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Finasteride Treatment Alters Tissue Specific Androgen Receptor Expression in Prostate Tissues

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Abstract

BACKGROUND—Normal and pathologic growth of the prostate is dependent on the synthesis of dihydrotestosterone (DHT) from testosterone by 5 α -reductase. Finasteride is a selective inhibitor of 5 α -reductase 2, one isozyme of 5 α -reductase found in abundance in the human prostate. The objective of this study was to investigate the effects of finasteride on androgen receptor expression and tissue morphology in human benign prostatic hyperplasia specimens.

METHODS—Patients undergoing transurethral resection of the prostate and either treated or not treated with finasteride between 2004 and 2010 at the University of Wisconsin-Hospital were retrospectively identified using an institutional database. Prostate specimens from each patient were triple-stained for androgen receptor, prostate-specific antigen, and basal marker cytokeratin 5. Morphometric analysis was performed using the multispectral imaging, and results were compared between groups of finasteride treated and non-treated patients.

RESULTS—Epithelial androgen receptor but not stromal androgen receptor expression was significantly lower in patients treated with finasteride than in non-treated patients. Androgen receptor-regulated prostate-specific antigen was not significantly decreased in finasteride-treated patients. Significant luminal epithelial atrophy and basal cell hyperplasia were prevalent in finasteride treated patients. Epithelial androgen receptor expression was highly correlated to the level of luminal epithelial atrophy.

CONCLUSIONS—In this study, finasteride decreased the expression of epithelial androgen receptor in a tissue specific manner. The correlation between epithelial androgen receptor and the extent of luminal epithelial atrophy suggests that epithelial androgen receptor may be directly regulating the atrophic effects observed with finasteride treatment.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Keywords

BPH; atrophy; multispectral imaging

INTRODUCTION

Benign prostatic hyperplasia (BPH) may be the result of a benign enlargement of the prostate and can lead to significant morbidity due to urethral obstruction and lower urinary tract symptoms (LUTS) [1]. Histologic evidence of BPH is found in 50% of men at the age of 50 and up to 90% of males at the age of 80 [2]. Studies have shown that development and maintenance of the prostate gland is androgen-dependent [3,4], with dihydrotestosterone (DHT) acting as the primary androgen responsible for differentiation, growth, and function.

5- α reductases (5 α -R) are enzymes that reduce the 4,5 double bond [5] of 3-oxo-5 α -steroids such as testosterone, progesterone, cortisol, and aldosterone. In the prostate, the conversion of testosterone to the more potent DHT is one well-characterized reaction of 5 α -R [6]. DHT has a two to fivefold higher affinity for androgen receptor (AR) than testosterone and a 10-fold higher potency for inducing AR signaling [7]. To date, three isozymes of 5 α -R have been identified (5 α -R1,2,3) with each performing similar functions in different tissues [8,9]. Traditionally, 5 α -R1 and 5 α -R2 have been associated with non-reproductive and reproductive tissues [9], respectively, but both enzymes are expressed in the normal human prostate, with 5 α -R2 being localized mainly to the stroma and accounting for the majority of DHT synthesis [9,10]. 5 α -R3 is expressed in basal epithelial cells in normal human prostate and may play a role in malignant disease [8].

Early observations of a cohort of men with congenital 5 α -R deficiency revealed that 5 α -R deficiency is associated with external genital ambiguity and the absence of a palpable prostate [11,12]. These observations have led to the development of synthetic 5 α -R inhibitors for clinical usage. Finasteride is a synthetic 4-azasteroid that acts as a competitive inhibitor of 5 α -R2 [13]. Finasteride decreases intraprostatic DHT levels by 60–85% [13,14], suppresses the activity of 5 α -R2 by 100-fold [15,16], and reduces the size of the prostate by 20% in men with BPH responsive to finasteride treatment [17]. The reduction of prostatic size often leads to an increase in urine flow and an alleviation of BPH symptoms [18]. Finasteride has shown to be effective in long-term treatment for progression of disease, though symptoms normally return if treatment is stopped [17]. Clinical responses of finasteride treatment are well documented [13], but there is limited data regarding the effect of finasteride on prostate tissue morphology, AR expression, and downstream AR-regulated biomarker expression in BPH tissue. The purpose of this study was to investigate the effects of finasteride on BPH tissue morphology and androgen regulated biomarker expression.

MATERIALS AND METHODS

Patient Cohort and Tissue Collection

After Institutional Review Board approval (2012-1033, 2012-0508), all patients undergoing transurethral resection of the prostate (TURP) for treatment of BPH at the University of

Wisconsin Hospital from 2004 to 2010 were identified using an institutional database. TURP was performed by multiple surgeons within the Department of Urology at the University of Wisconsin. Patients were randomly selected while blinded to treatment data. Exclusion criteria included an ambiguous history of finasteride treatment for BPH. Remaining patients were divided into finasteride treated and non-treated groups. TURP specimens from patients with BPH were acquired from the University of Wisconsin Pathology archive.

Immunohistochemistry

Prostate specific antigen (PSA) is primarily localized to the cytoplasm of prostate luminal epithelial cells [19], so PSA expression was used to mark prostate luminal epithelium. CK5 was used to mark basal cells of the prostate epithelium. Five-micrometer thick formalin-fixed, paraffin-embedded sections were air-dried and then baked in a 60° oven for 30 min. Slides were triple-stained using standard methods and the protocol highlighted in Table I, as described previously [20,21].

Image Morphometric Analysis

Morphometric analysis of immunohistochemical (IHC) staining was performed as described in previous studies [20]. Briefly, 8-bit multispectral image cubes were acquired with the 20× objective lens, manually using the Nuance™ scope and camera (PerkinElmer, Waltham, MA). Images of three representative acinar lobules free of cautery artifact were acquired for each patient's section. Care was taken to avoid glands with noticeable inflammation, since focal atrophy has previously been linked to inflammation in the prostate [22]. Nuance™ software (version 3.0.0, PerkinElmer) was used to build the spectral library using four control prostate tissue slides stained with one chromogen (DAB, warp red [WR], deep space black [DSB], and hematoxylin [HT]) (Fig. 1). The resulting spectral curves were used to unmix signals on the multicolored slides. In Form™ (version 1.4, PerkinElmer), a pattern-recognition-based image analysis software, was used for tissue (epithelium vs. stroma) and cell (nucleus vs. cytoplasm) segmentation and biomarker quantitation.

Subcellular AR and PSA optical density expression levels in the epithelium and/or stroma were quantitated. To assure 97% acceptable tissue and cellular segmentation accuracy, 18% of the total images were analyzed to set up an algorithm for differentiation [20]. Because AR binds androgens and translocates to the nucleus [23], nuclear expression of AR in both the epithelia and stroma was quantitated. In addition to mean optical density, positivity results were generated for AR in both the epithelia and stroma, as we have described previously [21]. The pixel area ratios of PSA-expressing luminal cells to CK5-expressing basal cells was used to assess the extent of glandular atrophy. The ratio of CK5-expressing basal pixels to the sum of CK5 and PSA-expressing pixels was used to determine basal cell hyperplasia. Mean nuclear size was calculated by dividing the total nuclear area in pixels by the number of cells, and then converting to μm^2 , as previously shown [21].

Manual Assessment of Basal Cell Hyperplasia and Luminal Epithelial Atrophy

A genitourinary pathologist (WH) blinded to patient treatment data assessed the extent of luminal epithelial atrophy and basal cell hyperplasia of the same image sets and a binary

“yes” and “no” algorithm, where “yes” indicates the presence of luminal epithelial atrophy or basal cell hyperplasia.

Statistical Analysis

Because staining runs were performed at different times, mean optical density (OD) results were normalized using Z-scores, using the following equation: $[(\text{OD value}) - (\text{mean of all OD values from experiment } x)] / \text{standard deviation (SD)}$, where x is a given experiment. IBM SPSS Statistics 19 and GraphPad Prism 5 were used for data analysis. A one-way ANOVA was used to evaluate differences between control and finasteride-treated groups for AR expression, PSA expression, and atrophy. Linear regression was used to plot lines of best fit on correlation scatter plots. Logistic regression was used to determine the relationship between binary manual assessment results and quantitative computational results. In all analyses, a two-tailed P -value of <0.05 was considered significant.

RESULTS

Patient Cohort

This study involved 49 patients. Of this patient population, 23 patients received finasteride treatment (median treatment length=7 months; IQR 2–32) versus 26 patients that had no history of finasteride or other 5 α -RI treatment. The average age of the population at time of surgery was 70.1 years. No differences were observed between the finasteride-treated and non-treated groups for initial serum PSA before surgery (4.39 ng/ml vs. 5.14; $P=0.206$), pre-TURP post-void residual (PVR) (308.0 ml vs. 238.2; $P=0.219$), post-TURP PVR (131.2 ml vs. 125.6; $P=0.853$), or patient weight (195.5 lbs vs. 195.3; $P=0.977$). Other clinical variables that were investigated include pre-TURP prostate size, pre- and post-TURP AUA score, and patient height. In all cases, no significant differences were observed. Results of clinical variable analysis are summarized in Table II.

Immunohistochemistry and Morphometric Analysis

Individual prostate slides stained with DSB, DAB, WR, and HT were used to create a spectral curve for separation of chromogens (Figs. 1 and 2). Epithelial nuclei in finasteride treated specimens (mean=49.45) were significantly larger than non-treated specimen nuclei (36.91; $P=0.0003$; Table III). Nuclear expression, as measured by normalized Z-scores from optical densities, of AR in prostate epithelial cells was found to be significantly lower in specimens with finasteride treatment (mean Z-score=-0.18; SD=1.02) than in specimens from non-finasteride treated patients (0.16; SD=0.94; $P=0.035$; Table III, Fig. 3). No difference was observed in the nuclear expression of AR in prostate stromal cells between finasteride treated (-0.11; SD=0.92) and untreated (0.09; SD=1.04; $P=0.223$) BPH patients. No significant difference was seen in cytoplasmic PSA levels in the prostate epithelium between finasteride treated (-0.16; SD=0.90) and non-finasteride treated patients (0.13, SD=1.04; $P=0.071$). The number of cells with nuclear AR positivity was lower in the prostate epithelium of finasteride treated patients (mean=77.64%; SD=11.82%) than non-finasteride treated patients (mean=82.63%; SD=10.13%; $P=0.007$). No difference was observed in stromal nuclear AR positivity between treated (mean=20.93%; SD=12.39%) and control patients (mean=23.94%; SD=13.01%; $P=0.15$). A significant difference in glandular

morphological changes was observed, as indicated by the ratio of glandular epithelium (marked by PSA) to basal cells (marked by CK5) between finasteride-treated (mean ratio=3.05; SD=2.05; Table IV) and control patients (4.64; SD=3.87; $P=0.003$). Basal cell hyperplasia, as determined by the pixel-area ratio of [CK5/(PSA + CK5)], was more prevalent in finasteride-treated patients (mean ratio=0.31; SD=0.17) than control patients (0.23; SD=0.12; $P=0.0003$).

A significant correlation was found between AR expression in the epithelia and luminal epithelial atrophy (Pearson $r=0.3433$; $P<0.0001$), but not between stromal AR and luminal epithelial atrophy (Pearson $r=0.0932$; $P=0.2634$; Fig. 4). A chart review revealed that 22 of 23 (94.7%) patients treated with finasteride opted for TURP due to a lack of benefit of treatment or progression of symptoms. Surgical indications were not available for 1 of 23 (5.3%) patients.

Assessment of Basal Cell Hyperplasia and Cellular Atrophy

Using logistic regression, subjective binary data generated by blinded pathological analysis was highly correlated to ratios generated from quantitation of IHC staining for both luminal epithelial atrophy (Area under curve [AUC]=0.82; $P<0.0001$) and for basal cell hyperplasia (AUC=0.88; $P<0.0001$; Supplemental Fig. S1).

DISCUSSION

Finasteride is a preferential inhibitor of 5 α -R2 that reduces prostate size by 20% in men responsive to treatment [17]. While it is known that 5 α -R2 activity is suppressed by finasteride, which in turn reduces intraprostatic DHT levels by up to of 85% [14], the downstream actions of finasteride are not entirely understood. Additionally, the responsiveness of patients to treatment is highly variable, with the basis for this variability still unclear.

Previous studies have shown that AR expression is increased in BPH when compared to normal prostatic tissue [21], suggesting that there are more androgen-responsive cells and protein in BPH. Because development and growth of the prostate is androgen-dependent [3], androgen deprivation is one common therapy for prostate cancer patients. Prostate cancer prevention trials using 5 α -reductase inhibitors such as finasteride or dutasteride were initially successful in reducing the incidence of low grade cancers, but the increase in high grade carcinomas is concerning and highlights a potential drawback of long-term use with 5 α -RIs [24,25]. Androgen deprivation therapy for prostate adenocarcinoma has previously been shown to result in smaller, dense nuclei in comparison to untreated adenocarcinoma [26]. In this study, the size of epithelial nuclei significantly increased with finasteride treatment. This result—while unexpected—may highlight some differences between benign and malignant prostatic disease in regards to androgen response.

In BPH, treatment with 5 α -reductase inhibitors such as finasteride is one way to decrease local and circulating levels of DHT, thus creating a local milieu consistent with androgen ablation. Previous studies have investigated the effects of 5 α RI treatment on prostate AR or AR-regulated gene expression [27,28], but these studies had mixed results. This is the first

study, to our knowledge, that uses immunohistochemistry and morphometric approach to evaluate the protein expression of AR, an AR-regulated target gene (PSA), and the extent of luminal epithelial atrophy and basal cell hyperplasia in BPH patients treated with finasteride. In the past, studies have been somewhat limited due to the inter- and intra-observational subjectivity that is inherent in manual or semi-quantitative methods for evaluation of IHC staining. Additionally, the objective and reproducible evaluation of histologic features such as glandular atrophy and basal cell hyperplasia is difficult using manual methods. However, new morphometric systems for quantifying IHC staining remove most of this subjectivity. Multispectral imaging that combines automated slide scanning and unique pattern recognition software provides marked advantages over traditional methods by reducing subjectivity and decreasing labor time while creating reproducible quantitative results. Additionally, we have described and validated the use of this technology in earlier studies [20,21].

Epithelial AR, when stimulated by androgen, is a transcription factor that regulates the synthesis of secretory proteins of the prostate [29]. While loss of function studies have shown that epithelial AR-knockout mice develop prostate glands that are de-differentiated and hyperproliferative compared to controls [29–31], reduction of epithelial AR with siRNA or antiandrogens reduces proliferation and increases apoptosis [32]. Contrasting this, when epithelial AR is overexpressed in transgenic mice, an associated increase in proliferation and formation of prostatic intraepithelial neoplasia (PIN) is observed [33], suggesting a positive relationship between AR expression and proliferation. In this study, a reduction in the level of epithelial AR in patients with BPH was associated with finasteride treatment. Therefore, decreasing epithelial AR may be associated with slowing the progression of BPH. However, since many of the finasteride treated men received insufficient clinical benefit and opted for TURP, this is consistent with the hypothesis that decreased epithelial AR may be involved with finasteride resistance in patients with BPH. Furthermore, in these men stromal AR did not change, and thus, the ratio of stromal AR to epithelial AR increased. This may be important because stromal AR is necessary for normal prostate development and cancer progression [3,34].

We found in our study that epithelial AR expression was significantly reduced in BPH patients treated with finasteride when compared to patients not treated with a 5 α -RI, whereas stromal AR expression was unchanged. Because PSA is regulated by epithelial AR, we hypothesized that epithelial PSA expression would also be lower in finasteride treated patients, which we did not observe. Though epithelial AR regulates PSA expression, studies with AR-knockout mice have shown low underlying levels of expression of other AR-regulated genes in the absence of epithelial AR expression [29,31], suggesting that other factors may play a role in the expression of these epithelial proteins. This may account for the lack of a significant decrease in PSA expression in our patient cohort, despite the decrease in epithelial AR expression. Alternatively, the apparent trends of reduction of stromal AR and epithelial PSA with finasteride treatment may not have reached statistical significance due to our limited sample size.

Upon initial examination of tissues, some BPH specimens had significant atrophy in the luminal cells of the prostate, which led us to hypothesize that finasteride was causing this

reduction in size through an AR-regulated mechanism. To date, there have been mixed results regarding the effects of finasteride on prostate tissue morphology and luminal epithelial atrophy. Previous studies have demonstrated that finasteride treatment results in little change in tissue morphology [35,36]. However, in one double-blind, placebo controlled study, Rittmaster et al. [37] observed a pronounced decrease in luminal epithelial cell size at 4 months of treatment. Similarly, in a retrospective study of 26 patients, Montironi et al. [38] observed an overall reduction in the size of luminal epithelial components in BPH patients treated with finasteride when compared to an untreated BPH control group. Our results indicate that finasteride treatment does result in a significant decrease in the size of the prostate luminal epithelium (Table IV). This result is consistent with the role of epithelial AR signaling—or lack thereof—in the epithelium.

Another feature observed upon initial histological examination was the presence of basal cell hyperplasia around some glands. One effect of 5 α -RI treatment is the local accumulation of testosterone in the prostate due to the blockage of the conversion of testosterone to DHT. Aromatase, an enzyme found in the prostatic stroma [39], catalyzes the conversion of androgens to estrogens, including testosterone to 17 β -estradiol (E2). Previous studies have shown that E2 has a hyperproliferative effect on basal cells of the prostate [40]. Therefore, we hypothesize that the basal cell hyperplasia associated with finasteride treatment in this study is the result of increased local E2 levels due to the blockage of the conversion of testosterone to DHT. This has important implications in both benign and malignant prostate disease, as the balance of androgens and estrogens is important in the promotion of these diseases [41,42].

The ratios used to determine the extent of luminal epithelial atrophy and basal cell hyperplasia were validated by comparing the results to binary manual assessment data. The high area under the curves is indicative of a strong relationship between traditional pathological methods of analysis and our newly developed ratios. Intra- and inter-observational error make the study of these histological features difficult, but the internal validation of these newly developed ratios allows for the use of these as surrogates for studying luminal epithelial atrophy and basal cell hyperplasia.

We postulated that the atrophy upon finasteride treatment in the luminal portion of the prostate epithelium was a downstream result of reduced epithelial AR expression. We found a significant correlation between luminal epithelial atrophy and epithelial AR expression in the patient population. However, this correlation was not observed when comparing stromal AR expression and luminal cell size (Fig. 4). We conclude that the decrease in luminal cell size may be directly or indirectly regulated by epithelial AR.

While epithelial AR has been studied extensively in the past, much less is known about the expression and role of stromal AR in the prostate. Previous developmental studies have shown that prostatic growth and development is mediated through stromal AR rather than epithelial AR [3]. Additionally, we have identified stromal AR as a key contributor to prostatic carcinogenesis, malignant transformation, and metastasis, as stromal AR-knockout prostatic tissues failed to undergo malignant transformation [34]. Stromal AR may not be essential for prostatic maintenance, but is needed for malignant transformation [34].

Through paracrine interactions, stromal cells induce epithelial growth and proliferation through the secretion of an array of growth factors [34]. The secretion—or lack of secretion—of particular growth factors by the stroma may account for the epithelial apoptosis that is typically observed in patients and animal models treated with finasteride [38,43], as stromal AR is a regulator of epithelial apoptosis in the prostate [44]. The association of epithelial AR with overall luminal epithelial size indicates that trophic changes in epithelial cells may be modulated by epithelial AR, but the inhibition of proliferation and induction of apoptosis is regulated by stromal AR [34,45].

While differences were observed with finasteride treatment between epithelial AR, epithelial luminal atrophy, and basal cell hyperplasia, patients that opt for surgery for alleviation of BPH symptoms generally have tried and failed treatment such as alpha blockers or 5 α -RIs. Our cohort of patients treated with finasteride, all of which received TURPs, followed this trend. A chart review revealed that 22 of 23 (94.7%) patients treated with finasteride opted for TURP due to a lack of benefit or progression of symptoms. More pronounced changes may be observed with specimens from patients that underwent a successful treatment regimen with finasteride. Further proteomic and genetic studies on patients that are both responsive and resistant to finasteride treatment are needed to elucidate the actions of finasteride on stromal and epithelial AR.

CONCLUSIONS

Finasteride treatment significantly decreases the expression of AR in epithelial cells of the human prostate. Additionally, using two newly developed formulas, we found that finasteride treatment also leads to an increase in luminal epithelial atrophy and basal cell hyperplasia in patients with BPH. The correlation between luminal epithelial atrophy and epithelial AR expression suggests that epithelial AR may be one key player in modulating the decrease in prostate volume that results from finasteride treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Spectral library. Four untreated control prostate slides stained with one chromogen (3,3'-diaminobenzidine [DAB], Warp Red [WR], Deep Space Black [DSB], or hematoxylin) were used to create a spectral curve with Nuance™ software for chromogenic separation of 8-bit multispectralcubes.

Fig. 2. Separation of multispectral chromogens. Using the resulting spectral curve from Figure 1, chromogens were unmixed from the triple-stained image (**A**) and quantitated using Nuance and in Form™ software. Prostate-specific antigen (PSA; Warp Red [WR]) was expressed primarily in the cytoplasm of luminal epithelial cells (**B**). Expression of androgen receptor (AR; 3,3'-diaminobenzidine [DAB]) was predominantly localized to the nuclei of both prostatic epithelial and stromal cells (**C**). High expression of cytokeratin 5 (CK5; Deep

Space Black [DSB]) was primarily localized to the basal layer (**D**), and the hematoxylin counterstain was used to define nuclei (**E**).

Fig. 3.

Biomarker expression. Biomarker expression was quantitated using multispectral imaging software. The number of AR-positive epithelial cells (**A**) was significantly lower in patients treated with finasteride (mean=77.64%) than control patients (82.63%) ($P=0.007$). No difference was observed in percent positivity of stromal AR between treated (20.93%) and control patients (23.94%) ($P=0.15$). Nuclear AR expression in the epithelium, when analyzed with normalized mean optical density Z-scores (**B**), was also significantly lower in patients treated with finasteride (mean Z-score=-0.18) than non-treated patients (0.16)

($P=0.035$). Using normalized Z-scores, no significant difference in stromal AR expression (**C**) was observed between patients treated with finasteride (-0.11) and non-treated patients (0.09) ($P=0.223$). No significant decrease in AR-regulated PSA expression (**D**) was observed between non-treated (0.13) and treated (-0.16) patients ($P=0.071$).

Fig. 4.

Correlation between luminal epithelial atrophy and AR expression. Scatter plots comparing the relationship between luminal epithelial atrophy and either epithelial or stromal AR expression were plotted and a line of best fit was calculated using a linear regression model. A significant correlation was found between luminal epithelial size and epithelial AR expression (**A**; Pearson $r=0.3433$; $P<0.0001$). No significant correlation was found between luminal epithelial atrophy and stromal AR expression (**B**; Pearson $r=0.0932$; $P=0.26$).

TABLE I**Staining Protocol**

Primary antibody	Secondary antibody	Chromogen
PSA (rabbit pAb, 1:400, Epitomics)	Mach 2 mouse Ig-AP (BM)	Warp Red (BM)
AR (mouse mAb, 1:50, Biocare Medical, BM)	Mach 2 mouse Ig-HRP (BM)	DAB (BM)
CK5 (chicken pAb, 1:1000, Covance)	Goat anti-chicken Ig-HRP (Pierce)	Deep Space Black (BM)
Counterstain		Hematoxylin (BM)

PSA, prostate-specific antigen; AR, androgen receptor; CK5, cytokeratin 5; HRP, horseradish peroxidase; DAB, 3,3'-diaminobenzidine.

TABLE II

Clinical Features of Patient Population

Variable	Tx	N	Range	Mean	SD	P-value
Initial PSA (ng/ml)	Non-F	18	1.1–11.6	5.14	3.16	0.206
	F	16	0.5–9.2	4.39	2.69	
Pre-TURP PVR (ml)	Non-F	10	25–542	238.2	159.6	0.219
	F	9	18–702	308.0	257.0	
Post-TURP PVR (ml)	Non-F	7	6–265	125.6	105.4	0.853
	F	14	6–334	131.2	118.1	
Pre-TURP AU/ASI	Non-F	2	20–32	26	6.57	0.067
	F	12	5–30	20	7.35	
Post-TURP AU/ASI	Non-F	0	—	—	—	—
	F	7	1–14	6	3.99	
Pre-TURP pros. size (grams)	Non-F	2	28–71	49.3	23.8	0.358
	F	12	25–90	41.7	17.6	
Patient weight (pounds)	Non-F	19	129–274	195.3	34.9	0.977
	F	17	150–262	195.5	33.3	
Age at surgery (years)	Non-F	21	54–88	70.3	9.4	0.788
	F	19	60–86	69.8	8.5	
Patient height (inches)	Non-F	5	59–72	68.1	5.1	0.226
	F	4	69–73	70.1	2.4	

PSA, prostate-specific antigen; TURP, transurethral resection of prostate; PVR, post-void residual, AUA, American Urological Association Symptom Index.

TABLE III
The Effects of Finasteride on Morphometric and Biochemical Change in the Prostate

Variable	Tx	N	Range	Mean	SD	P-value
Area (μm^2)						
Nuclear size	Non-F	26	20.36–56.52	36.91	6.81	0.0003
	F	23	24.13–183.5	49.45	28.6	
Z-score						
Epithelial AR	Non-F	26	–2.23–1.86	0.16	0.94	0.035
	F	23	–2.48–2.68	–0.18	1.02	
Stromal AR	Non-F	26	–1.89–2.83	0.09	1.04	0.223
	F	23	–1.83–2.11	–0.11	0.92	
Epithelial PSA	Non-F	26	–1.56–2.48	0.13	1.04	0.071
	F	23	–1.63–2.44	–0.16	0.90	
Positivity (%)						
Epithelial AR	Non-F	26	38.86–98.28	82.63	10.13	0.007
	F	23	35.00–96.59	77.64	11.82	
Stromal AR	Non-F	26	3.31–49.99	23.94	13.01	0.15
	F	23	1.35–51.12	20.93	12.39	

AR, androgen receptor; PSA, prostate-specific antigen; F, finasteride.

TABLE IV
The Effects of Finasteride on Luminal Epithelial Atrophy and Basal Cell Hyperplasia in BPH Specimens

Formula	Tx	N	Ratio			P-value
			Range	Mean	SD	
Luminal epithelial atrophy (PSA/CK5)	Non-F	26	0.36–28.43	4.64	3.87	0.003
	F	23	0.09–9.27	3.05	2.05	
Basal cell hyperplasia (CK5/[CK5+PSA])	Non-F	26	0.03–0.74	0.23	0.12	0.0003
	F	23	0.10–0.92	0.31	0.17	