History of diabetes, clinical features of prostate cancer, and prostate cancer recurrence—data from CaPSURE™ (United States)

J.M. Chan1,2,*, D.M. Latini1,2, J. Cowan1,2, J. DuChane1,2, & P.R. Carroll1,2
1Department of Urology, University of California, San Francisco, USA; 2Department of Epidemiology and Biostatistics, University of California, San Francisco

Received 15 December 2004; accepted in revised form 8 March 2005

Key words: diabetes, prostate cancer, risk group.

Abstract

Objectives: There is a growing epidemiologic literature suggesting an inverse association between history of diabetes and risk of incident prostate cancer. To our knowledge, the relationship between diabetes and tumor features and risk of recurrence among men with prostate cancer has not been examined previously. We hypothesized that men with diabetes would present with more favorable prostate cancer and experience lower risk of recurrence.

Methods: We identified 691 men with diabetes at the time of prostate cancer diagnosis, among 6722 men diagnosed with prostate cancer in 1989 to 2002 within CaPSURE™, a community-based prostate cancer registry study. We compared clinical and socio-demographic variables by diabetes status, using χ² tests, t-tests, and multinomial logistic regression. We examined recurrence rates for prostate cancer among patients with and without diabetes using Kaplan–Meier log-rank tests and Cox proportional hazard models.

Results: In multivariate analyses, history of diabetes was not associated with any diagnostic clinical parameter, and treatment-specific recurrence rates for prostate cancer generally did not differ by diabetes history. Among men with low-prognostic risk or who were younger at prostate cancer diagnosis, being diabetic (versus not) was associated with an elevated risk of recurrence after radiation therapy, in multivariate analyses.

Conclusions: Contrary to data suggesting that diabetes may be modestly protective against risk of incident prostate cancer, we did not observe any evidence of an inverse association between history of diabetes and aggressiveness at diagnosis or risk of recurrence, in this population of men with prostate cancer.

Introduction

In the epidemiologic literature, there is growing evidence supporting an inverse association between a history of diabetes and subsequent risk of developing prostate cancer. This is in contrast to other reports indicating that history of diabetes is generally associated with greater risk of other cancers or total cancer [1, 2]. Novas et al. recently published a meta-analysis of 14 studies published between 1971 and 2002, examining the association between diabetes and the likelihood of developing prostate cancer [1,23]. They reported a statistically significant modest inverse association of 0.91 (95% confidence interval 0.86–0.96) for history of diabetes mellitus and subsequent risk of prostate cancer; they reported that they found no evidence of publication bias or heterogeneity. Two cohorts and one case–control study, published since that meta-analysis, each observed statistically significant reductions in risk of developing prostate cancer of approximately 35%, associated with prior history of diabetes [4–6].

Potential explanations underlying this inverse association include (1) detection bias, whereby men with diabetes are screened less for prostate cancer due to focus on their diabetes or related comorbidities; (2) uncontrolled confounding, whereby unmeasured characteristics of men with diabetes are inversely associated with prostate cancer; (3) linkage between diabetes promoting genes and prostate cancer suppressing genes; (4) a direct...
effect of diabetes medications or diets on suppressing or delaying prostate cancer development; (5) a direct effect of insulin resistance or metabolism on suppressing prostate cancer initiation or promotion. A few large prospective studies have also observed an inverse association with greater time since diabetes diagnosis and the risk of incident prostate cancer [5–7]. Assuming there is a biological association, we hypothesized that men with a history of diabetes would present with less aggressive tumor features at diagnosis and experience a lower risk of recurrence compared to those without diabetes. To our knowledge, this has not been studied previously.

We examined the association of clinical and socio-demographic variables and history of diabetes, and diabetes as a predictor of treatment-specific (surgery or radiation) recurrence risk in a large cohort of men with prostate cancer from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE™).

Materials and methods

CaPSURE™

As of July 2003, a total of 10,018 men have ever-enrolled in CaPSURE™. Study specifics have been published previously [8]. In brief, this registry study started in 1995 to examine clinical outcomes, health related quality of life, and use of health care services in men with prostate cancer. There are currently 31 enrolling urologic practice sites across the country. Initially, all men with biopsy-proven prostate cancer were invited to join regardless of stage of disease or treatment plan. Since 1999, the majority of patients (99%) have entered the study within one year of diagnosis and prior to initial treatment. Detailed data on PSA levels, biopsy and pathologic Gleason score, TNM stage, treatments, medications, and clinic procedures are recorded whenever the patient visits the clinic. At study entry, patients complete a baseline questionnaire providing information on demographics, comorbid conditions, and health-related quality of life. Patients complete follow-up questionnaires every six months thereafter, focused on health-related quality of life and utilization of healthcare services, including emergency visits, outpatient procedures, radiology and diagnostic tests, physician consultations, medications, hospitalizations, and use of complementary and alternative medicine. Written consent was obtained from all participants, and this study was approved by the Institutional Review Boards of the University of California San Francisco and enrolling sites.

Clinical variables and definitions

Prior history of diabetes was assessed from the baseline questionnaire that asked about individual comorbid conditions, including a specific question on diabetes. We used body mass index to classify participants as normal (<25 kg/m²), over-weight (25–29.9 kg/m²), and obese (≥30.0 kg/m²). Prognostic risk groups at diagnosis were considered in the analyses, in addition to the individual diagnostic clinical characteristics. We used the D’Amico classification as follows: low risk = T1 – T2a, PSA ≤ 10 ng/ml, and Gleason grade <7 (no Gleason pattern 4–5 disease); intermediate risk = T2b, T2c, or PSA 10.1–20 ng/ml or Gleason grade = 7 or secondary 4–5 pattern; and high risk = T3–4 or PSA > 20 ng/ml or Gleason grade 8–10 or primary 4–5 pattern [9]. These risk groups reflect the subsequent risk of biochemical recurrence for surgery and radiation patients.

Treatment-specific recurrence outcomes were defined as follows: (1) for men undergoing radical prostatectomy as the primary therapy, recurrence was defined as two or more consecutive post-treatment PSA values of 0.2 ng/ml or greater, or initiation of a second treatment at least six months after surgery [10, 11], (2) for men undergoing radiation therapy (external beam or brachytherapy), recurrence was defined as three or more consecutive follow-up PSA tests above the post-treatment nadir, or initiation of second treatment at or after six months of the first treatment [12]. In the prospective recurrence analysis, men were considered diabetic when they reported a history of diabetes on the baseline questionnaire or self-reported use of diabetic medications, related devices, or related office visits in a follow-up survey. Reported diabetes medications were insulin and over 40 different oral medications including Glucophage, Glyburide, Actos, Metformin, and Avandia.

Statistical analysis

To be included in analysis, men had to have one of the above primary treatments and be diagnosed with prostate cancer between 1989 and 2002; for the recurrence analyses, they also and to have complete data on their initial clinical diagnostic tumor features. We compared baseline socio-demographic and tumor characteristics and treatment patterns among 6722 prostate cancer patients with and without diabetes using χ² and t-test methods. We used multinomial logistic regression with a backward stepwise selection process to examine multivariate associations, where diabetes status was the binary outcome, and socio-demographic and clinical variables were the potential predictors. A 0.05