Baseline prostate atrophy is associated with lower tumor volume in men with prostate cancer on repeat biopsy

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Abstract:

Introduction: Prostate atrophy (PA) is commonly identified in prostate biopsies. Previous studies suggest PA may be associated with lower PCa risk. However, it remains unclear whether PA is associated with smaller, less aggressive, and less advanced tumors. Thus, we sought to determine whether the presence and severity of baseline PA in men with initial biopsy negative for prostate cancer (PCa) is associated with PCa volume at 2- and 4-year repeat biopsy.

Material and Methods: We performed a retrospective analysis of 927 men 50-75 years-old with negative baseline biopsy and positive 2- or 4-year repeat biopsy for PCa in the Reduction by Dutasteride of PCa Events study. PA (present or absent), PA severity (mild or moderate/marked), and tumor volume were determined by central pathology. The association of baseline PA with repeat biopsy PCa volume was evaluated with linear and Poisson regressions in uni- and multivariable analyses.

Results: PA was identified in 559 (60%) baseline biopsies and was mild in 491 (88%) and moderate/marked in 68 (12%). PA was associated with larger prostate volumes (P<0.001). At 2-year biopsy, PA was associated with lower overall mean total tumor volume (2.21µL vs 2.94µL; P=0.016), mean number of biopsy cores involved (1.85 vs 2.08; P=0.016), mean percent of cores involved (18.4% vs 20.7%; P=0.008), average core involvement (0.23µL vs 0.29µL; P=0.019) and overall mean percent tumor involvement (1.82% vs 2.33%; P=0.018). Similar results were found in multivariable analysis and analysis of 4-year repeat biopsies. Compared to mild PA, moderate/marked PA was associated with greater reduction in tumor volume.

Conclusion: Amongst subjects with repeat prostate biopsy positive for PCa after negative baseline biopsy, the presence and severity of baseline PA were associated with lower PCa volume. This suggests PA may be associated with less aggressive PCa.

Introduction:

Prostate atrophy (PA) is a frequent benign histological finding in prostate needle biopsy specimens. Previous studies have shown that between 40 to 94% of prostate biopsies have histological changes compatible with PA.[1-7] However, the pathogenesis of PA remains not completely understood. Radiation, androgen deprivation, inflammation, and prostate hyperplasia have all been implicated as potential etiologies of PA.[8] Furthermore, the clinical significance of histological PA has been the subject of much study with mixed results. For example, some studies have suggested a potential association between specific types of prostate atrophy, such as proliferative inflammatory atrophy (PIA), and prostate cancer (PCa).[9,10] However, several studies failed to correlate PA with the risk of PCa.[1,2,4] Moreover, we and others have previously shown an association between baseline PA and a lower risk of subsequent PCa detection.[6,7]

Beyond PCa risk, for individuals who are eventually diagnosed with PCa, it is unclear whether the presence of PA correlates with smaller, less aggressive and/or less advanced tumors. This knowledge is particularly important because it may help the decision of whether or not and when to repeat a prostate biopsy. In other words, if atrophy is associated with lower PCa risk and less aggressive tumors, one may opt for a less intense biopsy screening schedule in patient with documented PA. Therefore, the present study evaluated whether the presence and severity of baseline PA in men with a baseline biopsy negative for PCa was associated with PCa volume among men with a positive 2- or 4-year repeat prostate biopsy in the REduction by DUtasteride of PCa Events (REDUCE) study, a randomized clinical trial with systematic prostate biopsies.[11] Since we have previously shown that PA was associated with a significantly lower risk of subsequent PCa detection and lower Gleason scores, we hypothesize PA would be associated with lower tumor volumes among those who were diagnosed with PCa.[7]

Materials and Methods:

Study sample

The design of REDUCE has been published previously.[11] In summary, men aged 50-75 years with serum PSA between 2.5 or 3.0 based on age (50-60 and 60-75 years, respectively) and 10ng/mL, and one negative prostate biopsy (6 to 12 cores) within 6 months prior to enrollment were eligible. Participants were excluded based on history of PCa, high-grade intraepithelial neoplasia, atypical small acinar proliferation, prostate volume (PV) > 80ml, previous prostate surgery or an International Prostate Symptom Score ≥ 25 or ≥ 20 on alpha-blockers or previous finasteride or dutasteride use. Participants were randomized to receive oral dutasteride 0.5mg or placebo daily and followed at 6-month intervals for 4 years. Medical history was obtained prior to randomization. PV was measured by transrectal ultrasonography at the time of randomization and 2 and 4 years later. Per study protocol, at least ten-core transrectal ultrasound-guided prostate biopsies were done at 2 and 4 years. All biopsies specimens including baseline biopsies were read centrally (at Bostwick Laboratories). The pathologist had no knowledge of randomization codes. PA and PCa were coded as present or absent. Each sample was subjectively reviewed by two independent pathologists; when discrepancies were encountered, consensus was achieved in every case after a brief discussion. The extent of PA was categorized as mild (1-2 high power fields at 40x magnification, on an Olympus BX41 microscope), moderate (3-7 field up to about half of the biopsy core or aggregate fragments) or marked (greater than 50% of the biopsy core involved with PA). Given the very low prevalence of marked PA, the groups moderate and marked PA were combined. The primary tumor volume variable was the pathology-measured overall tumor volume (in µL). We also assessed alternatives for overall tumor volume such as number of biopsy cores involved, percent of involved cores (number of cores involved divided by cores sampled, in %), average core involvement (overall tumor volume divided by number of cores sampled, in µL) and overall percent tumor involvement (overall tumor volume divided by overall volume sampled, in %). The study was approved by the institutional review board at all research site, and each participant provided written informed consent. Of the 8,231 participants in REDUCE, 6,316 (76.7%) underwent a study-mandated 2-year repeat prostate

biopsy. The characteristics of participants undergoing at least one study-mandated prostate biopsy have been described previously.[12] Of these, 958 had a positive 2-year repeat biopsy for PCa and were included in the 2-year biopsy study. We excluded 31 (3.2%) participants due to missing data. This resulted in a final 2-year biopsy study sample of 927 participants. Of the total REDUCE sample, 4,740 (57.6%) participants underwent a study-mandated 4-year repeat prostate biopsy. Of these, 470 had a positive 4-year repeat biopsy for PCa and were included in the 4-year biopsy study. After the exclusion of 26 (5.5%) participants due to missing data, the final 4-year biopsy study sample had 454 subjects.

Statistical analysis

Univariable analysis of baseline characteristics comparing men with and without PA were conducted using Student t-test for continuous variables and Fisher's exact test for categorical data. Poisson regression was used to evaluated the association of baseline PA with number of biopsy cores involved, and linear regression used to test the association of baseline PA with for all other tumor volume variables. Log-transformation was applied to overall tumor volume and average core involvement to achieve a quasi-normal distribution. Similarly, percent of involved cores and overall percent tumor involvement logit-transformed. Multivariable analyses were controlled for baseline age (continuous, in years), race (White, Black, Asian, American Hispanic or other), body-mass index (BMI, continuous, in kg/m2), digital rectal exam (DRE, coded as normal or abnormal), PV (continuous, in cm^3), PSA (continuous, in ng/mL), and randomization group (dutasteride or placebo). All covariables were obtained at baseline. Sensitivity analysis including only participants randomized to receive placebo (N = 531 for the 2-year biopsy sample and N = 240 for the 4-year biopsy sample) were performed. Finally, we analyzed the association of PA with 2- and 4-year clinically insignificant PCa defined as Gleason score ≤ 6, PSA < 10 ng/mL, fewer than 3 prostate biopsy cores positive for PCa, 50% or less cancer in each core, PSA density <0.15ng/mL/g. All statistical tests were two-tailed and done using Stata 12.0 (StataCorp, College Station, TX). $P < 0.05$ was considered statistically significant.

Results:

Of the 923 men included in the 2-year biopsy sample, 850 (91.7%) where White. The overall mean (standard deviation) baseline age, PSA, BMI and PV were 64.0 (5.9) years, 6.1 (1.9) ng/mL, 27.2 (3.6) Kg/m^2 and 42.7 (17.7) cm^3, respectively. Abnormal DRE was identified in 34 (3.7%) participants. A total of 396 (42.7%) participants were randomized to the dutasteride group and 531 (57.3%) to the placebo group.

PA was identified in 559 (60.3%) baseline prostate biopsies. Mild PA was detected in 491 (87.8%) while moderate/marked PA was observed in 68 (12.2%) cases. PA was significantly associated with higher prostate volumes ($P < 0.001$). PA was not associated with race, baseline age, BMI, PSA, DRE or randomization group (Table 1). At the 2-year prostate biopsy, the presence of baseline PA was significantly associated with lower overall mean total tumor volume (2.21µL vs 2.94µL; P = 0.016), lower mean number of biopsy cores involved (1.85 vs 2.08; P = 0.016), lower mean percent of cores involved (18.4% vs 20.7%; P = 0.008), lower average core involvement (0.23µL vs 0.29µL; P = 0.019) and lower overall mean percent tumor involvement (1.82% vs 2.33%; P = 0.018, Table 2 and Supplemental table 2). Similar trends were observed in multivariable analysis, however, the magnitude of the effect was attenuated and no longer statistically significant, except for percent of cores involved where P = 0.047 (Table 3). Likewise, at the 4-year biopsy, the presence of baseline PA was also significantly associated with lower overall mean total tumor volume (1.46µL vs 2.20µL; P = 0.022), lower mean number of biopsy cores involved (1.48 vs 1.80; P = 0.009), lower mean percent of cores involved (14.7% vs 18.4%; P = 0.002), lower average core involvement (0.18µL vs 0.24µL; P = 0.019) and overall lower mean percent tumor involvement (1.08% vs 1.93%; P = 0.004). In multivariable analysis, the results were virtually unchanged.

A biological gradient where more severe PA was associated with even greater reduction in tumor volume was detected in the analysis of PA severity (Table 4). However, the same dose-response relationship was not demonstrated in the 4-year biopsy analysis. Finally, in sensitivity analysis of the placebo group only, the results of the 2-year analysis were similar. The association of PA extent with risk of PCa in the 4-year biopsy was much attenuated and no longer significant

in the sensitivity analysis, though the sample size was considerably small (Supplemental tables 1 and 3). Lastly, we analyzed the association of PA with 2- and 4-year clinically insignificant PCa (Table 5). Baseline PA was associated with 63% increase in the odds of insignificant PCa at the 2-year prostate biopsy. Baseline PA was not associated with insignificant PCa at the 4-year prostate biopsy.

Discussion:

In the past decades, there has been several studies evaluating the clinical consequences of PA. For example, histological PA on needle biopsies has been implicated as one of the most common causes of false-positive PCa diagnosis.[13,14] Moreover, PA has been found to mimic PCa in ultrasound and magnetic resonance imaging.[15] However, the clinical significance of PA found in a negative needle biopsy for PCa as it relates to future PCa risk remains controversial. Still, we and others have shown an association of baseline PA and a lower risk of subsequent PCa detection.[6,7] Additionally, we found PA to be associated with lower cancer grade among those who are eventually diagnosed with PCa. Yet, whether PA is associated with other PCa characteristics such as tumor volume remains unknown. Thus, the present study evaluated 927 and 470 men with an initial negative baseline biopsy diagnosed with PCa on repeat biopsy done 2 and 4 years later, respectively. We found the presence of baseline PA was associated with significantly lower PCa volumes in the repeat prostate biopsy. Moreover, we found a biologic gradient were more severe PA was associated with even lower PCa volumes.

Numerous previous studies assessed the correlation between PA and PCa showing mixed results. For example, histological studies have described a morphologic transition of PIA to high-grade intraepithelial neoplasia and PCa.[16] Conversely, Postma *et al*, using data from 202 participants in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer, found no association between PA and PCa.[4] Similarly, Billis *et al* did not identify any topographical correlation between PA and PCa in prostate needle biopsies.[1] However, Servian *et al* found baseline PIA to be associated with nearly 40% reduction in subsequent PCa detection.[6] Similarly, we have previously reported a 40% reduction of PCa detection in a 2-year repeat prostate biopsy among individuals with PA in baseline biopsies.[7] Studies evaluating the relationship between PA and PCa aggressiveness have also shown inconsistent findings. For instance, Davidsson *et al* evaluating men with T1a-b PCa did not find any association between PA and advanced or lethal PCa.[2] Conversely, we have previously shown an association between PA and lower Gleason grades in REDUCE.[7] In the present study, we were able to correlate baseline PA to lower PCa volumes. This is reinforced by the presence

of a dose response relationship where more severe PA were associated with even lower tumor volumes. Thus, although some disagreement between studies still exists, the compound evidence suggests PA may be associated with reduced prostate carcinogenesis as evidenced by lower PCa risk, volume and grade.

The biological mechanisms linking PA to lower PCa risk and lower PCa volume are not known. However, there are numerous possible explanations for the association of PA and lower PCa incidence and aggressiveness. For example, androgen deprivation is a well-established etiology of PA and has been associated with lower PCa risk.[8,17] In this hypothesis, PA may be a marker of a low androgenic state which in turn is associated with lower incidence of PCa. Moreover, some of the other potential causes of PA including benign prostatic hyperplasia, inflammation, and ischemia have also been associated with lower PCa risk.[18-20] Thus, additional studies are needed to better understand the system of causally interacting biological processes that relate PA to lower PCa risk and aggressiveness.

The implications of the results obtained are multifold. First, given atrophy is associated with lower PCa risk and less aggressive PCa, the knowledge about the presence of PA in a prostate needle biopsy could be incorporated in the decision of whether or not and when to perform a repeat biopsy. Second, given the clinical significance of PA, our results encourage pathologists to systematically report the presence, extent and severity of PA in needle biopsies. Finally, our findings support further research of PA as a potential mechanism for therapies to prevent and/or mitigate PCa.

Although the REDUCE study has multiple strengths including its large international and multicentric population, central pathology, prospective data acquisition and per-protocol biopsies, it is not devoid of limitations. For example, we only included patients with PSA values between 2.5-10ng/mL and a negative baseline prostate biopsy, and no off-protocol biopsies, such as transrectal and transperineal needle biopsies, transurethral resections and prostatectomies were considered. Additionally, we were unable to assess specific subtypes of atrophy, including PIA, because they were not evaluated and reported for all biopsies. Finally, although cancer volume in prostate biopsies correlates with cancer volume in the entire prostate and overall

cancer aggressiveness, it is still important to validate our results in radical prostatectomy specimens.

In conclusion, among subjects enrolled in a clinical trial who were diagnosed with PCa in the 2- and 4-year repeat prostate biopsy after a negative baseline biopsy, the presence and severity of baseline PA was significantly associated with lower PCa volumes. These findings suggest baseline PA may be associated with less aggressive PCa.

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