Cancer Specific Mortality in Men Diagnosed with Prostate Cancer before Age 50 Years: A Nationwide Population Based Study

Andreas Thorstenson, Hans Garmo, Jan Adolfsson and Ola Bratt*

From the Section of Urology, Department of Molecular Medicine and Surgery (AT) and Department of Clinical Sciences, Interventions and Technology (JA), Karolinska Institute, Stockholm, Regional Cancer Centre (HG), Uppsala Örebro, Uppsala and Division of Urological Cancer, Department of Translational Medicine, Lund University (OB), Lund, Sweden, and Surgical Intervention Trials Unit, Nuffield Department of Surgical Sciences, University of Oxford (AT), Oxford, Cancer Epidemiology Group, Division of Cancer Studies, School of Medicine, King's College London (HG), London and CamPARI Clinic, Department of Urology, Cambridge University Hospitals (OB), Cambridge, United Kingdom

Purpose: We compared clinical characteristics and cancer specific mortality in men diagnosed with prostate cancer before vs after age 50 years.

Materials and Methods: A total of 919 men 35 to 49 years old and 45,098 men 50 to 66 years old who were diagnosed with prostate cancer between 1998 and 2012 were identified in PCBaSe (Prostate Cancer data Base Sweden). Cancer specific mortality was compared among age groups (35 to 49, 50 to 59, 60 to 63 and 64 to 66 years) with and without adjusting for cancer characteristics, comorbidity and education in a multivariable Cox proportional hazards model.

Results: Clinical cancer characteristics indicated that most nonmetastatic cancer in men younger than 50 years was detected after prostate specific antigen testing. The proportion of nonmetastatic vs metastatic disease at diagnosis was similar in all age groups. A strong association between younger age and poor prognosis was apparent in men in whom metastatic disease was diagnosed before age 50 to 55 years. The crude and adjusted HRs of cancer specific mortality were 1.41 (95% CI 1.12–1.79) and 1.28 (95% CI 1.01–1.62) in men diagnosed before age 50 and at age 50 to 59 years, respectively. In men with nonmetastatic disease crude cancer specific mortality increased with older age but adjusted cancer specific mortality was similar in all age groups.

Conclusions: Our findings suggest that an aggressive form of metastatic prostate cancer is particularly common in men younger than 50 to 55 years. Genetic studies and trials of intensified systemic treatment are warranted in this patient group.

Key Words: prostatic neoplasms, neoplasm metastasis, mortality, prognosis, age groups

Abbreviations and Acronyms

CCI = Charlson comorbidity index

NPCR = National Prostate Cancer Register of Sweden

PSA = prostate specific antigen

Accepted for publication June 10, 2016.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by Swedish Research Council PCBaSe Project 825-2012-5047, Swedish Cancer Society Grant 2012/475 (OB), Capio St. Görans Hospital, the Percy Falk Foundation, Prostatacancerförbundet and Stockholm Cancer Society.

* Correspondence: Department of Urology, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge CB2 0QQ, United Kingdom (telephone: +44-70982900043; e-mail: ola.bratt@med.lu.se).

Only around 1% of men with prostate cancer are younger than 50 years at diagnosis.[1,2] In 1972 the first report was published that suggested a worse prognosis in men diagnosed with prostate cancer before age 50 years.[3] This report has been followed by many others with similar results. A review article on age as a prognostic factor for prostate cancer concluded that prostate cancer diagnosed before age 45 to 55 years may be associated with a more aggressive phenotype than prostate cancer diagnosed in older men.[4] Possible explanations for the worse prognosis in the youngest

0022-5347/17/1971-0061/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2016.06.080
Vol. 197, 61-66, January 2017
Printed in U.S.A.

age group included germline mutations predisposing to aggressive prostate cancer, which are more common in younger than older men with prostate cancer, as well as lead time and duration bias.

However, most studies supporting the hypothesis that early onset prostate cancer is biologically different from later onset prostate cancer mainly included patients before or in the early phase of PSA testing, which is now widespread. Therefore, little is known about the current prognostic significance of young age at diagnosis of prostate cancer.

We used contemporary, nationwide, population based data to analyze whether clinical characteristics and cancer specific mortality in men diagnosed with prostate cancer before age 50 years differ from those in men who were older (50 to 66 years) at the time of diagnosis.

MATERIALS AND METHODS

Study Population and Data Collection

Men diagnosed with prostate cancer between January 1, 1998 and December 31, 2012 were identified in PCBaSe 3.0. The PCBaSe project was approved by the ethics review board at Umeå University. PCBaSe includes all data in NPCR, which captures 98% of prostate cancer cases in the Swedish Cancer Registry,[5] to which registration is mandated by law. NPCR includes data on TNM classification, cancer pattern, date of diagnosis, method of diagnosis, PSA at diagnosis and primary treatment. Conservative management was documented as watchful waiting until the end of 2007. It has been recorded as watchful waiting or active surveillance since January 2008.

We included all men between 35 and 66 years old at diagnosis in the current study. Men diagnosed before age 50 years were compared with men diagnosed between ages 50 and 66 years. Men 50 to 66 years old were divided into 3 age groups of similar size to allow for an assessment of nonlinear trends, including 50 to 59, 60 to 63 and 64 to 66 years. The upper age limit was chosen because diagnostic and therapeutic activities are increasingly affected by the shorter life expectancy of men older than 65 to 70 years.

Data on cancer characteristics, comorbidity and education were retrieved from PCBaSe as previously described.[6] Risk group classification included 1) nonmetastatic low risk—T1-2, N0/X, M0/X, Gleason 6 or less and PSA less than 10 ng/ml, 2) nonmetastatic intermediate risk—T1-2, N0/X, M0/X, Gleason 7 and/or PSA 10 to 19 ng/ml, 3) nonmetastatic high risk—T3-4, N0/X, M0/X, and/or Gleason 8-10, and/or PSA 20 to 49 ng/ml, and 4) metastatic—T4 and/or N1, and/or M1, and/or PSA greater than 50 ng/ml. Cancer in 1.5% of the men was graded according to the WHO grading system. This grade was converted to Gleason score, including grade 1—Gleason score 2-6, grade 2—Gleason score 7 and grade 3—Gleason score 8-10.

CCI was determined by grouping ICD codes from the discharge diagnoses in the inpatient register, as described previously.[6] The prostate cancer diagnosis was not included in CCI. LISA (Longitudinal Database on Socioeconomic Factors) was the source for data on education. Education was categorized as up to 9 years (primary school), more than 9 to 12 years (secondary school) or more than 12 years (university level). The information in PCBaSe on underlying and contributing causes, and date of death is obtained from the Cause of Death Register, which captures all deaths in Sweden. Followup was considered from the date of prostate cancer diagnosis to death, emigration or December 31, 2012, whichever was first.

Statistical Analysis

Multivariable Cox proportional hazard models were calculated with the 95% CI. The group of men diagnosed with prostate cancer at age 50 to 59 years served as the referent. The variables included were CCI (0, 1, 2 and 3 or greater), educational level, T stage, N stage, M stage, PSA, Gleason score, interaction between PSA and Gleason score, and mode of detection (health checkup, lower urinary tract symptoms, other symptoms or other reason). The model used a linear spline with knots at PSA 3, 10 and 20 ng/ml. The MICE (Multivariate Imputation by Chained Equations) algorithm was used for missing data. Men were censored in the model at the end of followup, at emigration and at death from another cause.

Cumulative incidences were used to assess the cause specific and other cause mortality (fig. 1).[7] Mortality was also calculated as the cumulative incidence of prostate cancer death for each specific age in 1-year classes and smoothed using locally weighted polynomial regression (fig. 2).[8] Statistical analysis was performed with R, version 3.0.1 (https://www.r-project.org/foundation/).

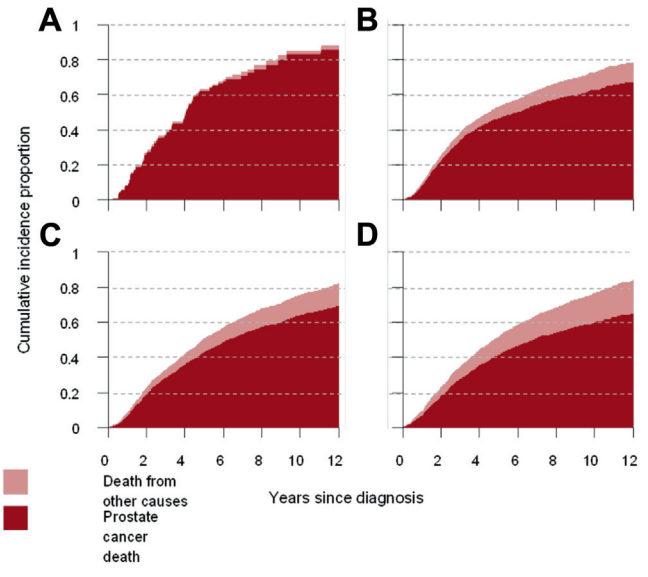

Figure 1. Stacked cumulative cancer specific and other cause mortality in men diagnosed with metastatic prostate cancer, defined as T4 and/or N1, and/or M1, and/or PSA greater than 50 ng/ml. *A*, age at diagnosis 35 to 49 years. *B*, age at diagnosis 50 to 59 years. *C*, age at diagnosis 60 to 63 years. *D*, age at diagnosis 64 to 66 years.