Editorial
Prostate diseases and male voiding dysfunctions

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Prostate Cancer Mortality and Use of 5-Alpha Reductase Inhibitors

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Prostate cancer prevention was a goal of intense research and expenditure in the nineties through the early two-thousands. The largest prevention trial ever planned was the Selenium and Vitamin E Prostate Cancer Prevention Trial (SELECT) which enrolled 35,533 men but closed early due to futility and concern for increased prostate cancer from vitamin E [1]. A slightly different story but similar fate occurred with the Prostate Cancer Prevention Trial, which randomized 18,882 men with no clinical evidence of prostate cancer to take the 5-alpha reductase inhibitor (5-ARI) finasteride *vs.* a placebo [2]. The trial showed a 24.8% overall relative risk reduction in prostate cancer incidence, yet widespread use of finasteride for prevention never occurred. The reason is that the trial also showed a small but significant increase in the incidence of higher grade prostate cancer in the treatment arm, which led to a US Food and Drug Administration black box warning on the medication. Ultimately, this risk was understood to be due to detection bias inherent in the use of finasteride, but the stigma remained [3]. Perhaps more importantly, the reduction in prostate cancer was only seen in low risk, clinically insignificant prostate cancer. A second 5-ARI trial with dutasteride, a more potent blocker, also reported similar results, for low risk prostate cancer prevention [4]. Due to the lack of benefit in clinically significant disease, and controversy surrounding potential harms, this class of medication was never adopted for prevention and remained a footnote in prostate cancer history.

A new study from Sarkar et al [5] suggests the 5-ARI story in prostate cancer is not over yet, however. Finasteride and dutasteride are commonly used to improve bladder outlet obstructive urinary symptoms in men with benign prostatic hyperplasia. In addition to a reduction in the size of the prostate, one of the most prominent effects of these medications is an approximate 50% reduction in the serum prostate specific antigen (PSA) concentration [6]. The appropriate PSA based screening for prostate cancer practice in men on 5-ARIs is to therefore normalize the PSA by doubling it in these men, for appropriate population based comparisons [7]. There has been speculation that this normalization is seldom done in primary care practices that pursue PSA screening in general, which may lead to delays in detection and worse outcomes for some men. Sarkar and colleagues [5] performed a retrospective cohort comparison of men in the Veterans Affairs

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database who were diagnosed with prostate cancer from 2001 to 2015. The cohort consisted of 80,875 men, of whom 8,587 (10.6%) had been prescribed a 5-ARI at least 1 year prior to diagnosis. The study found that men taking 5-ARIs had significantly higher rates of prostate cancer-specific (39% greater) and overall (10% greater) mortality. Interestingly, there was no difference in non-cancer related mortality. Secondary outcomes were also worse across all measures in the 5-ARI group, showing a significant delay in time to diagnosis of cancer (3.6 *vs.* 1.2 years), higher adjusted PSA value (13.5 *vs.* 6.4 ng/mL), higher grade (25.2% *vs.* 17% Gleason 8–10), stage (4.7% *vs.* 2.9% T3–4), presence of lymph nodal (3.0% *vs.* 1.7%), and metastatic disease (6.7% *vs.* 2.9%) at diagnosis.

In the absence of randomized controlled trials, these findings would raise greater concerns over the effects of 5-ARIs to directly influence the genomic behavior of prostate cancer, leading to aggressive and more lethal disease. But prior randomized controlled trials show at most a small increase in the incidence of more aggressive disease, a finding which is likely due to detection bias [3]. While this explanation is still possible based on the study's observational design, a more likely explanation is the delay in diagnosis in men taking 5-ARIs, related to the misinterpretation of their artificially lower PSA values. Although the absolute median delay in diagnosis time was only 2 years, in this cohort it was associated with a median PSA of 13.5 ng/mL, a value more than twice the median in men not taking 5-ARIs, and a significant predictor for more aggressive disease. Setting aside discussions about PSA based prostate cancer screening in general, and accepting that all major guideline-based organizations in the US, including the US Preventive Services Task Force, now recommend at least a discussion about PSA-based screening for certain aged groups, it appears imperative to address the appropriate adjustment of PSA values in men taking 5-ARIs. Further investigation into current primary care PSA screening practices appears warranted.

Conflicts of Interest

Dr. Canfield is a consultant for Pfizer and Genomic Health, but he made no influence on this work in relation with the company or its products. Dr. Wang is a consultant for the Boston Scientific Corporation and the Coloplast Corporation, but he made no influence on this work in relation with the company or its products. Dr. Foldes has no disclosures.

Authors Contribution

Conceptualization: All authors. Formal analysis: CAF, SEC. Methodology: CAF, SEC. Project administration: RW. Supervision: RW. Writing – original draft: CAF, SEC. Writing – review & editing: RW.

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