1.41 | (1.12–1.78) | 1.23 | (0.92–1.64) |
| p-trend | | | 0.001 | | 0.06 |
| per standard deviation | | 1.18 | (1.08–1.28) | 1.11 | (1.00–1.24) |
| IGFBP-3 | | | | | |
| Quartile 1 | 245/335 | 1 | | 1 | |
| Quartile 2 | 381/331 | 1.63 | (1.29–2.05) | 1.59 | (1.24–2.04) |
| Quartile 3 | 343/333 | 1.45 | (1.15–1.82) | 1.33 | (1.02–1.73) |
| Quartile 4 | 362/332 | 1.58 | (1.24–2.01) | 1.37 | (1.02–1.85) |
| p-trend | | | 0.003 | | 0.22 |
| per standard deviation | | 1.13 | (0.92–1.39) | 1.04 | (0.94–1.16) |
| Molar ratio of IGF-1 to IGFBP-3 | | | | | |
| Quartile 1 | 304/335 | 1 | | | |
| Quartile 2 | 324/333 | 1.08 | (0.87–1.35) | | |
| Quartile 3 | 377/335 | 1.27 | (1.01–1.58) | | |
| Quartile 4 | 326/328 | 1.12 | (0.89–1.40) | | |
| p-trend | | | 0.21 | | |
| per standard deviation | | 1.05 | (0.97–1.14) | | |

OR[1]=odds ratio estimated from conditional logistic regression

OR[2]=odds ratio estimated from conditional logistic regression with mutual adjustment for IGF-1 and IGFBP-3

Quartile cutpoints for batch 1 were: IGF-1 129.49, 168.94, 210.22 (ng/mL); IGFBP-3 2428.70, 2824.92, 3342.95 (ng/mL); molar ratio of IGF-1 to IGFBP-3 0.20, 0.22, 0.27

Quartile cutpoints for batch 2 were: IGF-1 138.02, 168.34, 204.79 (ng/mL); IGFBP-3 2376.43, 2940.46, 3384.96 (ng/mL); molar ratio of IGF-1 to IGFBP-3 0.20, 0.24, 0.27

Quartile cutpoints for batch 3 were: IGF-1 153.76, 181.94, 225.25 (ng/mL); IGFBP-3 3683.95, 4292.25, 4793.19 (ng/mL); molar ratio of IGF-1 to IGFBP-3 0.15, 0.17, 0.19

Quartile cutpoints for batch 4 were: IGF-1 176.29, 210.19, 256.10 (ng/mL); IGFBP-3 3107.43,3690.74, 4283.49 (ng/mL); molar ratio of IGF-1 to IGFBP-3 0.19, 0.22,0.26

**Table 4**

Association between plasma IGF-1 and IGFBP-3 and subgroups of prostate cancer among prostate cancer cases and matched controls nested in the Health Professionals Follow-up Study, 1993–2004

| | Cases/Controls | OR[1] | 95% CI | Cases/Controls | OR[1] | 95% CI | p[2] |
|---|---|---|---|---|---|---|---|
| | Gleason grade < 7 | | | Gleason grade ≥7 | | | |
| IGF-1 | | | | | | | |
| Quartile 1 | 129/171 | 1 | | 115/122 | 1 | | |
| Quartile 2 | 136/152 | 1.17 | (0.85–1.63) | 110/125 | 0.95 | (0.66–1.38) | |
| Quartile 3 | 188/155 | 1.61 | (1.18–2.20) | 136/137 | 1.07 | (0.74–1.53) | |
| Quartile 4 | 182/157 | 1.61 | (1.16–2.25) | 154/131 | 1.29 | (0.89–1.88) | |
| p-trend | | | 0.001 | | | 0.12 | |
| per standard deviation | | 1.27 | (1.12–1.44) | | 1.08 | (0.94–1.23) | 0.08 |
| per standard deviation[3] | | 1.19 | (1.03–1.39) | | 0.94 | (0.80–1.12) | 0.04 |
| | Organ confined | | | Advanced/fatal over follow-up | | | |
| IGF-1 | | | | | | | |
| Quartile 1 | 218/252 | 1 | | 42/40 | 1 | | |
| Quartile 2 | 216/241 | 1.04 | (0.80–1.35) | 29/40 | 0.69 | (0.36–1.32) | |
| Quartile 3 | 273/252 | 1.26 | (0.98–1.62) | 45/39 | 1.16 | (0.62–2.18) | |
| Quartile 4 | 285/247 | 1.38 | (1.06–1.79) | 30/27 | 1.10 | (0.53–2.30) | |
| p-trend | | | 0.01 | | | 0.56 | |
| per standard deviation | | 1.17 | (1.07–1.29) | | 1.13 | (0.86–1.49) | 0.80 |
| per standard deviation[3] | | 1.08 | (0.96–1.22) | | 1.08 | (0.76–1.53) | 0.98 |

OR[1]=odds ratio estimated from conditional logistic regression

p[2]=p-heterogeneity

[3]mutually adjusted for IGFBP-3