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Original article

Finasteride does not prevent bladder cancer: A secondary analysis of the Medical Therapy for Prostatic Symptoms Study

Niranjan J. Sathianathen, M.B.B.S.[a,b,*], Yunhua Fan, M.P.H.[a], Stephanie L. Jarosek, Ph.D.[a], Nathan L. Lawrentschuk, M.B.B.S., Ph.D.[b,c], Badrinath R. Konety, M.D., M.B.A.[a]

[a] *Department of Urology, University of Minnesota, Minneapolis, MN*

[b] *Department of Surgery, University of Melbourne, Urology Unit and Olivia Newton-John Cancer Research Institute Austin Health, Melbourne, Victoria, Australia*

[c] *Department of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia*

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Abstract

Background: Preclinical models have demonstrated that androgen receptor modulation can influence bladder carcinogenesis with an inverse association observed between serum androgen levels and bladder cancer (BC) incidence. It is still unclear whether 5α-reductase inhibitors, by preventing the conversion of testosterone to dihydrotestosterone, have a similar effect. This study aims to evaluate whether dihydrotestosterone-mediated androgen activity has an impact on BC incidence in a cohort of men included in a clinical trial of finasteride vs. placebo with rigorous compliance monitoring.

Methods: A secondary analysis was performed on all patients enrolled in the Medical Therapy for Prostatic Symptoms (MTOPS) Study and included in the biopsy substudy. Men were stratified into groups based on receiving finasteride and the incidence of BC compared between the groups.

Results: After exclusions for poor finasteride compliance ($n = 338$) and missing serum hormone results ($n = 9$), 2,700 men were eligible for analysis. In total, 0.8% ($n = 18$) of the cohort was diagnosed with BC during the trial period. There was no difference in the incidence of BC between men who received finasteride and those who did not (0.74% [$n = 9$] vs. 0.61% [$n = 9$], $P = 0.67$). Neither serum testosterone levels, prostate cancer diagnosis nor urinary bother (measured by International Prostate Symptom Score) demonstrated an association with BC diagnosis. These relationships were consistent in the subgroup of men in the biopsy substudy.

Conclusion: There was no observable relationship between decreased dihydrotestosterone levels and BC diagnosis.

Keywords: Androgen receptor; Bladder carcinoma; Finasteride; Urinary bladder

1. Introduction

With the continuing high prevalence of smoking in society, the burden of bladder cancer (BC) on an individual- and societal-level remains considerable [1]. Among males, BC has the fourth highest incidence [2]. Research examining the molecular mechanisms underlying BC development and progression has outlined a potentially important role for the androgen receptor (AR) in the preclinical setting. The urothelial AR has been implicated in promoting bladder tumorigenesis and progression [3]. Several studies have demonstrated that AR expression is inversely correlated to BC grade and stage; as well as being down-regulated in neoplastic tissue compared to normal urothelium [4,5]. Using mouse models, chemical castration or treatment with an antiandrogen was shown to decrease the incidence of carcinogen-induced tumors, whereas testosterone supplementation increased carcinogenesis [6–8]. Additionally, the AR is suggested to also be involved in disease progression [9,10]. Subsequently, there was considerable interest in using these findings to prevent BC.

*Corresponding author. Tel.: +1-660-334-0774; fax: +1-612-626-0428.
E-mail address: nsathian@umn.edu (N.J. Sathianathen).

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Finasteride, a common medical treatment for benign prostatic hyperplasia and androgenetic alopecia, is a potent 5α-reductase inhibitor which impedes the conversion of testosterone to dihydrotestosterone (DHT). Therefore, based on the results of the aforementioned preclinical studies it was hypothesized that finasteride could prevent the development of BC. There currently is no prospective, randomized data to support this but a recent secondary-analysis of the Prostate, Lung, Colorectal, and Ovarian cancer screening (PLCO) trial reported that finasteride use was associated with decreased incidence of BC (hazard ratio = 0.63, 95% CI: 0.49–0.86) [11]. Although this is initially encouraging there are several limitations to this study which warrant consideration when interpreting the results. As acknowledged by the authors, the analysis was based on self-reported use of finasteride with no data available regarding dose nor compliance. Furthermore, the PLCO dataset did not record DHT or testosterone levels and thus it is not possible to confirm the underlying mechanism of their observed association and establish causality.

By performing a secondary analysis of the Medical Therapy for Prostatic Symptoms (MTOPS) this study aims to characterise whether inhibiting the conversion of testosterone to DHT can prevent the development of BC. The MTOPS trial was a double-blinded, randomized study that enrolled men at least 50 years of age from 1993 to 1998 to determine whether medical therapy with an alpha-blocker (doxazosin) or 5α-reductase inhibitor (finasteride) alone, or in combination, would prevent the progression of benign prostatic hyperplasia.

2. Materials and methods

2.1. Medical Therapy of Prostatic Symptoms trial and data

Data from all men enrolled in the MTOPS was included in this analysis. Eligible men were allocated to 1 of 4 treatment groups: placebo, doxazosin, finasteride, or combination of both active treatments. The dose of finasteride was 5 mg daily. A prostate biopsy substudy was undertaken in parallel with the MTOPS trial where randomized patients had their DHT and testosterone blood levels checked at the second screening visit and then at 12, 60, and 72 months/end of study [12]. Medication compliance was evaluated for all patients at 3 and 4 weeks and then every 3 months until study completion at 72 months. Diagnosis of BC was recorded as an adverse event during the duration of the trial using Thesaurus of Adverse Reaction Terms (COSTART) system. A history of current evidence of BC at the time of enrollment was an exclusion criteria outlined in the MTOPS protocol and hence all diagnoses of BC can be considered to be new or incident cases.

Approval to use the MTOPS data was granted by The National Institute of Diabetes and Digestive and Kidney

Table 1
Patient demographics

	Overall	No finasteride	Finasteride	*P*
n	2,700	1,484	1,216	
Mean Age (SD)	62.4 (7.3)	62.6 (7.4)	62.6 (7.2)	0.97
Mean BMI (SD)	27.7 (4.1)	27.6 (3.9)	27.9 (4.4)	0.13
Race (*n*, %)				0.77
White	2,234 (82.7)	1,225 (82.6)	1,009 (30.0)	
Minority	466 (17.3)	259 (17.5)	207 (17.0)	
Past medical history (*n*, %)				
Congenital disease	87 (3.2)	48 (3.2)	39 (3.2)	0.97
Lung disease	297 (11.0)	168 (11.3)	129 (10.6)	0.56
Heart disease	526 (19.5)	306 (20.6)	220 (18.1)	0.10
Hypertension	776 (28.7)	427 (28.8)	349 (28.7)	0.97
Renal disease	205 (7.6)	127 (8.6)	78 (6.4)	0.04
Rheum/vascular disease	627 (23.2)	334 (22.5)	293 (24.1)	0.33
Diabetes mellitus	225 (8.3)	130 (8.8)	95 (7.8)	0.38
Endocrinopathy	123 (4.6)	73 (4.9)	50 (4.1)	0.32
Liver disease	94 (3.5)	57 (3.8)	37 (3.0)	0.26
Gastrointestinal disease	732 (27.1)	404 (27.2)	328 (27.0)	0.88
Skin disease	572 (21.2)	319 (21.5)	253 (20.8)	0.66
Organic CNS disease	118 (4.4)	57 (3.8)	61 (5.0)	0.14
Neoplastic disease	139 (5.2)	73 (4.9)	66 (5.4)	0.55
Anemia	61 (2.3)	27 (1.8)	34 (2.8)	0.09
Hematologic disease	53 (2.0)	25 (1.7)	28 (2.3)	0.25
Urinary tract infection	283 (10.5)	151 (10.2)	132 (10.9)	0.57
Urinary retention	96 (3.6)	45 (3.0)	51 (4.2)	0.10
Episode of gross hematuria	208 (7.7)	124 (8.4)	84 (6.9)	0.16
Microscopic hematuria	195 (7.2)	111 (7.5)	84 (6.9)	0.57