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Prostate Cancer Characteristics in the US Preventive Services Task Force Grade D Era: A Single-Center Study and Meta-Analysis

Matthew B. Clements Basil Abdalla Stephen H. Culp Raymond A. Costabile Tracey L. Krupski

Department of Urology, University of Virginia, Charlottesville, VA, USA

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Abstract
Background: In May 2012, the US Preventive Services Task Force assigned prostate-specific antigen-based screening a grade D recommendation, advising against screening at any age. Our objective was to compare prostate cancer characteristics pre- and post-recommendation with an adjusted analysis of our data and a pooled analysis including other primary data sources. ***Methods:*** We identified all incident prostate cancer diagnoses at our institution from 2007 to 2016. Multivariable log binomial regression was used to determine the relative risk (RR) of metastasis at diagnosis, ≥Gleason Group 4, and high D'Amico risk disease pre- versus post-recommendation. The meta-analysis included primary data studies evaluating these outcomes. ***Results:*** At our institution, 287 (44.6%) and 224 (48.8%) patients were diagnosed in the pre- and post-cohorts. The RR of metastatic disease at diagnosis did not differ between groups ($p = 0.224$), nor did the risk of high D'Amico category disease ($p = 0.089$). The risk of ≥Gleason Group 4 was 1.58 times higher post-recommendation ($p = 0.007$). The pooled risk of ≥Gleason Group 4 disease was 1.5 ($p < 0.001$) post-recommendation and was 1.29 ($p = 0.006$) for high D'Amico risk disease. ***Conclusions:*** While the number of metastatic cases did not differ after the recommendation, the risk of high-grade cancers increased at both a local and aggregated level.

Introduction

Prostate cancer is a heterogeneous disease and large studies have failed to show that surgical or radiotherapy interventions improve overall survival [1, 2]. These findings led to concerns surrounding overtreatment of prostate cancer, and in May 2012, the US Preventive Services Task Force (USPSTF) assigned prostate-specific antigen (PSA)-based screening a grade D classification, recommending against screening in any age-group [3]. As a result, PSA-based screening is estimated to have decreased by 18–39% [4–6]. Use of the digital rectal exam has similarly decreased by 64% [6]. The evidence supporting the grade D recommendation has been under scrutiny given its far-reaching impact, and the USPSTF recently changed

karger@karger.com
www.karger.com/uin

Matthew B. Clements
Department of Urology
University of Virginia, Box 800422
Charlottesville, VA 22908 (USA)
matthew.b.clements@gmail.com

their recommendation on screening to a grade C [7]. This period of decreased screening provides a unique opportunity to measure the real-world effects on prostate cancer characteristics during the Grade D era.

There are likely subsets of men with prostate cancer who benefit from screening, but we currently lack a biomarker that adequately stratifies patients. The D'Amico risk groupings use clinical data to stratify prostate cancer risk and have since been adopted by the National Comprehensive Cancer Network [8]. The new Gleason grade groups have been shown to add independent prognostic value for biopsy in terms of recurrence-free survival [9].

Previous single-center analyses and population-based studies did not adjust for important confounders such as family history and comorbidities. Secondary data are limited by missing data, clerical error, and limited follow-up. We sought to evaluate prostate cancer characteristics in terms of Gleason group, D'Amico risk, and metastasis at diagnosis in the era of the grade D recommendation, compared to a pre-recommendation cohort. We evaluated our outcomes using our granular institutional data in 4-year periods before and after the recommendation and incorporated our data into a pooled quantitative synthesis of primary data sources.

Methods

Approval was obtained by our Institutional Review Board. Patients undergoing prostate biopsy were identified using CPT code 55770 in our institutional clinical data repository. We performed a retrospective review of the electronic medical record to create a database including demographic and prostate cancer characteristics at diagnosis of all biopsied patients. The pre-USPSTF cohort was defined as patients diagnosed from October 1, 2007, to October 31, 2011. The post-USPSTF cohort was defined from June 1, 2012, to June 30, 2016. Patients diagnosed between the release of the draft recommendation in October 2011 and the final recommendation in May 2012 were censored from analysis. The PSA levels for patients on 5-alpha reductase inhibitors were doubled for the statistical analysis [10]. Patients with biopsies performed after a previous diagnosis (surveillance) were excluded as were patients diagnosed with Gleason score ≤5. Oncologic characteristics included Gleason score/group, number/percentage of positive cores, clinical stage, and presence of metastasis at diagnosis. Patients were categorized into D'Amico risk groups as per the original criteria [8]. In cases where clinical stage or metastasis was difficult to determine, cases were reviewed by 2 study team members to reach consensus.

Our institutional data were then incorporated into a pooled analysis of primary studies identified through a structured review. We performed a systematic search of MEDLINE for English-language articles published from May 1, 2013, to June 1, 2017, comparing pre- and post-USPSTF prostate cancer characteristics (online suppl. Appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000507656). For inclusion, a study was required to report one of the following: Gleason group (or score categorized as ≥8–10), D'Amico risk category, or presence of metastatic disease. A data collection interval of at least 1 year prior to and following the May 2012 recommendation was required for inclusion, and only observational studies with primary data were included. Studies including biopsy results from surveillance and subset analyses were excluded. Two recent review articles were searched for additional sources, as well as abstracts from the 2013 to 2017 American Urological Association and American Society of Clinical Oncology annual meetings [11, 12].

Univariate analysis of patient demographics and prostate cancer characteristics in the pre- and post-USPSTF cohort was performed using the χ^2 or Fisher's exact test for categorical and Student's *t* test or Wilcoxon rank sum for continuous variables. We used a log binomial regression with a robust variance estimator to model the relative risk (RR) of our primary outcomes: metastasis at diagnosis (visceral or bone), ≥Gleason Group 4 disease, and high D'Amico category disease. We also performed regression analyses in a subset of African American (AA) patients, to evaluate if they were disproportionately impacted by the recommendation.

The same 3 primary outcomes were included in the quantitative synthesis of studies identified in the systematic review. For all outcomes, we estimated pooled RRs with 95% confidence intervals (CIs) using a random-effects model, as described by DerSimonian and Laird [13]. Study heterogeneity was assessed using the I [2] index and *Q* statistic. Publication bias was assessed using funnel plots. All analyses were completed using the R® programming language version 3.4.0 (Vienna, Austria), with a p value of <0.05 was considered significant for all analyses.

Results

A total of 643 patients in the pre- and 459 in the post-recommendation cohort underwent a prostate biopsy during the respective study periods. Of those, 248 (44.6%) in the pre- and 224 (48.8%) in the post-cohort were diagnosed with prostate adenocarcinoma (Table 1). In the post-recommendation cohort, fewer patients were Caucasian ($p = 0.002$), but patients were otherwise similar in terms of baseline characteristics. On univariate analysis, Gleason group ($p < 0.001$) and D'Amico risk category ($p = 0.029$) differed between groups, but the clinical stage did not ($p = 0.348$). PSA at presentation did not differ ($p = 0.126$). Both the median number of positive cores ($p = 0.001$) and percent positive cores ($p = 0.011$) were greater post-recommendation. On multivariable modeling, the RR of metastatic disease was 1.45 in the post-cohort but was not statistically significant ($p = 0.224$). AA patients were significantly more likely to present with metastasis (RR 3.87, $p < 0.001$), as were those with increasing CCI (RR 1.24, $p = 0.015$). Patients were more

Table 1. Demographic and prostate cancer-related characteristics in the pre-USPSTF and post-USPSTF cohorts at the time of initial diagnosis

Variable	Pre-USPSTF	Post-USPSTF	*p* value
n biopsied	643	459	
Prostate cancer diagnosed (%)	287 (44.6)	224 (48.8)	0.191
Age (mean [95% CI]), years	63.4 (62.7, 64.1)	63.2 (62.5, 64.0)	0.738
Charlson Comorbidity Index (median [IQR])	0 (0, 1)	0 (0, 1)	0.232
Race (%)			
Caucasian	478 (74.3)	306 (66.7)	0.002
AA	134 (20.8)	109 (23.7)	
Other	31 (4.8)	44 (9.6)	
MRI prior to biopsy	6 (0.9)	64 (13.9)	<0.001
PSA (median [IQR])	7.3 (4.9, 13.6)	8.0 (5.5, 14.6)	0.126
Gleason group (%)[1]			
1 (Gleason 3 + 3)	135 (21.0)	76 (16.6)	0.018
2 (Gleason 3 + 4)	69 (10.7)	55 (12.0)	
3 (Gleason 4 + 3)	29 (4.5)	33 (7.2)	
4 (Gleason 4 + 4 or 5 + 3)	25 (3.9)	26 (5.7)	
5 (Gleason 9 or 10)	28 (4.4)	34 (7.4)	
Tumor stage (%)[1]			
T1c	179 (27.8)	127 (27.7)	0.308
T2	95 (14.8)	86 (18.7)	
T3–T4	13 (2.0)	11 (2.4)	
D'Amico risk group (%)[1]			
Low	111 (17.3)	62 (13.5)	0.029
Intermediate	100 (15.6)	91 (19.8)	
High	75 (11.7)	71 (15.5)	
Number of positive cores (median [IQR])	3 (1, 5)	4 (2, 7)	0.001
% positive cores (median [IQR])	25 (8, 50)	33 (17, 59)	0.011
Metastasis present at diagnosis (%)	19 (3.0)	21 (4.6)	0.210

PSA, prostate-specific antigen; CI, confidence interval; USPSTF, US Preventive Services Task Force; AA, African American. [1] Three hundred fifty-six (55.5%) in the pre-USPSTF group and 235 (51.2) in the post-USPSTF group had no cancer diagnosed in each category.

likely to have ≥Gleason Grade 4 disease at presentation post-recommendation (RR 1.58, $p = 0.007$), and similar trends were seen for patients with increasing age, AA race, and with increasing CCI (all $p < 0.05$). For the high D'Amico group analysis, the risk in the post cohort approached, but did not reach significance (RR 1.28, $p = 0.089$), and those with a family history of prostate cancer had a higher risk (RR 1.47, $p = 0.024$), whereas this was not demonstrated in the other models (online suppl. Appendix 2). In a subset of 243 AA patients, there was an increased risk of Gleason Group ≥4 disease post-recommendation (RR 2.04, 95% CI 1.11, 3.77), but this did not differ significantly from the remainder of the cohort (RR 1.42, 95% CI 0.97, 2.10). Diagnosis after the recommendation remained insignificant in the AA subset for the metastasis and high D'Amico risk outcomes. Excluding patients with an MRI prior to biopsy ($n = 70$) for a sensitivity analysis, we found no difference in metastatic disease (RR 1.80, $p = 0.074$), increased risk of Gleason Group ≥4 disease (RR 1.68, $p = 0.004$), and high D'Amico risk disease remained insignificant (RR 1.30, $p = 0.087$).

Our MEDLINE search returned a total of 205 studies (Fig. 1). A total of 28 abstracts were screened for inclusion, with 5 full-text and 9 conference abstracts assessed for eligibility by 2 independent reviewers (MB and SHC) as per PRISMA statement recommendations [14]. Five studies met inclusion criteria for the ≥Gleason Group 4 outcome, and 3 studies met criteria for the high D'Amico category outcome, in addition to our institutional data, which were included in both analyses [15–19]. No articles other than the current study met the a priori inclusion criteria for risk of metastasis at diagnosis.

The pooled RR of ≥Gleason Group 4 disease after the USPSTF recommendation was 1.52 (95% CI 1.18, 1.97).

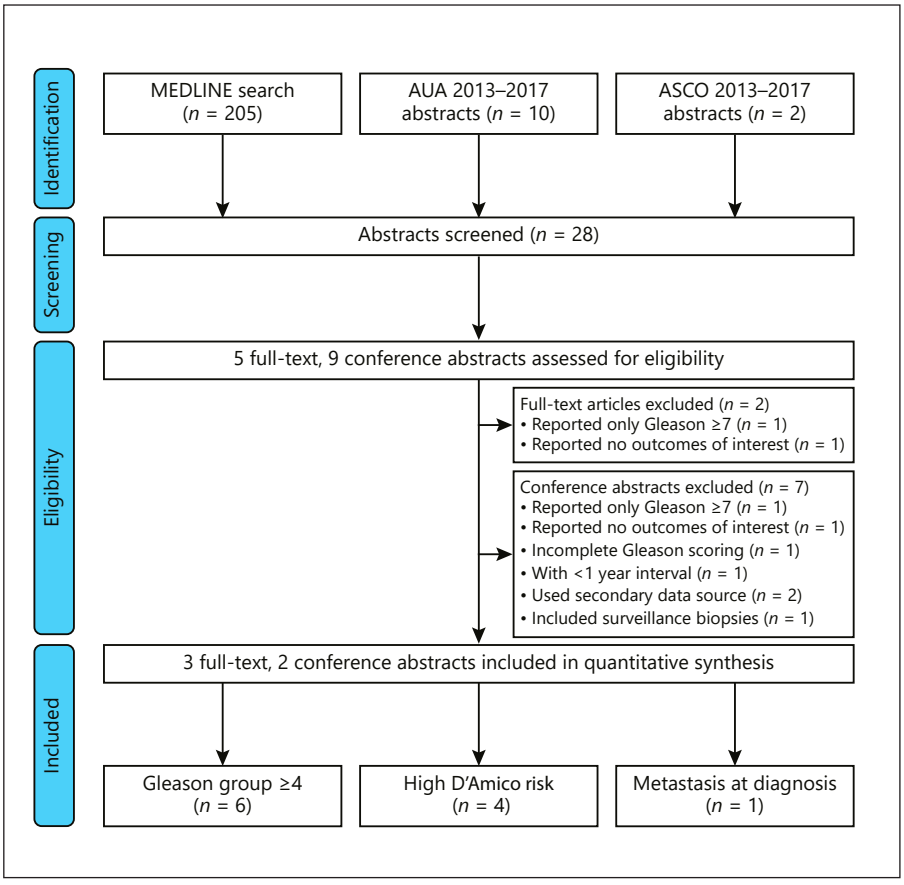

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Fig. 1. Flow diagram of structured MEDLINE search and review of conference abstracts, and eligibility assessment by 2 independent reviewers (MBC and SHC). Conflicts were arbitrated by a third party (TLK). AUA, American Urological Association.

There was significant heterogeneity with an I [2] of 56.22 and Q p value of 0.031, necessitating use of the random-effects model (Fig. 2). The RR of high D'Amico category disease was 1.29 (95% CI 1.07, 1.54), without significant heterogeneity (Q $p = 0.527$). There was no substantial evidence of publication bias for either analysis, as demonstrated in the corresponding funnel plots (online suppl. Appendix 3).

Discussion

The impetus behind the USPSTF recommendation was to avoid overdiagnosis and treatment of "pseudodisease," defined as asymptomatic cancer that either will not progress or will progress so slowly that it would have remained asymptomatic in the person's lifetime [3]. Our study suggests that the task force succeeded in minimizing diagnosis of low-risk prostate cancer. We found in both our single-center data and pooled analysis that men diagnosed post-recommendation had a significantly higher risk of ≥Gleason Group 4 disease. The meta-analysis revealed the RR of high D'Amico category disease was significantly greater in the post-recommendation cohort and similar to our adjusted analysis. The hope is that this better identifies the men who truly need treatment and minimizes the quality of life harms [20] that come from treating men who may not benefit in terms of overall survival from treatment.

The benefit of decreasing low-risk prostate cancer diagnoses must be weighed against the increase of higher risk disease at presentation. Albertsen et al. [21] previously showed that with ≥Gleason 8 disease, prostate cancer-related mortality rate was 121/1,000 person-years, compared to 65/1,000 person-years for Gleason 7 disease. The volume of disease must also be considered. The significant increase in both number of positive biopsy cores and percent positive cores ($p = 0.001$, $p = 0.011$) in our study suggests a higher burden of disease post-recommendation, which has been shown to predict recurrence after prostatectomy and disease-free survival after radiation therapy [22, 23].

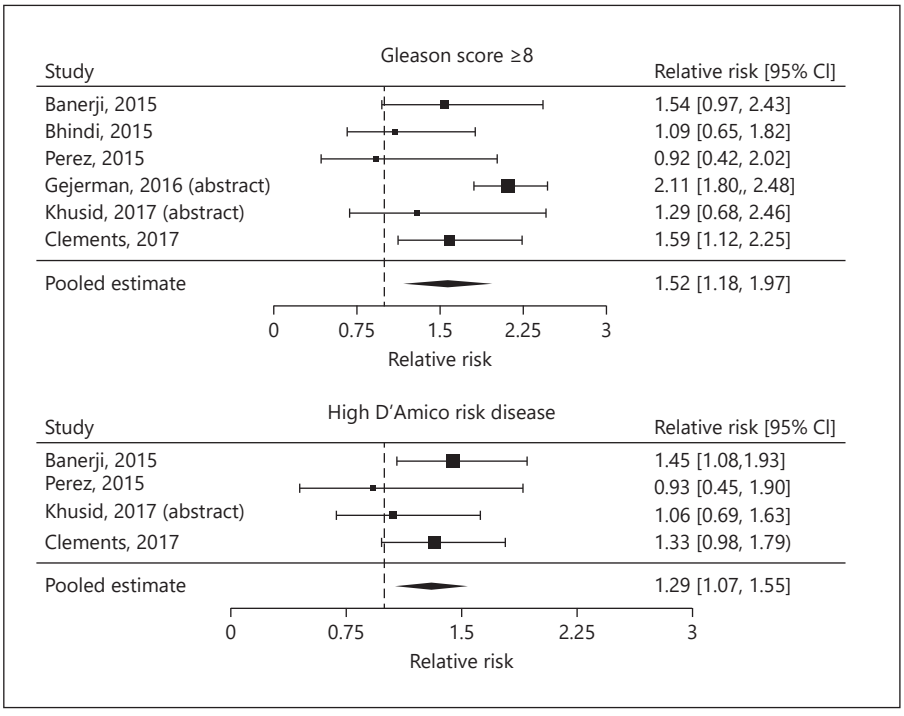

Fig. 2. Forest plots summarizing the random-effects model used to estimate RR for Gleason Group ≥4 and high D'Amico Risk in patients diagnosed post-USPSTF grade D recommendation, compared to pre-recommendation. USPSTF, US Preventive Services Task Force; RR, relative risk; CI, confidence interval.

After the Grade D recommendation was released, early population-based reports from the National Cancer Database showed that the number of predicted diagnoses had decreased by 28% overall, and by 37.9 and 23.1% for low- and high-risk prostate cancer, respectively [24]. SEER data showed a 19.6% decrease in annual percent change beginning in May 2011, including a decrease of 10.8% for ≥Gleason 8 cancer [25]. We felt that an analysis controlling for confounding factors provided a higher level of evidence and complemented the conclusions of the larger studies.

Presenting both adjusted single-center data and a pooled analysis demonstrates the external validity of our results. We found an increased risk of ≥Gleason Grade 4 disease (RR 1.58, $p = 0.007$), but no statistically significant difference in D'Amico category (RR 1.28, $p = 0.89$) or metastasis at diagnosis (RR 1.45, $p = 0.224$). We found similar results in the meta-analysis for ≥Gleason Group 4 disease (RR 1.52, $p = 0.001$) and high D'Amico category disease (RR 1.29, $p = 0.006$). The point estimates in the pooled analysis are very similar to those of our adjusted estimates, suggesting that the lack of statistical significance for the high D'Amico category outcome ($p = 0.089$) was due to lack of power. Importantly, our analysis did not demonstrate that AA patients were disproportionately impacted by the recommendation, although they were at substantially increased risk for all 3 outcomes.

Patients are being diagnosed with fewer low-risk prostate cancers at the cost of those that are biopsied having a higher risk of aggressive disease. While underpowered to be statistically significant, we saw an 11% increase in metastatic cases in the post-USPSTF cohort. Gaylis et al. [26] also showed an increase in metastatic disease from 5.04% in 2011–2014 compared to 7.71% in 2013–2014, but did not meet criteria for inclusion in our meta-analysis, as they did not examine a full 1-year period before the recommendation. Gulati et al. [27] modeled the impact of no-screening and age-restricted (<70 years) PSA-based screening. With discontinued versus age-restricted screening, their 2 models showed 44 and 46% increases in metastatic cases, respectively, which supports our preliminary findings at the time of diagnosis. There is level 1 evidence that radiation therapy and prostatectomy decrease the rate of metastatic disease [2]. This raises the concern that in the trade-off between minimizing diagnosis of low-risk disease, we may relegate a small percentage of men to development of metastatic disease without opportunity for preventive treatment.

Our work is limited by lack of information on the entire at-risk population served by our institution, so we restricted our analyses to those undergoing prostate biopsy. We did not include patients diagnosed with metastatic disease by an extra-prostatic biopsy, but this subset should be a miniscule volume. We did not have diffusion-

weighted MRI imaging until 2015, which may have led to a bias in the detection of higher grade cancer, although importantly a sensitivity analysis did not change our conclusions when excluding patients with an MRI prior to biopsy.

In summary, we found an increased risk of ≥Gleason Group 4 disease and high D'Amico category disease at an aggregate level in the post-USPTF recommendation era. Results of the pooled analysis were similar to our robust, multivariable single-institution models. The roughly 50 and 30% increases in RR of Gleason Group 4 or 5 and high D'Amico risk from pooled analysis are useful estimates to use in shared decision-making with patients when counseling on the risks and benefits of PSA-based screening. Future research with longer term follow-up is needed to determine if the higher prostate cancer risk characteristics lead to worse disease-specific survival.

Statement of Ethics

A retrospective review of the electronic medical record was performed. Approval was obtained by our Institutional Review Board.

Conflict of Interest Statement

Tracey Krupski has been a consultant for FKD Therapies (INSTILADRIN® phase III trial) and for Viventia Bio Inc. (Vicinium Phase III trial). The authors have no other disclosures to declare.

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Author Contributions

M.B.C. contributed to the study conception and design, analysis and interpretation of the data, drafting of the article, revision the article, and data collection. B.A. assisted in data collection (substantial) and in drafting and revision of the manuscript. R.A.C. contributed to the study conception and design, approving the final version for submission, and general supervision of the project. S.H.C. contributed to the analysis and interpretation of data, general supervision of the project, and revision of the article. T.L.K. contributed to the study conception and design, analysis and interpretation of the data, draft and revision of the manuscript, providing writing assistance, and general supervision of the research project.

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