Histologic Changes in Prostate Cancer Detected Subsequent to the 2012 United States Preventive Services Task Force (USPSTF) Prostate Cancer Screening Recommendation

Carl A. Olsson, MD,[1-3] Hugh J. Lavery, MD,[1] Kamlesh K. Yadav, PhD,[1] Ann E. Anderson, MD,[1,2] Deepak Kapoor, MD[1,2]

[1]Department of Urology, Icahn School of Medicine at Mount Sinai, Elmhurst, NY; [2]Integrated Medical Professionals, PLLC, Melville, NY; [3]Columbia University Medical Center, New York, NY

We report changes in the histopathology of prostate cancer diagnosed in a large urology group practice after the final United States Preventive Services Task Force (USPSTF) Grade D recommendation against prostate-specific antigen screening. All prostate biopsies performed from 2011 through 2015 in a large urology group practice were retrospectively reviewed; 2012 was excluded as a transition year. The changes in biopsy data in years following the USPSTF decision (2013-2015) were then compared with baseline (2011). A total of 10,944 biopsies were evaluated during the study period. Positive biopsy rates rose from 39.1% at baseline to 45.2% in 2015 ($P < 0.01$) with a marked shift toward more aggressive cancer throughout the study period. The absolute number of patients presenting with Gleason Grade Group 4 or 5 increased from 155/year at baseline to 231, 297, and 285 in 2013, 2014, and 2015, respectively ($P < 0.05$), unrelated to age or racial changes over time. Black men represented 16% of the cohort. Since the USPSTF recommendation against prostate cancer screening, trends toward a substantial upward grade migration and increased volume of cancers were noted in a cohort of nearly 11,000 patients in a real- world clinical practice. Additionally, continuing reductions in cancer detection in the United States may exacerbate these trends.

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KEY WORDS

Prostate cancer, histopathology • Prostate cancer screening • Prostate cancer, grade migration

The United States Preventive Services Task Force (USPSTF) released a recommendation against screening for prostate cancer (grade D) in draft form in October 2011 that was finalized and published in May 2012.[1] Since that recommendation, there have been marked decreases noted in rates of prostate-specific antigen (PSA) screening,[2-4] prostate biopsies performed,[5-7] and new diagnoses of prostate cancer.[8,9] By 2014, rates of initial diagnosis of prostate cancer had fallen by approximately 18% nationally in the United States and are continuing to fall to the present day.[9,10]

The stated goal of the grade D recommendation for prostate cancer screening was to reduce the overdiagnosis and overtreatment of low-risk prostate cancers that are unlikely to result in morbidity and mortality in a given patient's lifetime.[1] Initial publications have confirmed that there has been a reduction in the diagnosis of all prostate cancers. Other reports have suggested an increase in the absolute rates of higher grade and stage prostate cancer,[5,6] with implications that cancers are being diagnosed later in their natural history. However, some of the cohorts studied have been small with short follow-up, prompting us to objectively assess whether changes in prostate biopsy histology had occurred and whether these changes have persisted over time.

To assess the effect of the USPSTF recommendation on a large, real-world clinical population, we queried the electronic medical record system of our large urology group practice in the metropolitan New York City area from 2011 through 2015. Our primary endpoints were the overall rates of positive prostate biopsies along with the Gleason scores of each biopsy core, which were converted into Gleason Grade Groups (GGGs) from 1 to 5, corresponding to 2014 International Society of Urological Pathology (ISUP) Consensus Conference recommendations.[11]

Materials and Methods

In the fall of 2010, our large urology group practice in the greater New York City metropolitan area, servicing 1.6 million active patients, began a laboratory information system (LIS) that included all prostate biopsies. This coincided with the development of our own pathology division certified by the College of American Pathologists.

This LIS database was retrospectively queried for all patients undergoing initial prostate biopsy from January 1, 2011 through December 2015. The calendar year of 2012 was considered a transition year, given the draft USPSTF recommendation in late 2011 and its final publication in 2012; thus, biopsies in that year were excluded. The baseline group consisted of biopsies performed during calendar year 2011; calendar year 2010 was excluded as a partial year.

Patients with prostate cancer in their biopsy constituted the primary study population. Patients with a prior diagnosis of prostate cancer undergoing surveillance biopsy were excluded, as were men undergoing saturation or MRI-ultrasound fusion-targeted biopsies. Patient age and self-identified race at the time of biopsy were collected and reported.

All biopsies were standard, systematic 12- to 14-core specimens. Overall percentage-positive biopsies as well as percentage-positive cores containing cancer were calculated and reported. Each cancer-containing biopsy core was individually reviewed by two of three fellowship-trained genitourinary pathologists working in our practice and evaluated for Gleason score, which was then converted into a GGG ranging from 1 to 5 as previously described.[11] The patient's overall GGG was defined as the highest group in any core. High-risk cancers were defined as those with a GGG of 4 or 5, corresponding to a Gleason score of $4 + 4 = 8$ or higher.

Data from the calendar year 2011 were considered baseline and compared to annualized data from 2013-2015. Statistical analysis was performed with SPSS v.23 (IBM, Armonk, NY), with *z*-tests, chi-squared, and *t*-tests used where appropriate with significance defined as $P < 0.05$. The authors declare no conflict of interest.

Results

A total of 10,994 prostate biopsies were performed in the study period, with annual prostate biopsies summarized in Table 1. Positive biopsy rates increased from 39.1% in 2011 to 45.2% in 2015 ($P < 0.01$). Demographic data is presented in Table 2. The age of the patients remained relatively constant at 66 years throughout the study period. Race distribution showed no substantial variation over the study period, with ~80% white, ~16% black, and 4% other (Native Americans, Asians, and Pacific Islanders).

Among the 4622 patients with positive biopsies, a total of 56,816 biopsy cores were obtained, of which 18,654 were positive (33.1%). (Table 1) The proportion of positive biopsy cores increased from 32.1% at baseline to 34.8% in 2014 ($P < 0.01$) and marginally lost significance in 2015 ($P = 0.09$), suggesting a trend toward increased volume of cancer per positive biopsy over time.

The association of Gleason grades with increasing positive biopsies was analyzed by overall and percentage trends in GGG distribution over time (Table 3). GGG 5 biopsies per year more

TABLE 1

Percentage Positive Biopsies and Percentage Positive Cores Over Time

Year	N	Positive	% Pos	*P* Value	Total Cores	Pos Cores	% Pos	*P* Value
2011	2421	946	39.1%	n/a	11,409	3655	32.1%	n/a
2013	2949	1219	41.3%	0.09	14,790	4619	31.3%	0.44
2014	2775	1179	42.5%	0.01	14,521	5014	34.8%	0.01
2015	2799	1266	45.2%	0.00	16,096	5366	34.0%	0.09
Total	10,944	4622	42.2%		56,816	18,654	33.1%	

P values compare test year vs baseline year (2011).
n/a, not applicable; Pos, positive.

TABLE 2

Patient Demographics

	Age		Race				
Year	Value	*P* Value	White	Black	API	NA	Multi
2011	66.2	n/a	80.2%	15.5%	3.3%	0.6%	0.4%
2013	65.5	0.00	78.6%	16.1%	4.2%	0.2%	0.9%
2014	65.7	0.03	79.8%	14.9%	4.3%	0.2%	0.8%
2015	65.9	0.22	78.9%	16.4%	3.9%	0.1%	0.7%
Total	65.8		79.3%	15.7%	4.0%	0.2%	0.7%

P values compare test year vs baseline year (2011).
API, Asian Pacific Islander; NA, Native American; Multi, multiple races.

TABLE 3

Number of Patients With Highest Gleason Grade Groups Over Time

Year	1 (%)		2 (%)		3 (%)		4 (%)		5 (%)		Total	Mean GGG	*P* Value
2011	403	(42.6%)	243	(25.6%)	145	(15.3%)	94	(9.9%)	61	(6.4%)	946	2.12	
2013	603	(49.4%)	235	(19.2%)	150	(12.3%)	103	(8.4%)	128	(10.5%)	1219	2.11	0.90
2014	461	(39.1%)	244	(20.6%)	177	(15.0%)	127	(10.7%)	170	(14.4%)	1179	2.41	0.00
2015	554	(43.7%)	239	(18.8%)	188	(14.8%)	114	(9.0%)	171	(13.5%)	1266	2.30	0.00

P values compare mean Gleason Grade Group in test year vs baseline year (2011).
GGG, Gleason Grade Group.

than doubled from 6.4% at baseline (n = 61) to 13.5% (n = 171) in 2015 ($P < 0.01$). Although the absolute number of GGG 1 (Gleason 6, low risk) cancers varied by year, the percentage of GGG 1 cancer remained relatively constant from 2011 to 2015 (42.6% and 43.7%, respectively; $P = 0.59$). The incidence of GGG 2 cancers decreased significantly (25.6% to 18.8%; $P < 0.01$) whereas the change in GGG 3 (15.3% to 14.8%) and GGG 4 (9.9% to 9.0%) from 2011 to 2015 were not significant ($P = 0.76$ and 0.46, respectively). However, the total number of GGG 4 plus GGG 5 cancers found rose from 155 at baseline to 231, 297, and 285 in subsequent years ($P < 0.05$), while overall mean GGG increased from 2.12 to 2.30 from 2011 to 2015, respectively ($P < 0.01$).

Discussion

Since the USPSTF recommendation against PSA screening, there have been a number of studies reflecting significant change not only in the decrease in incidence of prostate cancer screening and number of prostate cancers diagnosed in the United States, but also the stage and grade of newly diagnosed patients.[2-9] Studies emanating from individual hospitals and healthcare systems clearly indicate significant reductions in PSA testing, referrals for elevated PSA, performance of prostate biopsies, and lower detection rates of prostate cancer.[3,5-7] It is clear that these changes are at least temporally associated with the USPSTF recommendation, even if a causal link has yet to be definitively established.

More recent studies have reflected similar changes nationally. One study based on the National Health Interview Survey (NHIS) showed significant declines in PSA-based screening in men over age 50 years; the decline was from 33.2% to 24.8% in men aged 50 to 59 years and from 51.2% to 43.6% in men aged 60 to 74 years.[4] A review of the National Cancer Database (NCDB) revealed a nationwide decrease of 28% in incident diagnoses of prostate cancer in the single year after the USPSTF draft recommendation.[8] Similarly, a review of SEER data showed a predicted decrease in prostate cancer detection in men over 50, from 213,562 men in 2011 to 180,043 men in 2012, a drop of 33,519 (15.7%) cancers detected in a single year.[9] A recent analysis of >20,000 men before and after the USPSTF decision, also using the NHIS, found that the largest declines in men reporting PSA screening occurred between 2010 and 2013 and the declines were greatest in men aged 50 to 54 years (from 23% to 18%) and men aged 60 to 64 years (from 45% to 35%). These declines were greater than observed in the elderly population (age >75 years), the opposite of the intended effect of reducing screening among those least likely to benefit.[1]

There is mounting evidence that the cancers being identified are of higher risk. A single institutional study reported a 31% reduction in prostate biopsies two and a half years after the USPSTF recommendation. These authors also reported a statistically higher PSA level, and significantly higher clinical stages and D'Amico risk scores at the time of diagnosis.[5] A second communication also reported an increase in the percentage of new prostate cancers of GGG 8 or higher from 21% to 30% in the 3 years following the USPSTF recommendation.[12]

Our cohort of patients is unique in that it represents the same group of pathologists reading each of nearly 11,000 prostate biopsies performed over a 4-year period, eliminating the variation seen in multi-institution trials. In addition, our local study population is one of few reflecting a true representation of the black population.[13] Our data suggest that the detection rate of high-grade cancers has increased in both absolute and relative terms since the USPSTF recommendations against prostate cancer screening. Meanwhile, the rates of detection of low-risk disease, the reduction of which was the stated goal of the USPSTF, did not significantly change. Indeed, the only significant decrease in detection was in GGG 2 cancers, intermediate-risk tumors that are possibly among the most likely to benefit from early detection and treatment. Overall, there was a significant increase in GGG, with the most substantive increase noted in GGG 5. This data supports other findings of more advanced cancers in the years following the USPSTF recommendation.[5,12]

The representation of blacks in our cohort with rates roughly comparable with national demographics (16%) is another strength of our study. It has been noted that most prostate cancer clinical trials have disproportionately low rates of black participants, especially the Prostate, Lung, Colon and Ovarian (PLCO) trial at 4.4%.[13,14] As black men have higher rates of prostate cancer incidence, stage at diagnosis, and prostate cancer–specific mortality,[15] it is possible that their under-representation may impact the overall outcomes reported in such trials.

Several limitations to our manuscript should be addressed. Important additional clinical details, including PSA, clinical staging, and medical comorbidity could not be obtained from our clinical electronic medical record system (separate from the prostate pathology LIS) without an extensive

manual chart abstraction, which was unfeasible given the size of the cohort. This prevented multivariable analysis that may have provided us with more confidence that our findings were causally related to a population-wide reduction in PSA screening rather than the correlation we have noted. However, we felt the changes in histopathology findings described above were important to inform the ongoing PSA screening debate and should be reported, especially considering the size and clinical relevance of our studied population.

Unlike most other reports of the post–USPSTF era, we have seen an increase in the number of prostate biopsies performed in our large group. Although the number of urologists in the group remained constant, the market share of the group expanded during the study period, which may account for the increase in number of prostate biopsies seen. In addition, there is likely to be considerable variability nationally in the United States relating to the degree to which the incidence of prostate biopsies has declined.

The reasons for the apparent upward grade migration are also unclear. It is possible that the findings are related to higher rates of black men in our cohort compared with others. The typical explanation is that with reduced screening, cancers are being detected later in their natural history and are thus more aggressive, potentially reversing the marked reduction in patients presenting with advanced or metastatic disease following the widespread adoption of PSA screening in the early 1990s.[16] However, we did not see an increase in the age of patients at initial diagnosis, and did not have clinical staging information to assess extent of disease at presentation. More accurate detection of prostate cancer within individual patients is unlikely, as follow-up biopsies in men undergoing active surveillance, image-guided MRI fusion biopsies, and saturation biopsies were excluded from analysis. Furthermore, all urologists in the group are very experienced in transrectal ultrasonography and prostate biopsy technique and are well past their initial learning curve. We also have no reason to believe that the underlying rate of prostate cancer in the served community is increasing due to an unrecognized epidemiologic trend (such as a new carcinogenic environmental exposure). The large and diverse geographical area encompassed by the group also argues against this.

There are two other issues deserving of comment. First, in response to numerous objections to the Grade D recommendation against prostate screening by USPSTF in 2012, the task force solicited formal commentary from concerned parties worldwide. The result of this reconsideration was the issuance of a heavily nuanced Grade C recommendation concluding (with moderate certainty) that there is a small benefit of PSA-based screening for prostate cancer in some men aged 55 to 69 years; if such men willingly desire screening and undertake shared decision-making between themselves and their doctors, screening could be allowed. The Task Force persisted in maintaining the Grade D recommendation for screening in men age ≥70 years; this article was published in *JAMA* earlier this year.[17]

Second, the number of new cases of prostate cancer detected annually in the United States will have dropped by 53,240 (24.5%) by the end of this year (2018), as reflected in the anticipated frequency of 164,490 cases this year, compared with 271,730 new cases reported in 2010.[9,10] This decrease was clearly promoted by USPSTF actions in delivering the Grade D recommendation against prostate cancer screening in 2012. Although these actions were designed to avoid discovery of cancers that would not be injurious to the patient, there seems to have been at least one unintended consequence of advice against prostate cancer screening: the worsening of cancers once detected. Several articles have suggested increased PSA levels, cancer grade, and presence of metastases at the time of diagnosis.[5,6,12] For example, Hu and colleagues reporting SEER

MAIN POINTS

- The authors have noted a significant increase in prostate cancer grade and volume in a large, diverse patient cohort since the USPSTF recommendation against prostate cancer screening.
- The reasons for this increase are not entirely clear but are clearly related temporally to the USPSTF 2012 Grade D recommendation against screening and warrant further evaluation.
- This apparent relationship between lowering incidence and worsening cancers in the United States is continuing to be experienced to the present day.

data from 2004 to 2013 showed a significant increase of number and percentage of men with metastases present at presentation between 2011 and 2013.[18] Whether these data will result in earlier increased mortality from prostate cancer remains to be seen.

Conclusions

We have noted a significant increase in prostate cancer grade and volume in a large, diverse patient cohort since the USPSTF recommendation against prostate cancer screening. The reasons for this increase are not entirely clear but are clearly related temporally to the USPSTF 2012 Grade D recommendation against screening and warrant further evaluation. This apparent relationship between lowering incidence and worsening cancers in the United States continues at the present day. ■

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