Increasing aggressive prostate cancer

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Introduction: *To compare prostate biopsy (Pbx) characteristics, before and after the 2012 United States Preventive Services Task Force (USPSTF) prostate cancer screening guidelines in our practice.*

Materials and methods: *We completed a retrospective comparative analysis of 1703 sequential patients that had a Pbx in 2010 to 2012 (3 years) with 1006 patients biopsied in 2018, 2019 and 2021 (3 years). Data from a total of 2709 Pbx was collected on patient age, race, prostate-specific antigen (PSA), digital rectal examination (DRE) and Gleason sum score (GSS). The data was analyzed to determine whether the 2012 USPSTF screening recommendations against prostate cancer screening may have affected prostate cancer characteristics. Two study groups were defined as Group A and Group B. Group A represents Pbx prior to the 2012 USPSTF screening guidelines (2010-2012) and Group B represents Pbx in 2018-19 and 2021. The patient population consisted of 76% Black, 14% White and 11% other.*

Results: *The number of patients that had a Pbx in Groups A vs. B: 567 patients/year vs. 335 patients/year. The annual positive Pbx rate for Group A vs. B: 134/year vs. 175/year. High grade prostate cancer (GSS 7-10) in Groups A vs. B: 51.5% vs. 59%. The proportion of patients with a PSA 10 ng/mL or greater in Groups A vs. B: 25.4% vs. 31%. The PSA 10 ng/mL and over and GSS 7-10 was higher in Group B for all age groups. In 2021, GSS 7-10 was present in 64% of 70-80 year olds. In Group B, GSS 6 decreased by 7.5% while GSS 7-10 increased by 7.5% compared with Group A.*

Conclusions: *Our data through the year 2021 shows that after the 2012 USPSTF recommendations against prostate cancer screening, Pbx decreased and prostate cancer diagnosis and high grade (GSS 7-10) prostate cancer increased. As our patient population consists of 76% Black patients and 33% of men age 70-80 years old, our results support annual prostate cancer screening for US men 50-80 years old and especially high-risk patients that include Black men, men with a family history of prostate cancer and healthy men age 70-80 years old. Annual DRE- and PSA- based prostate cancer screening will likely markedly decrease prostate cancer morbidity, mortality and the cost of prostate cancer management.*

Key Words: prostate cancer, PSA, screening, United States Preventive Services Task Force

Introduction

Prostate cancer is the most common cancer in men and the second-leading cause of cancer death in U.S. men. One in eight men will be diagnosed with prostate cancera during their lifetime. In 2017, the American Cancer Society (ACS) reported an estimated 161,360 new cases of prostate cancer and 26,730 deaths due to prostate cancer in US men. In 2021, the ACS recorded a rise of new prostate cancer cases to 248,530 and deaths due to prostate cancer to 34,130. The incidence of prostate cancer among all races is 123.2 (per 100,000 population); it is the highest (198.4) in Black men and 114.8 in Caucasian men. Black men have 60% more cases of prostate cancer and more advanced stages of prostate cancer compared to Caucasian men. The incidence of prostate cancer is the highest in men 65 years and older (66%).[1,2] In 20 years prior to 2012, PSA- and DRE- based prostate cancer screening was associated with more than a 50% lower rate of prostate cancer mortality.[3] There are 3.1 million prostate cancer survivors in the US.[4] Treatment of localized prostate cancer results in a 10 year survival of 98%.[5]

In 2012, the USPSTF recommended against prostate cancer screening for all age groups (grade D).[6,7] Survey

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data indicate that subsequent to 2013, 50%-56% of primary care doctors did not offer prostate cancer screening to their patients.[8,9] In 2013, national prostate cancer screening decreased by 18%.[10] Unfortunately, a 72% rise in metastatic prostate cancer compared to that in 2004 has been reported.[11-13] It is estimated that if the prostate cancer screening is discontinued, 6000 additional deaths due to prostate cancer would occur annually in the US.[14] In 2018, the USPSTF upgraded its recommendation for prostate cancer screening to Grade C in men 55-69 years old and continued to recommend against screening in men 70 years and older.[15] As the life expectancy for US men is approximately 84 years of age, an increasing number of healthy elderly men will be at risk for high-grade prostate cancer.[16] A 10-year study of 230,081 US veterans found that 10.5% died from prostate cancer and 77.4% of the prostate cancer deaths occurred in men between the age of 70 to 89 years.[17] There are approximately 24 million US men age 70 years and older. Men in the age group 70-80 years have a higher incidence of prostate cancer, more aggressive cancer, more metastasis, and more deaths due to prostate cancer. Medicare and Medicaid cover annual prostate cancer screening. In our previous studies, we showed that after the 2012 USPSTF recommendations against prostate cancer screening, the number of prostate cancer diagnoses, and especially high-grade prostate cancer, increased.[18,19] In this study, we updated our data through 2021 to determine if this rising trend continues.

Materials and methods

In 2014, we published a retrospective analysis of 402 prostate cancer patients diagnosed by prostate biopsy (Pbx).[20] The study examined the Pbx characteristics of prostate cancer patients from 2010-2012 (3 years). In 2018, we published a comparison of Pbx characteristics prior to (2010-12) and after (2015-2017) the 2012 USPSTF recommendations against prostate cancer screening.[21] In 2019, we published a comparison of Pbx characteristics performed through 2018.[18] In 2020, we analyzed an additional 310 patients who had a prostate biopsy in 2019 showing that the trend continued.[19] The current analysis updates our database through 2021. Data was collected on patient age, race, PSA, DRE and GSS. We believe that the COVID-19 pandemic did not affect our study results because the GSSs from 2019 vs. 2021 were not significantly different.

All cases are collected from our community clinical practice of a group of 10 board-certified urologists located in Prince George's County, Maryland, in the Washington DC metro area. Pbx was performed on men with a PSA of over 2.5 ng/mL, an abnormal DRE, or both. Most of the patients had a trans-rectal ultrasound guided (TRUS) 12 core Pbx under intravenous sedation on an outpatient basis (some patients were biopsied under local anesthesia). MRI fusion biopsy was not used in our practice during the study time period. Our practice was to obtain a pelvic MRI and/or CT imaging after the prostate cancer diagnosis as part of staging for extracapsular extension, seminal vesicle involvement and/or pelvic lymph nodal involvement. All patients were cleared for the procedure by their primary care physician.

Patient age was stratified as under 55, 56-69 and 70-80 years. The charts of 2,709 consecutive patients from our practice were reviewed, and the information was entered in a database. The data was analyzed to determine whether the 2012 USPSTF screening recommendations affected prostate cancer characteristics. Two study groups were defined, Group A - patients diagnosed prior to the USPSTF screening recommendations (2010-2012) and Group B - patients diagnosed after the USPSTF screening recommendations in 2018-19 and 2021. The year 2020 was omitted due to office disruption from the COVID-19 pandemic. We separated the GSS into two groups, GSS 6 and GSS 7-10. We defined the GSS 7-10 group as high grade because it harbors a Gleason pattern 4 or higher component.

We analyzed multi-way contingency tables using Bayesian log-linear Poisson regression.[22] These models have the general structure (for three way tables),

$$\text{count}_{ijk} \sim \text{Poisson}(\mu_{ijk}) \quad (1)$$

$$\log \mu_{ijk} = \lambda_0 + \lambda_i + \lambda_j + \lambda_k + \lambda_{ij} + \lambda_{ik} + \lambda_{kj} + \lambda_{ijk}. \quad (2)$$

To regularize the problem, we employed the weakly informative priors $\lambda_{(.)} \sim N(0,5)$ on the model parameters. These parameters have the simple interpretation of being log likelihood ratios. Using, PyMC3, we utilized Markov Chain Monte Carlo in order to sample from the model posteriors. We note log likelihood ratios with posterior 94% credible intervals that exclude zero.

The study was approved by the Western Institutional Review Board (study number 1087891).

Results

Patient characteristics

The patient characteristics are shown in Table 1. The age categories were divided into three groups, < 55, 56-69 and 70-80 years old. Patient race is indicated as Black, White, and others. The study was conducted in the Washington DC metro area, Prince George's

TABLE 1. **Patient characteristics in Group A (2010-12) vs. Group B (2018, 2019, 2021)**

	Group A (n = 402) 2010-2012	**Group B (n = 526) 2018, 2019, 2021**
Age (years)		
< 55	36 (9%)	47 (9%)
56-69	226 (56%)	311 (59%)
70-80	140 (35%)	168 (32%)
Race		
African-American	-	398 (76%)
Caucasian	-	72 (14%)
Other	-	56 (11%)
PSA (ng/mL)		
< 4	45 (11.2)	30 (6%)
4-9.9	255 (63.4%)	329 (63%)
≥ 10	102 (25.4%)	165 (31%)
unspecified		2 (0.4%)
Gleason sum score		
6	195 (48.5%)	215 (41%)
7-10	207 (51.5%)	311 (59%)
Digital rectal exam		
Normal	151 (37.5%)	331 (63%)
Abnormal	251 (62.4%)	195 (37%)

PSA = prostate specific antigen

County (PGC), Maryland. According to the 2015 American Community Survey, PGC had 62% Blacks, 14% Whites and 25% other races. Our study had a Black representation of 76%, Whites 14% and others 11%. Although, we were not able to extract the race from the data set for group A, since the study consisted of patients in the same county and in the same urology practice, we assume that the demographics are consistent between study groups.

We show the breakdown by PSA levels of < 4, 4-9.9 and ≥ 10 ng/mL. The GSS are shown as 6 and 7-10. The GSS was grouped as 7-10 to indicate high grade tumors that have a Gleason grade 4 component. The DRE is categorized as either normal or abnormal.

Pbx statistics, Table 2

In the pre-USPSTF period (Group A), 1703 total Pbx were performed over 3 years. The Pbx rate was 567 biopsies/year. There were 402 positive prostate biopsies over 3 years (24%). The annual positive biopsy rate is 134 positive biopsies/year. In the post-USPSTF period (Group B), there were 1006 total Pbx, an annual rate of 335 biopsies/year. The Pbx decreased in Group B by 41%. There was 526 total positive Pbx in Group B (52%) and the annual positive Pbx rate was 175 positive biopsies/year. The total number of positive Pbx increased in Group B, 52% vs. 24% in Group A, a relative increase of 100%. The total number of positive Pbx annualized was 31% higher in Group B vs. Group A. The positive Pbx rate of patients 70-80 years old in both Groups A and B averaged 33% (of the total patient population).

TABLE 2. **Comparison of biopsy statistics in Group A (2010-12) vs. Group B (2018, 2019, 2021)**

	Group A 2010-2012	**Group B 2018, 2019, 2021**
Total biopsies (n = 2709)	1703	1006
Annual biopsy rate	567	335 (41%↓)
Total positive biopsies	402 (24%)	526 (52%)
Annual positive biopsy rate	134/year	175/year (31%↑)

TABLE 3. **Comparison of prostate-specific antigen (PSA) levels by age in patients with a positive Pbx, Groups A vs. Group B**

Age (years)	n	PSA < 4 ng/mL	PSA 4-9.9 ng/mL	PSA 10 ng/mL and over
Group A (2010-12)				
< 55	36	5 (13.9%)	25 (69.4%)	6 (16.6%)
56-69	226	23 (10.2%)	150 (66.4%)	53 (23.5%)
70-80	140	17 (12.1%)	80 (57.1%)	43 (30.7%)
Total	402	45 (11.2%)	255 (63.4%)	102 (25.4%)
Group B (2018, 2019, 2021)				
< 55	47	3 (6%)	33 (70%)	11 (23%)
56-69	310	16 (5%)	202 (65%)	92 (30%)
70-80	169	11 (7%)	97 (57%)	61 (36%)
Total	526	30 (6%)*	332 (63%)	164 (31%)*

*the log odd ratio comparing the total Group B vs. A is statistically significant for PSA < 4 ng/mL (mean 0.524 +/- 0.132) and for PSA 10 ng/mL and over (mean 1.262 +/- 0.192)

PSA levels by age in patients with a positive Pbx, Table 3

The PSA in Group A was under 4 in 11%, 4 to 9.9 in 63% and 10 and over ng/mL in 25%. In Group B, the PSA was under 4 in 6%, 4 to 9.9 in 63% and 10 and over ng/mL in 31%. According to the statistical analysis, there was a statistically significant reduction in early prostate cancer presentation with PSA < 4 ng/mL in Group B (log odd ratio mean 0.524 +/- 0.132). Group B was also found to have a statistically significant increase in patients with an advanced prostate cancer presentation with PSA 10 ng/mL and over (log odd ratio 1.262 +/- 0.192).

GSS by age in patients with a positive Pbx, Table 4

In Group A, GSS of 6 was in 195 patients (49%), in Group B, 215 patients (41%). In Group A, GSS of 7-10 was in 207 patients (52%) and in Group B, 311 patients (59%). According to the statistical analysis, GSS 7-10 was statistically higher in Group B (by 8%) as compared to Group A (log odd ratio 1.392 +/- 0.197). High grade (GSS 7-10) disease was more frequent in all age groups in Group B vs. Group A. In the age group 70-80, the overall GSS 7-10 was high and especially statistically higher in Group B vs. Group A, 64 vs. 61%, respectively.

Discussion

This study reviewed our community-based urologic practice and found that the Pbx rate decreased by 41% in the post-2012 USPSTF period (Group B). Despite

TABLE 4. **Comparison of Gleason sum score (GSS) by age in Group A (2010-2012) vs. Group B (2018, 2019, 2021)**

Age (years)	n	GSS 6	GSS 7-10
Group A (2010-2012)			
< 55	36	18(50.0%)	18(50.0%)
56-69	226	122(54%)	104(46.0%)
70-80	140	55(39.3%)	85(60.7%)
Total	402	195(48.5%)	207(51.5%)
Group B (2018,2019,2021)			
< 55	47	21 (45%)	26 (55%)
56-69	310	133 (43%)	177 (57%)
70-80	169	61 (36%)	108 (64%)
Total	526	215 (41%)	311 (59%)*

*the log odd ratio comparing the total Group B vs. A is statistically significant for GSS 7-10 (mean 1.392 +/- 0.197)

a significantly reduced Pbx rate, the prostate cancer detection rate increased by 2x (100%) post-2012 USPSTF recommendations. High grade prostate cancer was increased after the 2012 USPSTF recommendations for each age group and overall consisted of 59% of all positive Pbx (compared to 51.5% prior to the 2012 USPSTF recommendations).

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) on which the USPSTF based their 2012 recommendation against prostate cancer screening was flawed as it was found to be 90% contaminated and hence should not form the basis of national guidelines.[23,24] Unfortunately, following the 2012 USPSTF guidelines against prostate cancer screening, there was a 64% decrease in DRE and a 39% decrease in PSA screening.[25] Other large studies have replicated our results and have shown that after the 2012 USPSTF guidelines, Pbx have decreased, positive Pbx have increased and have been associated with increased rates of high-grade tumors and more advanced disease presentations.[26-33] Jemal et al found the incidence for regional and distant stage disease increased for men aged 50-74 and ≥ 75 by 5.2% per year from 2010-2016, based on an analysis of the US Cancer Statistics Public Use Research Database.[34]

The benefit of prostate cancer screening was reconfirmed by Alpert in which a review of 400,887 patients under age 80 showed that annual PSA- based screening was associated with a decrease in prostate cancer deaths by 64% and all-cause mortality by 24%.[35] Annual PSA- and DRE- based prostate cancer screening decreased from 61.8% in 2008 to 50.5% in 2016 while prostate cancer metastasis increased from 6.4% in 2008 to 9% in 2021.[33]

Our study is unique because 76% of the study population was Black, a high-risk group. The 2012 USPSTF guidelines were based on studies in which high-risk populations were underrepresented (only 4% were Black in the PLCO study).[36-38] A recent study showed that GSS 6 is more aggressive in Blacks compared to non-Blacks and is associated with 100% increase in the prostate cancer death rate.[39] High-risk populations, especially Blacks and healthy men 70-80 years old, are disproportionately adversely affected by the current USPSTF guidelines.

Our data of TRUS Pbx rates showed that 64% of men 70-80 years old had high grade GSS 7-10 (Group B). In our prior study of 5100 US men 70-80 years old with average-risk prostate cancer patients (84% with PSA less than 10 ng/mL), 61% had a GSS of 7-10.[40] The published US literature shows that men 70 years and over have a higher prevalence of prostate cancer, more locally advanced prostate cancer, more metastatic prostate cancer, and more deaths due to prostate cancer.[41-43] Currently, the USPSTF recommends against prostate cancer screening in men 70 years and older. As 33% of all positive Pbx patients were in the 70-80 years age group, our study shows that limiting screening for high-risk men over age 70 is definitely harmful.

Since 2013, more locally advanced prostate cancer, metastatic prostate cancer, and prostate cancer specific deaths have been documented. The 5-year survival rate in metastatic prostate cancer is 30% and the cost of treating metastatic prostate cancer is well over $200,000.[44] More importantly, patients with metastatic prostate cancer have more pain, a much lower quality of life, and almost certain prostate cancer-specific death. The Center for Medicare and Medicaid Services (CMS) spent 11.8 billion dollars in 2010 and 15.3 billion dollars in 2016 for prostate cancer care.[45] The annual cost of the screening PSA test is about $25 (Labcorp).

At least 75,000 new patients with prostate cancer per year in the US are diagnosed with low-risk disease (including Gleason grade group 1), and active surveillance (AS) is the preferred management strategy for most of these patients as recommended by the major guidelines.[46,47] According to a series of 10,000 men undergoing radical prostatectomy, 50% of grade group 1 patients are upgraded.[48] A recent study of 8,726 men with GSS 6 on AS found that 60% of Black and 48% of Caucasian men had disease progression and required treatment.[49] Eighty-eight percent of men with Gleason grade group 2 (GS 3+4=7) on AS eventually require treatment.[50,51] The finding of bilateral involvement with prostate cancer is a risk factor for early failure of AS.[52] It is crucial for both patients and urologists that patients on AS have vigilant follow up.

Over the last several years, new tools to facilitate prostate cancer detection and risk stratification have entered clinical practice. These include imaging technology such as the multi-parametric prostate MRI,[53] novel genetic and molecular tests,[54] chemical assays[55] and enhanced imaging such as the Prostate Specific Membrane Antigen (PSMA) PET/CT.[56] These new diagnostic and risk stratification tools give clinicians the ability to counsel patients regarding which prostate cancers are indolent and appropriate for AS and which are aggressive and need early treatment. Use of these tools help to rule out high-grade prostate cancer prior to enrolling patients in AS, especially in high-risk groups such as Black men, men with a family history of prostate cancer and men age 70-80 years old. In the US, 50% of positive Pbx have GSS 6 and half of those progress under AS. Therefore, half of those GSS 6 patients may benefit by AS followed

by deferred treatment. Currently, there is no test that can definitively determine which GSS 6 prostate cancer will progress and which will not.

Conclusions

This study shows that the annual Pbx rate decreased by 41% after the 2012 USPSTF prostate cancer screening guidelines but the annual prostate cancer detection rate increased by 31%. High-grade GSS (7-10) prostate cancer increased by 8% after the 2012 USPSTF guidelines. Despite a 41% reduction in the total number of biopsies there was a 2x increase in the total number of positive biopsies. As our patient population included 76% Black men and 33% men age 70-80 years old, these findings suggest that the USPSTF should consider endorsing prostate cancer screening in high-risk populations to decrease the rising trend of prostate cancer morbidity, mortality, and the high cost of treating advanced prostate cancer. We strongly recommend that PSA- and DRE- based annual prostate cancer screening be made available to all US men age 50 and over; especially to Black men, men with a family history of prostate cancer, and healthy men 70-80 years old. Medicare covers annual prostate cancer screening for men 65 years and older; Medicaid covers annual prostate cancer screening for men 50 years and older. Proper screening will likely markedly reduce prostate cancer morbidity, mortality, and the cost of prostate cancer care. □

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