5-α Reductase Inhibitors and Risk of Overall and Lethal Bladder Cancer

Scholarly Report submitted in partial fulfillment of the MD Degree at Harvard Medical School

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Scholarly Report Title: 5-α Reductase Inhibitors and Risk of Overall and Lethal Bladder Cancer

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Abstract

Purpose: To determine if an association exists between 5-α Reductase Inhibitor (5-ARI) use and the risk of overall bladder cancer or lethal bladder cancer.

Materials and Methods: This prospective cohort study included 39,427 men in the United States who were part of the Harvard School of Public Health's Health Professionals Follow-up Study. We identified men who did not carry a diagnosis of cancer (other than non-melanoma skin cancer) in 1996 and prospectively followed them for 5-ARI use, cancer incidence, metastases, and mortality until 2012 using biannual questionnaires and, beginning in 2000, an annual bladder cancer specific cancer survey for men carrying that diagnosis. The primary exposure variable was 5-ARI use

Results: Over the course of 16 years (595,377 person-years) of follow-up, there were 943 diagnosed cases of bladder cancer, of which 159 were cases of lethal bladder cancer. Ever use of 5-ARIs was reported by 4105 men (10.4%) between 1996 and 2012. No association with 5-ARI ever use and bladder cancer was detected in either our age-adjusted model (HR 1.24, 95% CI 0.98-1.56) or in our multivariate analysis (HR 1.15, 95% CI 0.91-1.46, p=.25). Similarly, no significantly changed risk was of bladder cancer was detected when an analysis was conducted examining duration of 5-ARI exposure.

Conclusions: There was no statistically significant relationship between 5-ARI usage, ever vs. never or duration of use, and the development of overall or lethal bladder cancer in either age adjusted or fully adjusted models.

Glossary of Abbreviations

5-ARI……5-α Reductase Inhibitor

ADT…….Androgen Deprivation Therapy

AR……Androgen Receptor

BPH……..Benign Prostatic Hyperplasia

FDA……..Food & Drug Administration

HPFS……Health Professionals Follow-up Study

HR……Hazard Ratio

MTOPS…….....Medical Therapy for Prostatic Symptoms

NDI……...…National Death Index

Scholarly Project Question

My specific aims were to evaluate the association between 5-ARI use and risk of (1) overall bladder cancer and (2) lethal bladder cancer using data from the Health Professionals Follow-Up Study (HPFS). My strategy was to use data from the Health Professionals Follow-Up Study (HPFS) to examine the association between 5-ARI use and risk of incident bladder cancer, overall and lethal. The HPFS is a large prospective cohort of 51,529 US male health professionals maintained by investigators at the Harvard T.H. Chan School of Public Health. The study was pursued as a collaboration between investigators at the Massachusetts General Hospital and the Harvard T.H. Chan School of Public Health.

Student and Collaborator Contributions

The study was conceived jointly by Dr. Sarah Markt and Dr. Keyan Salari as a follow-on study of an earlier HPFS study of 5-ARIs in the risk of overall and lethal prostate cancer. I was responsible for applying for funding which was subsequently awarded by the American Urological Association's Urology Care Foundation under the provisions of their Summer Medical Student Fellowship. Dr. Keyan Salari assisted me by providing a mentor statement of support and editing my funding application submission. I completed the data acquisition (in the form of biannual survey review of several cycles of HPFS bladder cancer returns), analysis and statistical interpretation of the data, including development of our statistical model, and all initial manuscript authorship. The data was compiled and checked for accuracy by Dr. Sarah Markt. I was solely responsible for the creation of the tables and drafting the manuscript. The statistical model and output, as well as the subsequent draft manuscript I produced, were edited by Drs. Sarah Markt and Keyan Salari who provided multiple rounds of suggestions for modification to both the manuscript and the statistical model for data analysis.

5-α Reductase Inhibitors and Risk of Overall and Lethal Bladder Cancer

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Abstract

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Conclusions: There was no statistically significant relationship between 5-ARI usage, ever vs. never or duration of use, and the development of overall or lethal bladder cancer in either age adjusted or fully adjusted models.

Introduction

Bladder cancer is the 4th most common cancer among men in the US and is roughly 4 times more common in men than in women.[1] Additionally, principally due to the high recurrence rate and need for long-term invasive monitoring, bladder cancer has the highest lifetime treatment costs per patient of all cancers.[2] Controlling for greater exposure to cigarette and occupational carcinogens, men still carry an excess burden of disease that remains largely unexplained.[3] Because of the significant gender disparity in the incidence of bladder cancer, there has been a great deal of interest in the hormonal axis as a potential biological explanation.[3]

There is accumulating evidence of a role for the androgen receptor (AR) in the pathogenesis of bladder cancer.[4] AR is expressed by a subset of bladder tumors, and two recent retrospective studies found finasteride, a 5-α reductase inhibitor (5-ARI) that blocks conversion of testosterone to dihydrotestosterone, and androgen deprivation therapy (ADT) to be associated with decreased risk of bladder cancer diagnosis and recurrence, respectively. The objective of this specific study is to confirm and extend these findings in a large prospective cohort, the Health Professionals Follow-Up study. Our central hypothesis is that 5-ARI use decreases the risk of bladder cancer.

Preclinical animal models have implicated the androgen receptor (AR) in the pathogenesis of bladder cancer.[5] In humans, AR expression has been detected in normal and malignant bladder urothelium from both male and female patients.[6] Recently, a large retrospective study demonstrated that men with bladder cancer on ADT for concomitant prostate cancer have significantly reduced risk of bladder cancer recurrence.[7] Another study in

nearly 11,000 Finnish men demonstrated a 23% reduction in bladder cancer death in men on 5-ARI therapy after diagnosis.[8] 5-ARIs (e.g., finasteride or dutasteride) are well-tolerated medications familiar to urologists that may have a beneficial effect on bladder cancer development and/or recurrence without the attendant side effects of ADT. A recent study of the Prostate, Lung, Colorectal, and Ovarian cancer screening trial suggests that finasteride use is associated with a one-third reduction in risk of incident bladder cancer.[9] Notable limitations of that study include that many confounders for bladder cancer, such as alcohol use, were not available, and that bladder cancer mortality was not assessed due to few events and lack of follow-up. Furthermore, there is additional recent conflicting evidence from a secondary analysis of the Medical Therapy for Prostatic Symptoms (MTOPS) Study suggesting that there is no association between 5-ARI use and the diagnosis of bladder cancer.[10]

In order to elucidate how 5-ARI use affected the incidence of overall and lethal bladder cancer, we performed a prospective cohort study among 39,427 men in the United States. Our central hypothesis was that 5-ARI use may reduce risk of developing bladder cancer and, more importantly, lethal bladder cancer. In our analysis, we show that 5ARI use was not associated with the development of either lethal or overall bladder cancer risk.

Materials and Methods:

Prospective Cohort Characteristics and Study Design

Our cohort of study subjects was drawn from Health Professionals Follow-up Study (HPFS), a prospective cohort of 51,529 male health professionals aged 40-75 when enrolled in 1986. The study design and use of the HPFS data was endorsed by the Human Subjects

Committee at the Harvard School of Public Health and all subjects assented to taking part in the study with written consent forms. The study participants were first mailed an initial survey in 1986, establishing baseline patient characteristics including information on date and location of birth, ethnic/racial origin, anthropometric measurements, supplement and prescription drug use, past medical conditions, exercise and personal behaviors, and food choices. Subsequently, men were surveyed via mail every two years from 1988 to 2012. In 2000, an additional annual bladder cancer-specific questionnaire was mailed to men containing only queries specific to their disease in order to determine the course of their cancer progression and query about any metastatic spread. This HPFS population has been the subject of a number of previous studies on bladder cancer for topics related to bladder cancer disease outcomes and epidemiology.[11,12]

In order to fully capture the exposure of interest, we constrained the study cohort by only examining participants who returned the 1996 questionnaire (the first year in which 5-ARI exposure and related questions were included n =43,219). Additionally, we chose to exclude 3,792 participants carrying cancer diagnoses (with the exception of non-melanomatous skin cancers) prior to 1996. After exclusion criteria were applied, 39,427 men remained; these men were prospectively followed for study drug intake, bladder cancer diagnosis, histopathology, bladder cancer progression and metastasis, and death until 2012.

Determining 5-ARI Use in Study Population

The principal exposure of interest was 5-ARI use from 1996-2012. Beginning in 1996, HPFS biannual questionnaires began asking participants about their use of finasteride under the commercial label of Proscar, manufactured by Merck. Because of additional formulations entering the market for indications other than benign prostatic hyperplasia, beginning in 2004,

surveys were modified to include a question about use of either Proscar, Propecia (also manufactured by Merck), or Avodart (manufactured by GlaxoSmithKline). Dose specific information and brand of drug was not assessed in the survey. Participant exposure was determined by adding up survey windows in which they noted use.

Assessment of Bladder Cancer Outcomes

The principal outcomes of interest were the development of a bladder cancer diagnosis or development of lethal bladder cancer from 1996-2012. Both medical records and tumor pathology reports provided additional information via abstraction and included information on tumor grade and stage, medical, radiologic, or surgical treatment, and whether there was any metastatic spread noted. Lethal cases were determined by HPFS notification from participant next of kin, information from the United States Postal Service, or from the National Death Index. The NDI uses a 4 physician panel to review information including medical records, patient health history, death certificates and has been shown to have sensitivity higher than 98% in accurately assigning cause of death.[13]

Statistical Analysis

Analysis of each study participant's results began with their first survey return in 1996 and terminated with either their death or when the study ended in 2012. Study drug ever-use was compared with never use to determine incidence ratios. Cox-proportional hazard models were then calculated, with age as the time scale, in both a simple age adjusted model as well as in a multivariate analysis controlling for age, smoking history, vigorous physical activity, race, body mass index, diabetes mellitus diagnosis, and α-blocker use.

All statistical analysis was conducted using R version 3.5.2 (2018-12-20 "Eggshell Igloo" - Copyright (C) 2018 The R Foundation for Statistical Computing) with 95% confidence intervals, 2-sided *P* values, and an assumption of statistical significance when *P* was calculated to be < .05. Tests for internal validity of the Cox-proportional hazard model including the Wald test and the log-likelihood test were met on each reported test outcome, validating the proportional hazard model.

Results:

Over the course of 16 years (595,377 person-years) of follow-up, there were 943 diagnosed cases of bladder cancer, of which 159 were cases of lethal bladder cancer. Ever use of 5-ARIs was reported by 4105 men (10.4%) between 1996 and 2012. 5-ARI users tended to be older and were more likely to also use an α-blocker (**Table 1**).

Overall and Lethal Bladder Cancer by Ever Exposure and by Duration of Exposure

No association with 5-ARI ever use and bladder cancer was detected in either our age-adjusted model (HR 1.24, 95% CI 0.98-1.56) or in our multivariate analysis (HR 1.15, 95% CI 0.91-1.46, *p*=.25) adjusted for age, smoking history, vigorous physical activity, race, body mass index, diabetes diagnosis, or α-blocker usage (**Table 2**). Similarly, no significantly changed risk was of bladder cancer was detected when an analysis was conducted examining duration of 5-ARI exposure. In our fully-adjusted model, ever-users with <4 years of cumulative 5-ARI use were not significantly more or less likely to develop total (HR 1.12, 95% CI 0.83-1.50) or lethal (HR 1.70, 95% CI 0.95-3.06) bladder cancer. Likewise, >=4 years of cumulative use was not associate with significantly altered risk of total (HR 1.13, 95% CI 0.78-1.63) or lethal (HR 0.95, 95% CI 0.38-2.36) bladder cancer (**Table 3**).

Sensitivity Analysis

Because 5-ARIs and α-blockers are commonly used for the same indications and for urinary symptoms in men, and because these symptoms may have led to alterations in diagnostic probability (i.e. men with lower urinary tract symptoms were more likely to visit their PCP or urologist or undergo cystoscopy), we conducted a sensitivity analysis with α-blockers as the primary exposure variable (**Table 3**). In this fully-adjusted analysis, α-blocker use was not found to be significantly associated, with the development of either total (HR 1.18, 95% CI 0.99-1.41) or lethal (HR 1.16, 95% CI 0.76-1.76) bladder cancer.

Discussion:

There are promising therapeutic consequences to better understanding how 5-ARIs may influence the carcinogenesis and disease progression of bladder cancer. Although a number of animal models have convincingly demonstrated a role of androgen signaling in bladder cancer pathogenesis, clinical studies have produced inconsistent results.[6,8–11] In this prospective cohort study, no significant association was found with ever 5-ARI use or with duration of 5-ARI use and the development of any bladder cancer, lethal or otherwise. Although not rising to the level of significance, we found a positive HR associated with use of both α-blockers as well as 5-ARIs. There have been a number of past studies suggesting that BPH is an independent risk factor for the development of bladder cancer, due to the suspected influence of chronic inflammation induced by urinary stasis and the increased time urine with carcinogens spends in contact with bladder epithelium in these patients; because were not able to adjust our model for a diagnosis of BPH independent from prescription of a 5-ARI or α-blockers, this could have confounded our model.[12,14]

Strengths and Limitations

Our study was strengthened by its large size, high rate of participation in survey return rate, presumed accuracy of reporting among a cohort of health professionals, and long duration follow-up. It was not, however, without weaknesses; these include its racial homogeneity (91% white) and reliance upon self-reporting.

Conclusions:

No association was found between 5-ARI use and the development of bladder cancer, including lethal cases, in either our age-adjusted or fully-adjusted models. The most significant limitation in our study was the limited number of lethal bladder cancer cases, leading to wide-confidence intervals among the lethal case analyses.

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Table 1. Study Population Characteristics at Baseline in 1996 by 5-ARI Use During Study Period

Characteristic	5-ARI Use	
	Never Users (n = 35,322)	Ever Users (n = 4,105)
Age, mean (SD), yrs	62.5 (9.3)	64.0 (8.7)
BMI, % in category[1]		
<21	3.2	3.0
21-22.9	10.7	11.0
23-24.9	21.1	20.0
25-27.4	26.9	27.3
27.5-29.9	13.8	13.7
30+	10.5	10.7
Race/ethnicity, %[2]		
White	91.0	91.7
African American	0.8	0.6
Asian	1.7	1.2
Other	1.5	1.4
Smoking status, %[3]		
Never Smoker	40.7	43.2
Former Smoker	43.4	44.5
Current Smoker	6.4	3.6
Diabetic, % with diagnosis	6.3	6.3
Current α-blocker use, %	3.1	9.5
Vigorous activity, % in highest quintile	16.8	17.1

[1] BMI data missing in 13.8% of never users and 14.3% of ever users.
[2] Race data missing in 5.0% of never users and 5.1% of ever users.
[3] Smoking status missing in 9.6% of never users and 8.7% of ever users.

Table 2. Hazard Ratio of Bladder Cancer by 5-ARI and α-blocker Use Among 39,427 Male Health Professionals (1996-2012)

	Ever vs Never Use		
	Age-Adjusted HR (95% CI)	Fully Adjusted HR (95% CI)[4]	*P* Value
5-ARI Use Among 39,427 Male Health Professionals (1996-2012)[5]			
Total Bladder Cancer	1.24 (0.98-1.56)	1.15 (0.91-1.46)	.25
Lethal Bladder Cancer[6]	1.47 (0.89-2.43)	1.42 (0.84-2.38)	.19
α-blocker Use Among 39,427 Male Health Professionals (1996-2012)[7]			
Total Bladder Cancer	1.27 (1.07-1.50)	1.18 (0.99-1.41)	.06
Lethal Bladder Cancer[6]	1.26 (0.84-1.87)	1.16 (0.76-1.76)	.49

[4] Hazard ratio adjusted for age, smoking history, vigorous physical activity, race, body mass index, diabetes mellitus diagnosis, and α-blocker use.
[5] Follow-up: 595,377 person-years. Reference group is men who never used 5-ARIs.
[6] Lethal cases defined as metastatic or fatal disease.
[7] Follow-up: 595,377 person-years. Reference group is men who never used α-blockers.

Table 3. Hazard Ratio of Bladder Cancer by Duration of 5-ARI Use Among 39,427 Male Health Professionals (1996-2012)[8]

	Never Use	Ever Use, <4 yrs	Ever Use, >=4 yrs
	HR [Reference]	Fully Adjusted HR (95% CI)[9]	Fully Adjusted HR (95% CI)[b]
Total Bladder Cancer	1 [Reference]	1.12 (0.83-1.50)	1.13 (0.78-1.63)
Lethal Bladder Cancer[10]	1 [Reference]	1.70 (0.95-3.06)	0.95 (0.38-2.36)

[8] Follow-up: 595,377 person-years.
[9] Hazard ratio adjusted for age, smoking history, vigorous physical activity, race, body mass index, diabetes mellitus diagnosis, and α-blocker use.
[10] Lethal cases defined as metastatic or fatal disease.