Plasma insulin-like growth factor-1 and binding protein-3 and subsequent risk of prostate cancer in the PSA era

Elizabeth A. Platz1*, Michael N. Pollak2, Michael F. Leitzmann3, Meir J. Stampfer4, Walter C. Willett4 & Edward Giovannucci4

1Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health; and the Brady Urological Institute and the Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, MD; 2Cancer Prevention Research Unit, Departments of Medicine and Oncology, Jewish General Hospital and McGill University, Montreal, Canada; 3Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD USA; 4Departments of Nutrition and Epidemiology, Harvard School of Public Health, and the Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham & Women's Hospital, Boston, MA

Received 13 May 2004; accepted in revised form 20 September 2004

Key words: cohort study, insulin-like growth factor, prostate cancer, risk.

Abstract

Objective: The insulin-like growth factor (IGF) axis is thought to contribute to the growth and progression of prostate cancer. Some prospective studies support a direct association between IGF-1 and prostate cancer, in particular advanced disease, whereas both inverse and direct associations with prostate cancer have been reported for insulin-like growth factor binding protein-3 (IGFBP-3), the major IGF-1 binding protein in circulation. We prospectively investigated the associations of plasma IGF-1 and IGFBP-3 concentrations with prostate cancer detected in the PSA era.

Methods: We identified 462 prostate cancer cases diagnosed after providing a blood specimen in 1993, but before January 1998 among men in the Health Professionals Follow-up Study. Controls were 462 age-matched men without prostate cancer who had had a PSA test after providing a blood specimen. We measured plasma concentrations of IGF-1 and IGFBP-3 by ELISA. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) of prostate cancer.

Results: Men with higher concentrations of IGF-1 (comparing extreme quartiles OR = 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) had a higher risk of prostate cancer. After mutual statistical adjustment, these associations were attenuated for both IGF-1 (OR = 1.17, 95% CI 0.69–1.99, p-trend = 0.29) and IGFBP-3 (OR = 1.40, 95% CI 0.80–2.44, p-trend = 0.56). We found no significant association of IGF-1 with regionally invasive or metastatic (≥T3b, N1, or M1) prostate cancer, although the number of these cases was small (n = 42).

Conclusions: Our findings for IGF-1 and prostate cancer diagnosed in the PSA era are similar to most previous studies, albeit weaker in magnitude. Our suggestive positive findings for IGFBP-3 are similar to some studies, but in direct contrast to others.

Introduction

Insulin-like growth factor-1 (IGF-1) may contribute to the growth and progression of prostate cancer via the promotion of proliferation and the inhibition of apoptosis, as demonstrated in vitro in normal and prostate cancer cells [1, 2]. IGF-1 is mainly produced in the
liver, but also in other tissues, including in the prostate. Most circulating IGF-1 is bound to IGF binding protein (IGFBP)-3. In the prostate, IGFBP-3 promotes apoptosis [3] by interactions with the retinoid X receptor [4].

Several previous epidemiologic studies reported that circulating concentration of IGF-1 measured in mid-life is associated with a higher risk of prostate cancer [5–12]. One prospective US study observed associations for advanced disease and cases diagnosed in the era prior to the routine screening for elevated PSA, but not for early stage cases or cases diagnosed in the PSA era [13], whereas a Swedish prospective study observed an association for IGF-1 and IGFBP-3 among men overall, with advanced disease, and with early stage disease, although more weakly so [12]. Although IGFBP-3 would be predicted to decrease the risk of prostate cancer by limiting the bioavailability of IGF-1 and independently of IGF-1 by promoting apoptosis, both inverse and direct associations with prostate cancer have been reported [14]. However, when IGFBP-3 concentration was statistically adjusted for IGF-1 concentration, in several studies an inverse association was suggested overall [6, 9, 11, 13] or at least in a subset of men [8].

With the widespread adoption of PSA testing in the US, the nature of diagnosed prostate cancer has shifted to largely small volume, organ-confined disease. Whether these early stage cases are susceptible to the growth and anti-apoptotic effects of IGF-1 and the apoptotic effects of IGFBP-3 is unknown. Thus, to address whether the IGF-axis is associated with risk of prostate cancer by limiting the bioavailability of IGF-1 and independently of IGF-1 by promoting apoptosis, both inverse and direct associations with prostate cancer have been reported [14]. However, when IGFBP-3 concentration was statistically adjusted for IGF-1 concentration, in several studies an inverse association was suggested overall [6, 9, 11, 13] or at least in a subset of men [8].

Materials and methods

Study population

Incident prostate cancer cases and matched controls were selected from among participants in the prospective Health Professionals Follow-up Study. At enrollment in 1986, the 51,529 US men were aged 40–75 years. At baseline and then biennially the participants responded to a mailed questionnaire that included questions on demographics, lifestyle, and medical history. At baseline and then every four years they completed a semi-quantitative food frequency questionnaire. Deaths among cohort members were identified by reports from next-of-kin, the postal service, or searches of the National Death Index [15].

Between 1993 and 1995, 18,018 of the men provided a blood specimen, which was collected in tubes containing sodium EDTA and was shipped by overnight courier while chilled. After centrifuging and aliquoting into plasma, erythrocytes, and buffy coat, the samples were stored in liquid nitrogen freezers. Among the men who provided a blood specimen, 94.6% responded to the 1998 questionnaire and 3.5% died before the end of follow-up. We excluded from the analysis men with a cancer diagnosis (except non-melanoma skin cancer) that preceded the date that a blood sample was provided. This study was approved by the Human Subjects Committee at the Harvard School of Public Health.

Prostate cancer cases and controls

After receiving written permission from a participant who reported a prostate cancer diagnosis on a follow-up questionnaire, or from the next-of-kin of decedents, we sought medical and pathology records. Study investigators blinded to information from the questionnaire reviewed these records to confirm the diagnosis and to abstract stage at diagnosis and Gleason sum. Diagnosis records were not obtained for 7.1% of the men who provided a blood specimen and who reported prostate cancer, but we included these unconfirmed diagnoses as cases because we found that the reporting of a prostate cancer diagnosis by these health professionals was accurate. We excluded as cases men with T1a disease (i.e., incidental microscopic focal tumors) to avoid detection bias due to differential rates of surgery for benign prostatic hyperplasia. Cases were classified as regionally invasive or metastatic (T3b, N1, or M1), organ/confined or minimal extraprostatic extension (T1b to T3a and N0M0), Gleason sum ≥7, and Gleason sum <7. We confirmed 462 non-T1a prostate cancer cases between the date that a blood specimen was provided and January 31, 1998, the end of follow-up for this analysis.

Eligible controls were men still alive at the date of the case’s diagnosis, who did not have a diagnosis of cancer, and who had had a PSA test after the date of blood draw (opportunity for prostate cancer detection). 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).