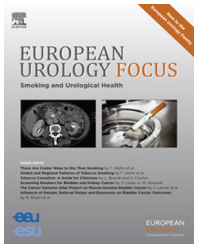
available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus



Platinum Priority – Prostatic Disease
Editorial by XXX on pp. x–y of this issue

Statin Use and Prostate Cancer Survival in the Finnish Randomized Study of Screening for Prostate Cancer

Teemu J. Murtola [a,b,†,*], *Antti I. Peltomaa* [a,†], *Kirsi Talala* [a], *Liisa Määttänen* [c], *Kimmo Taari* [d], *Teuvo L.J. Tammela* [a,b], *Anssi Auvinen* [e]

[a] *School of Medicine, University of Tampere, Tampere, Finland;* [b] *Department of Urology, Tampere University Hospital, Tampere, Finland;* [c] *Finnish Cancer Registry, Helsinki, Finland;* [d] *Department of Urology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;* [e] *School of Health Sciences, University of Tampere, Tampere, Finland*

Article info

Article history:
Accepted May 18, 2016

Associate Editor:
James Catto

Keywords:
Prostate cancer
Mortality
Statins

Abstract

Background: Recent research has suggested that statins have an effect on prostate cancer prognosis. It is currently unclear how prostate cancer screening, tumor and patient characteristics, or treatment selection may affect this association.
Objective: To evaluate the risk of prostate cancer death among statin users. To determine how disease and treatment characteristics affect the association.
Design, setting, and participants: This is a population-based cohort study consisting of a general male population of Finland participating in the Finnish Randomized Study for Prostate Cancer Screening. The cohort of consisted of 6537 prostate cancer cases diagnosed in the Finnish Randomized Study of Screening for Prostate Cancer population during 1996–2012. The cohort was linked to the National Prescription Database for information on the use of statins and other drugs.
Intervention: Statin use before and after prostate cancer diagnosis compared with nonuse.
Outcome measurements and statistical analysis: Hazard ratios (HRs) for the risk of prostate cancer death by amount, duration, and intensity of statin use. Cox proportional hazards regression with postdiagnostic statin use as a time-dependent variable.
Results: During the median follow-up of 7.5 yr postdiagnosis 617 men died of prostate cancer. Statin use after diagnosis was associated with a decreased risk of prostate cancer death (HR 0.80; 95% confidence interval 0.65–0.98). A decreasing risk trend was observed by increasing intensity of usage (doses/year). The risk decrease was clearest in men managed with androgen deprivation therapy. Prediagnostic statin use was not associated with risk of prostate cancer death (HR 0.92; 95% confidence interval 0.75–1.12).
Conclusions: Decreased risk of prostate cancer death by statin use after diagnosis suggests that statins may delay or prevent prostate cancer progression. The risk decrease was significant only in men managed with androgen deprivation therapy, but statistical power was limited to estimate the association in men managed with surgery or radiotherapy.
Patient summary: Use of statins after prostate cancer diagnosis was associated with a decreased risk of prostate cancer death. The risk decrease was dose-dependent and observed especially among patients treated with hormone therapy.

† These authors contributed equally.
* Corresponding author. Department of Urology, Tampere University Hospital, Teiskontie 35, M-building, 3rd Floor, Room 313, PL 2000, Tampere 33521, Finland. Tel. +358 3 311 65015; Fax: +358 3 311 64358.
E-mail address: teemu.murtola@uta.fi (T.J. Murtola).

http://dx.doi.org/10.1016/j.euf.2016.05.004

1. Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are well established in the treatment and prevention of cardiovascular disease. Recent research has linked statin usage with a decreased risk of advanced prostate cancer [1,2], improved recurrence-free survival after radical treatment [3], and lowered prostate cancer mortality [4–8]. However, not all studies agree [9,10]. It is currently unclear how prostate cancer screening, tumor and patient characteristics, treatment selection or timing, and dosing of statin use may affect this association.

We evaluated the risk of prostate cancer death among statin users in a cohort of prostate cancer cases from the Finnish Randomized Study for Prostate Cancer Screening, with a prespecified hypothesis that statins would be associated with a lowered risk.

2. Materials and methods

2.1. Study cohort

Finnish Randomized Study of Screening for Prostate Cancer is a randomized population-based trial evaluating whether systematic prostate-specific antigen (PSA)-based screening reduces prostate cancer mortality [11]. In 1996–1999, all 55–67-yr-old men residing in the metropolitan areas of Helsinki or Tampere (80 458 men) were identified from the Finnish Population Register Center. After excluding prevalent prostate cancer cases, 80 144 men were randomized either to be invited for PSA screening at 4-yr intervals (31 866 men, the screening arm), or to the control arm without any intervention (48 278 men).

2.2. Sources and categorization of clinical data

Information on prostate cancer TNM stage, Gleason score, and primary treatment (radical prostatectomy, external beam radiotherapy, brachytherapy, androgen deprivation therapy [ADT], or observation) were retrieved from hospital records [11], and diagnoses registered by the Care Registers for Social Welfare and Health Care maintained by the National Institute for Health and Welfare. The total number of prostate cancer cases diagnosed between 1996 and 2012 was 6537.

Cases with missing information in any of the variables were included in the analysis as a separate group. Prostate cancer cases were categorized into high- and low-risk according to European Association of Urology guidelines: cases with PSA at diagnosis 20 ng/ml or lower, T1–T2b, and Gleason 7 or less were considered as low/medium risk, whereas cases with PSA above 20 ng/ml, Gleason 8-10, T2c–T4, and all N+ cases were considered as high-risk cases [12].

2.3. Definition for prostate cancer death

Statistics Finland registers all deaths that occur in Finland. The registry has used the 10th revision of the International Classification of Diseases-10 since 1996. The causes for all deaths occurring between 1996 and 2003 among participants diagnosed with prostate cancer in each trial arm were validated by a cause-of-death committee [11]. Excellent concordance was found between recorded causes of death and clinical files ($\kappa = 0.95$), thus proving reliability of the cause of death registry. In this analysis deaths with prostate cancer (International Classification of Diseases-10 code C61) as the primary cause of death were defined as prostate cancer deaths.

2.4. Sources of socioeconomic and laboratory data

Information on socioeconomic factors from population censuses was available from the Statistics Finland for 1444 cases (22.1% for the total cohort).

Serum cholesterol and fasting blood glucose levels at baseline were obtained for a subcohort of 1649 men (25% of the study cohort) living in the Tampere region from the laboratory database of Fimlab, the main provider of laboratory services in the Pirkanmaa region.

2.5. Information on medication use

The screening trial population was linked to the National Prescription Database maintained by the Social Insurance Institute (SII) of Finland. SII is a governmental agency providing reimbursements for physician-prescribed medication as part of the National Health Insurance [13]. For each purchase of a prescription drug approved by the SII (most prescription drugs in Finland), all Finnish citizens are entitled to at least 50% reimbursement, deducted usually from the customer payment at the pharmacy.

All reimbursed drug purchases are recorded by the SII prescription database since 1995. The recorded information includes the date, anatomical therapeutic chemical code, product number, and the number of packages for each drug purchase. The product number was used to determine drug strength and number of pills for each purchase.

We obtained information on all cholesterol-lowering drugs (statins, fibrates, bile-acid binding resins, ezetimibe, and acipimox), antidiabetic drugs (both oral drugs and insulins), antihypertensive drugs, nonsteroidal anti-inflammatory drugs including aspirin and drugs used in the treatment of benign prostatic hyperplasia (α-blockers and 5α-reductase inhibitors) for 1995–2009.

2.6. Categorization of the exposure variable

We standardized the daily dose between statins using the defined daily doses listed by World Health Organization [14]. The yearly cumulative milligram amount of statin purchases was divided by 1 defined daily dose for the yearly amount of usage. Each year with recorded statin purchases was considered as year of usage. Duration of usage was the cumulative number of years of usage. Intensity of statin use was further calculated by dividing the yearly amount of statin use with the number of years of usage.

2.7. Statistical analysis

The analysis was limited to prostate cancer cases. Separate analyses were performed to evaluate the impact of medication use before and after prostate cancer diagnosis.

Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CI) for risk of prostate cancer death by medication use. The regression model was adjusted for age only, and additionally for tumor Gleason score, tumor stage (M1 tumors vs localized tumor), PSA level at diagnosis, usage of other drugs (antidiabetic drugs, antihypertensive drugs, aspirin, and other nonsteroidal anti-inflammatory drugs, α-blockers, and 5α-reductase inhibitors), and the screening trial arm (multivariable-adjusted model). Nonusers were used as the comparison group. Follow-up started at the date of prostate cancer diagnosis (the baseline), and was continued until death, emigration, or January 1, 2013, whichever came first. The time scale was years since prostate cancer diagnosis.

The impact of prediagnostic statin use on risk of prostate cancer death was evaluated with multivariable adjusted Cox regression model with prediagnostic statin use as a time-independent variable. This analysis included statin use from 1995 until the year of prostate cancer

Please cite this article in press as: Murtola TJ, et al. Statin Use and Prostate Cancer Survival in the Finnish Randomized Study of Screening for Prostate Cancer. Eur Urol Focus (2016), http://dx.doi.org/10.1016/j.euf.2016.05.004