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

European Association of Urology

Platinum Priority – Brief Correspondence

Editorial by Carlo La Vecchia on pp. 411–412 of this issue

Finasteride Reduces Risk of Bladder Cancer in a Large Prospective Screening Study

Edwin E. Morales [a], *Sonja Grill* [b], *Robert S. Svatek* [a], *Dharam Kaushik* [a], *Ian M. Thompson Jr.* [a], *Donna P. Ankerst* [b], *Michael A. Liss* [a,*]

[a] *Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA;* [b] *Life Sciences Mathematics Unit, Technische Universitaet Muenchen, Munich, Germany*

Article info

Article history:
Accepted August 17, 2015

Associate Editor:
James Catto

Keywords:
Bladder cancer
Finasteride
PLCO

Abstract

The androgen receptor has been implicated in the development and progression of bladder cancer (BCa), largely based on studies of animal models. We investigated whether finasteride was associated with a reduced incidence of BCa as observed by self-report in the Prostate, Lung, Colorectal, and Ovarian cancer screening trial. Cox proportional hazard regression analysis was performed to determine the association of finasteride use with time to diagnosis of BCa, controlling for age and tobacco use. Of the 72 370 male participants who met inclusion criteria, 6069 (8.4%) had reported the use of finasteride. BCa was diagnosed in 1.07% (65 of 6069) of those who reported finasteride compared with 1.46% (966 of 66 301) of those who reported no use during the trial. In a multiple Cox regression analysis, self-reported use of finasteride was associated with a decreased risk of development of BCa (hazard ratio: 0.634; 95% confidence interval, 0.493–0.816; $p = 0.0004$), controlling for age and smoking. Limitations of this study include that it is observational and not randomized, that many of the confounding variables for BCa, such as alcohol use, were not available for use in the analysis, and that finasteride use was by annual self-report, which is subject to missing values and error.
Patient summary: Finasteride is a common medication used to reduce the size of the prostate and to promote hair growth by manipulating testosterone in men. Men are more likely than women to develop bladder cancer (BCa), but our study noted that men using finasteride were less likely to have a BCa diagnosis.

* Corresponding author. Department of Urology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, MC 7845, San Antonio, TX 78229-3900, USA. Tel. +1 210 305 6513; Fax: +1 210 567 6868.
E-mail address: Liss@uthscsa.edu (M.A. Liss).

1. Introduction

The androgen receptor (AR) has been implicated in the development and progression of urothelial cancer of the bladder, largely based on studies of animal models [1–3]. As a result, AR modulation, including androgen deprivation therapy (ADT), has been suggested as an interventional treatment in bladder cancer (BCa) [3,4]. Finasteride is a 5α-reductase inhibitor (5-ARI) that competitively inhibits the production of dihydrotestosterone, the most potent natural androgenic AR activator. To investigate the effect of finasteride on BCa, we compared the self-reported use of finasteride in subjects in the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial with the risk of BCa [5,6].

http://dx.doi.org/10.1016/j.eururo.2015.08.029
0302-2838/

2. Materials and methods

2.1. PLCO trial data

The PLCO trial was a randomized US study to determine the effect of prostate-specific antigen screening (for 6 yr) and digital rectal examination screening (for 4 yr) on prostate cancer mortality in 76 685 men with a >13-yr study follow-up [5]. BCa diagnosis was assessed at annual visits and confirmed with pathology records. Participants completed questionnaires on BCa and demographic, behavioral, and clinical risk factors including use of finasteride or another 5-ARI during the past year.

2.2. Statistical analysis

Differences in participant characteristics between finasteride users and nonusers were assessed using the Wilcoxon test for continuous measures and the chi-square test for count measures. The primary predictor was reported finasteride use on any annual questionnaire (at least 1 yr vs never), and the primary outcome was BCa diagnosis. However, cumulative years on finasteride and BCa mortality were considered as secondary predictors and outcomes, respectively. Cox proportional hazard regression analysis was performed to determine the association of finasteride use with time to diagnosis of BCa and BCa mortality, controlling for confounding factors of age, smoking status, body mass index (BMI) at baseline, race, family history of BCa, randomization arm, colon comorbidity, prostatitis, duration of time smoked cigarettes, and education. Optimal models were selected using the Bayesian Information Criterion.

To correct for observational bias in the participant selection of finasteride, we performed an additional propensity score analysis for the association of finasteride use with time to diagnosis of BCa. We first calculated propensity scores using logistic regression with use of finasteride as the outcome variable and different groups of variables as predictors. We then performed a weighted Cox proportional hazards regression using the scores as inverse weights to assess the effect of finasteride on time to BCa diagnosis. All statistical tests were performed at the two-sided 0.05 significance level, and all analyses were performed with the R statistical package (R Foundation, Vienna, Austria).

3. Results

Of the 72 370 male participants who met the inclusion criteria, 6069 (8.4%) reported use of finasteride. Table 1 shows their baseline characteristics. Patients who ever took finasteride during the study were more likely than those who never did to be older, nonsmokers, nonwhite, in the control arm of the study, have a postgraduate education, and to have prostatitis, although differences were small with significance driven by large sample sizes (all $p < 0.10$).

Based on Kaplan-Meier estimates of the empirical survival curve, the rate of men developing BCa by the end of 13 yr was 1.3% for those who reported finasteride use versus 1.8% for those who did not (log-rank test $p = 0.002$); for BCa mortality these percentages were 0.2% versus 0.3%, respectively ($p = 0.62$). In a multiple Cox regression analysis (Fig. 1), self-reported usage of finasteride was associated with a decreased risk of development of BCa with a hazard ratio (HR) of 0.634 (95% confidence interval [CI], 0.493–0.816; $p = 0.0004$), controlling for age (HR: 1.073; 95% CI, 1.060–1.085; $p < 0.0001$), former smoker (HR: 2.282; 95% CI, 1.951–2.669], and current smoker (HR: 3.634; 95% CI, 2.974–4.441; $p < 0.0001$), compared with the reference group of people who never smoked before). The HR for cumulative years of finasteride use was 0.912 per year of finasteride use (95% CI, 0.835–0.994; $p = 0.037$), adjusting for age and smoking status.

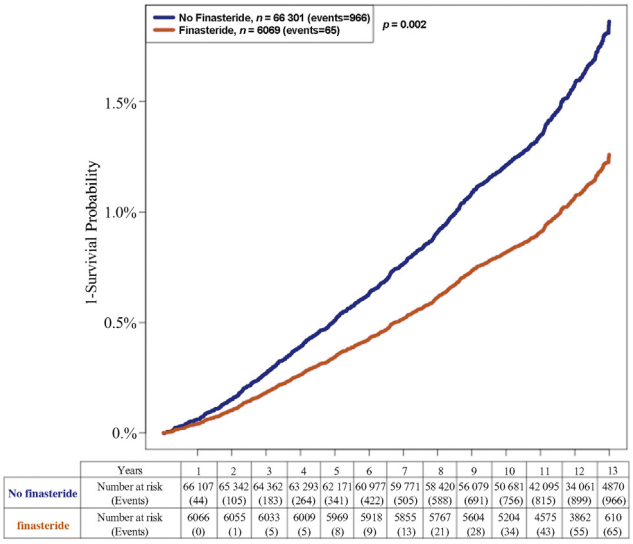

Fig. 1 – Cox regression analysis curve for bladder cancer diagnosis ($p = 0.002$).

There was no statistically significant effect of self-reported finasteride use and time to BCa mortality. In the adjusted propensity score analysis for time to BCa diagnosis, finasteride remained significantly associated with decreased BCa risk when adjusting for the same variables as in the multiple Cox regression analysis: age and smoking status (HR: 0.642 [95% CI, 0.497–0.829]; $p = 0.0007$). However, when adjusting for all variables (age, smoking status, BMI at baseline, race, family history of BCa, randomization arm, colon comorbidity, prostatitis, duration smoked cigarettes, and education), the effect of finasteride on time to BCa diagnosis was only borderline significant (HR: 0.733 [95% CI, 0.552–0.974], $p = 0.03$). A sensitivity analysis of other choices for the propensity scores gave HRs and p values within the range of these two values.

4. Discussion

Although preclinical models have suggested a potential beneficial effect of finasteride on BCa development, these data are the first from a large-scale trial to demonstrate a possible preventive/therapeutic role of finasteride for BCa.

As with any population study, significant limitations include the bias of a retrospective subset analysis. Moreover, this is an observational comparison of self-reported use of finasteride not confirmed by pill counts or prescription analysis and thus lacks any causal interpretation as could be afforded by a randomized controlled clinical trial. Other confounders may have influenced the diagnoses of BCa. A reduction in lower urinary tract symptoms and/or microscopic hematuria from finasteride use may have reduced the rate of cystoscopy. We did not observe an influence of finasteride on BCa mortality due to the few events and lack of