CONTEMPORARY DISTRIBUTION OF HIGH-GRADE PROSTATE CANCER IN THE CIRCUMSTANCES OF OPPORTUNISTIC TESTING

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SAVREMENA DISTRIBUCIJA VISOKOGRADUSNIH KARCINOMA PROSTATE U OKOLNOSTIMA OPORTUNOG TESTIRANJA

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ABSTRACT

Screening has dramatically changed the distribution of the mean age, stage and grade of prostate cancer (PCa) at diagnosis. However, regional-level data that characterize contemporary PCa patients are limited. The aim of the study was to ascertain main clinical and pathological characteristics of PCa at the present time in the circumstances of opportunistic testing.

High-grade PCa according to age, serum prostate specific antigen (PSA), volume prostate, PSA density (PSAD), digital rectal examination (DRE) number of positive cores biopsies and the average percentage of cancer in biopsy at diagnosis has been retrospectively evaluated in 100 men with biopsy-proven PCa, at Clinical Centre Kragujevac, from September 2016 until September 2017. PCa were stratified according to Gleason score (GS) into low/intermediate-grade (GS ≤ 7) and high-grade (GS ≥ 8). To identify the determinants associated with high-grade PCa, we performed univariate and multivariate logistic regression.

The most prevalent PCa were the low/intermediate-grade (65%), followed by high-grade (35%). The mean age of the patients was 71.5 (range: 56–88) years and median PSA was 14.6 (range: 1.4–935) ng/ml. There were significant differences in age, PSA, PSAD, DRE, number of positive biopsy and average percentage of cancer in biopsy between patients with or without high-grade GS. Logistic analysis demonstrated the PSAD and age have strong prognostic value of high-grade PCa.

In conclusion, our study has shown the worrying frequency of high-grade PCa in the circumstances of opportunistic testing. Older men and higher level of PSAD had a much higher probability of high-grade PCa.

Keywords: *prostate cancer; age; Gleason score; biopsy;*

SAŽETAK

Skrining karcinoma prostate (PCa) je dramatično promenio distribuciju srednje starosti, stadijuma i gradusa tumora bolesnika pri postavljanju dijagnoze. Međutim, regionalni, savremeni podaci bolesnika sa PCa su veoma oskudni. Cilj studije je da proceni glavne kliničke i patološke karakteristike bolesnika sa PCa u sadašnje vreme u okolnostima oportunog testiranja.

Retrospektivno su ispitivani visokogradusni PCa na 100 biopsijskih dokazanih PCa u odnosu na starost, serumski nivo prostata specifičnog antigena (PSA), volumena prostate, gustine PSA (PSAD), digitorektalni pregled (DRE), broja pozitivnih iglenih biopsija i prosečnog sadržaja karcinoma u biopsijskom materijalu, u Kliničkom centru Kragujevac, u periodu od septembra 2016 do septembra 2017 godine. PCa su klasifikovani u odnosu na Glison skor (GS) na nisko/umerenogradusne (GS ≤ 7) i visokogradusne (GS ≥ 8). Univarijantna i multivarijantna logistička regresija je sprovedena radi utvrđenja determinati povezanih sa visokogradusnim karcinomima.

Najučestaliji PCa su bili nisko/umerenogradusni (65%), a potom visokogradusni (35%). Prosečna starost bolesnika bila je 71,5 (u opsegu: 56–88) godina, a medijana PSA vrednosti bila je 14,6 (u opsegu: 1,4–935) ng/ml. Utvrđena je značajna razlika u starosti, PSA, PSAD, DRE, broju pozitivnih iglenih biopsija i prosečnog sadržaja karcinoma u biopsijskom materijalu između bolesnika sa ili bez visokogradusnih karcinoma. Logistička analiza je pokazala da su PSAD i starost najmoćniji prediktori visokogradusnih PCa.

U zaključku, naša studija je pokazala zabrinjavajuću učestalost visokogradusnih PCa u okolnostima oportunog testiranja. Stariji muškarci i više vrednosti PSAD imaju višu verovatnoću prisustva visokogradusnih PCa.

Ključne reči: *karcinom prostate; starost; Glison skor; biopsija;*

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ABBREVIATIONS

AUC - area under the receiver operating characteristic curve;
CI - confidential interval;
GS - Gleason score;
DRE - digital rectal examination;
IQR - interquartile range;
LR - logistic regression;
ORs - odds ratios;
PCa - prostate cancer;
PSA - prostate-specific antigen;
PSAD - PSA density;
SD - standard deviation;
SEER - The Surveillance Epidemiology and End Results;
TRUS - transrectal ultrasound;

INTRODUCTION

Prostate cancer (PCa) remains the most common cancer in men in Europe (excluding skin cancer) (1). With the introduction of the prostate-specific antigen (PSA) testing, PCa incidence rate increased drastically, and peaked in 1992. The rate subsequently declined, and then appeared to stabilize from 1995 to 2005 (2). PCa is usually suspected on the basis of digital rectal examination (DRE) and/or an elevated PSA. Definitive diagnosis depends on histopathologic verification. Abnormal DRE is an indication for biopsy, but as an independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound (TRUS).

Age at diagnosis, cancer stage, and grade are among the most important factors used to determine the PCa treatment modality such as prostatectomy, radiation, or active surveillance. With the widespread use of the PSA test, the mean age at diagnosis dropped substantially and the distribution of PCa stage and grade has also dramatically changed, with localized and moderately differentiated tumors becoming predominant (3). In USA, among newly diagnosed patients in 2004 – 2005, the majority (94%) had localized (ie, stage T1 or T2) PCa and a median serum PSA level of 6.7 ng/mL. The average age at PCa diagnosis decreased over time from 72.2 to 67.2 years (3).

The Gleason grading system remains one of the most powerful prognostic predictors in PCa. High-grade PCa, also called poorly differentiated PCa, has Gleason scores (GS) from 8 to 10, is a deadly disease that needs aggressive treatment (4). The incidence of a biopsy GS of 8 – 10 among newly diagnosed patients also decreased over time. Recent Surveillance Epidemiology and End Results (SEER) data show that nearly half of all PCa diagnosed in recent years are of low grade (GS 2–6), and there is about 14% of poorly differentiated PCa (5).

Cancer registry of central Serbia of Institute of Public Health of Serbia gives the epidemiological parameters of malignant neoplasms in the territory of central Serbia, however, demographic and clinical factors were not examined in this study (6). To our knowledge, a comprehensive examination of recent PCa incidence rates and trends in the Serbian population is lacking, especially by cancer stage and grade.

Based on these considerations, the aim of the study was to ascertain main clinical and pathological characteristics of high-grade PCa at the present time in the circumstances of opportunistic testing, and to identify the determinants associated with high-grade PCa. We hypothesized that older age and higher PSAD would be associated with an increased risk of aggressive disease.

PATIENTS AND METHOD

This is a retrospective study carried out using the database of 239 patients at Clinical Centre Kragujevac, who had undergone ultrasound-guided prostate biopsies, from September 2016 through September 2017. Patient referrals were obtained in the course of routine clinical care, regardless of PSA level or clinical findings, and not as part of a population based screening trial. After obtaining institutional review board approval, the data were collected about clinicopathological characteristics for each patient as regards prebiopsy assessment and included following: age, PSA, volume of prostate, PSAD, DRE, total number of cores taken, GS, number of positive cores biopsies and average percentage of cancer in biopsy. Exclusion criteria were patients with incomplete data, and medical therapy known to affect PSA levels. PCa were stratified according to GS into the following groups: low/intermediate-grade who has GS≤6 or GS=7 and high-grade who have GS≥8 (7). Also, the cohort was stratified into 10-*year age* groups (less than 60, 60–70, 70–80 and more than 80 yr old) and into three groups according to PSA level (PSA 1.4–10 ng/mL, 10.1–20 ng/mL and >20 ng/mL) to investigate the increasing effect of age and PSA on outcome.

A member of the urology team performed a DRE or prostate biopsy on all patients. The DRE was classified as normal, or suspicious/positive. At presentation, the serum PSA measurement (UniCel DxI 600 Access Immunoassay System, Beckman Coulter, USA) was performed. All patients underwent prostate biopsy according to protocol. A Toshiba (Aplio 300) ultrasound device with 5-10-MHz probe was used to obtain ultrasound data and prostate biopsy. All patients underwent ultrasound-guided prostate biopsies performed us-

Table 1. Baseline patients' clinicopathological characteristics **(N**=221).

Characteristics		All	BPH (n=121)	PCa (n=100)	P value
Age	mean ± SD, years	69.8 ± 7.3	68.5 ± 7	71.5 ± 7.3	0.002
PSA	median (IQR) ng/ml	11.2 (15.1)	9.9 (8.9)	14.6 (40.8)	0.000
Volume prostate	median (IQR), ml	49 (32.5)	55 (37)	44.5 (29.7)	0.008
PSAD	median (IQR), ng/ml/ml	0.24 (0.41)	0.19 (0.68)	0.38 (0.68)	0.000
DRE	abnormal n, (%)	53 (24)	13 (10.7)	40 (40)	0.000
Number of biopsy cores	median (IQR)	10 (0)	10 (0)	10 (0)	0.056

BPH–benign prostatic hyperplasia; PCa–prostate cancer; SD–standard deviation; PSA–prostate-specific antigen; IQR–interquartile range; PSAD–prostate-specific antigen density; DRE–digital rectal examination;

Table 2. Baseline clinicopathological characteristics in patients with different Gleason grade prostate cancer **(N**=100).

Characteristics		Low/intermediate grade PCa n=65	High-grade PCa n=35	P value
Age	mean ± SD, years	69.5 ± 6.9	75.1 ± 6.7	0.000
PSA	median (IQR) ng/ml	10.5 (13.25)	59 (136.4)	0.000
Volume prostate	median (IQR), ml	43 (27)	46 (27)	0.303
PSAD ml	median (IQR), ng/ml/	0.29 (0.39)	1 (2.56)	0.000
DRE	abnormal n, (%)	23 (35.4)	17 (48.6)	0.208
Number of positive biopsy		3 (4)	5 (6)	0.028
Average percentage of cancer in biopsy		33.4 ± 27	50 ± 23.3	0.000

PCa–prostate cancer; SD–standard deviation; PSA–prostate-specific antigen; IQR–interquartile range; PSAD–prostate-specific antigen density; DRE–digital rectal examination;

ing an 18-gauge biopsy instrument (Md-Tech, Pro-Mag I 2.5, USA). A median of ten biopsy cores was obtained (range, two to 12 cores), and evaluated per each hospital's standard procedure and by local pathologists. Prostate volumes were obtained by measuring the gland in three dimensions, and volume was estimated using the following formula: 0.52 [length (cm) × width (cm) × height (cm)]. The PSAD was calculated by dividing the serum PSA by the calculated prostate volume.

Statistical Analyses

Descriptive statistics was used for demographic and baseline characteristics. We expressed continuous variables as the mean and standard deviation (SD) when normally distributed or as the median and interquartile range (IQR) if their distribution was skewed. Categorical variables in different groups were expressed as frequencies and percentages, and were compared using the Chi-square test. Continuous numerical data were analyzed using t-test or the Mann-Whitney U test when the data are not normally distributed.

Univariate and multivariate logistic regression (LR) was used to identify and quantify the potential and independent determinants associated with high-grade PCa with Backward–Wald stepwise. The results of regressions were expressed in odds ratios (ORs) with 95% confidential interval (CI). For model derived from LR analysis and the strongest predictor we calculated area under the receiver operating characteristic curve (AUC). The SPSS (version 23.0) software package was used for all analyses. Statistical significance was set at $p < 0.05$.

RESULTS

Patients' characteristics

A total of 221 patients were analyzed. Prostate cancer was detected in 100 (45.2%) of patients. Table 1 shows the clinicopathological characteristics of patients with/without PCa included in the study. There were significant differences in age, PSA levels, volume of prostate, PSAD and DRE findings between patients with or without PCa. DRE was positive in 40% of patients with PCa, and median PSA was 14.6 ng/ml (range: 1.4–935 ng/ml): 34 (34%), 23 (23%), and 43 (43%) had a PSA included between 1.4 and 10 ng/ml, between 10.1 and 20 ng/ml, and greater than 20 ng/ml, respectively. The rates of prostate cancer patients were 6%, 44%, 35% and 15% at the 6^{th}, 7^{th}, 8^{th} and 9^{th} decades of life, respectively.

The majority of tumors (40%) were determined to be GS 6 or less, followed by high (35%), and then intermediate grade group (25%). There were significant differences in age, PSA levels, PSAD, DRE, number of positive biopsy and average percentage of cancer in biopsy between patients with or without high-grade GS (Table 2). A significant correlation between GS grade and age decades was demonstrated (p = 0.017), and high-grade cancer was detected in more than two-thirds (68.6%) of patients older than 70 years, and for no one under the age of 60 years. Figure 1 shows the distribution of high-grade PCa according to age decades. Also, a significant correlation between GS and PSA level was demonstrated (p = 0.000), and about three-fourths (74.3%) of patients with high-grade cancer has PSA level above 20 ng/ml.

Table 3. Logistic regression analysis of high-grade prostate cancer predictors.

Factor	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.124 (1.052–1.201)	0.001	1.111 (1.025 – 1.205)	0.011
PSA	1.025 (1.012–1.038)	0.000		
Volume prostate	1.011 (0.997–1.026)	0.118		
PSAD	3.693 (1.766–7.720)	0.001	2.988 (1.504–5.940)	0.002
DRE	1.725 (0.748–3.976)	0.201		

OR–odds ratio; CI–confidence interval; PSA–prostate-specific antigen; PSAD–prostate-specific antigen density; DRE–digital rectal examination;

Figure 2 shows the distribution of high-grade PCa according to PSA ranges. Overall, the probability of high-grade PCa increased significantly with increasing age decades and PSA ranges. Low/intermediate grade and high-grade PCa were present in 25 (35.4%) and 17 (48.6%), respectively, of the DRE positive PCa patients, but difference was not statistically different (p = 0.208). The median number of positive biopsy cores and average percentage of cancer in biopsy were more pronounced in high-grade PCa patients indicating a higher tumour volume (Table 2).

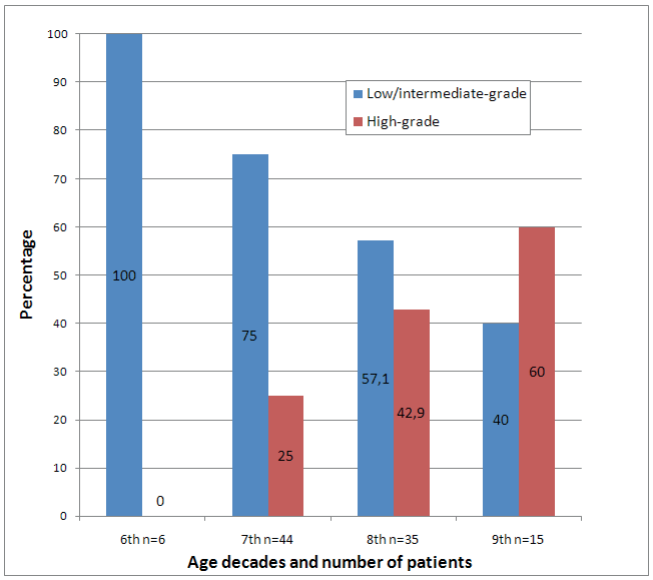

Figure 1. Distribution of high-grade prostate cancer and number of patients according to age decades.
Percentages are expressed in relation to the total number of patients in the age decade's group.

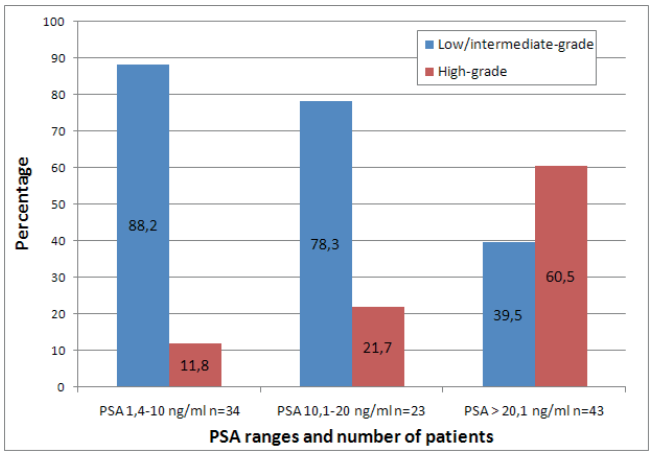

Figure 2. Distribution of high-grade prostate cancer and number of patients according to PSA level.
Percentages are expressed in relation to the total number of patients in the PSA level group.

The logistic regression analysis

In a univariate analysis, 3 risk factors displayed significant correlation with high-grade PCa (Table 2). During multivariable analysis two sustained their prognostic significance (Table 2). The analysis demonstrated that the age and PSAD have strong prognostic value of high-grade PCa (Table 2). A global metric of test accuracy (AUC) for model and individual predictor are showed in Figure 3. AUC for the model and the strongest predictor was shown to have good discriminatory ability (84%, 95% CI 75.9–92%, and 77.5%, 95% CI 67.3–87.8%, respectively), and in pairwise comparison of ROC curves difference between areas LR model and PSAD (6.48%) was significant (p = 0.043).

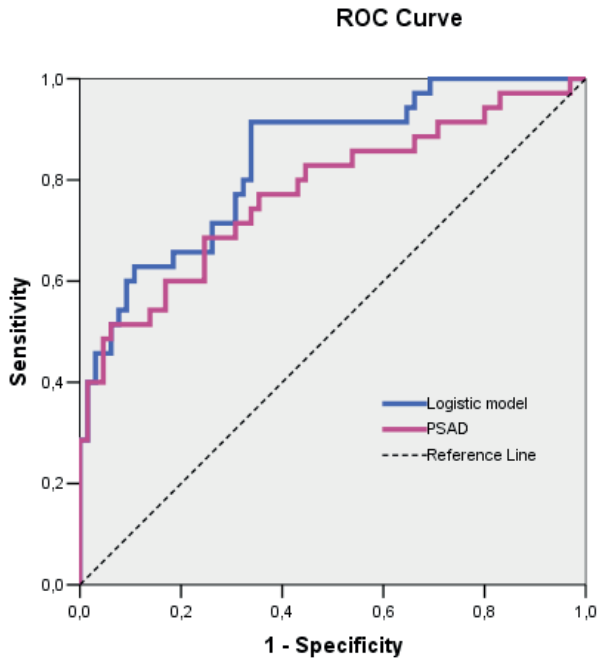

Figure 3. ROC curves analysis.
A global metric of test accuracy (AUC) for model and the most significant predictor (PSAD).

DISCUSSION

There are several findings from this study to emphasize. First, these regional-level data show the worrying frequency of high-grade PCa at the present time in the circumstances of opportunistic testing; secondly, our study has shown that older men have a higher probability of being diagnosed with more aggresive disease; and thidrly, high-grade disease may be predicted using PSAD and age with good discriminatory ability.

Previous studies have recognized criteria associated with high-grade PCa. They included age, family history, genetics, race/ethnicity, obesity, and others (8). In line with previous studies, several of those predictors have reached statistical significance in the univariate or multivariate analysis in our study. We found that the probability of high GS increases with increasing age and PSA, which is in line with numerous previous reports (9, 10). However, in some studies it has been shown that younger (men aged ≤55 years) and more elderly male (>75 years) patients are more likely to have a more aggressive disease (11). There are several possible explanations for this observation, including a higher chance of Gleason grade progression and changes in biopsy technique. Before all, older age may be associated with decreased frequency of screening, allowing tumors more time to grow and possibly dedifferentiate before diagnosis, although Gleason grade progression is controversial (12). Futhermore, it is possible that tumor biology changes with age, such that tumors that develop in older men tend to be more aggressive (13). Biological reasons for progressive dedifferentiation with aging can be the result of common disease mechanisms. The underlying mechanism linking both processes are the time dependent accumulation of cellular damage, such as the role of genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, decreased nutrient sensing and altered metabolism, but also cellular senescence and stem cell function.

Gleason score, which was introduced in 1974, represents a significant histopathological parameter commonly used to assay the prognostic outcome of PCa. Gleason scores 8–10 are often considered as one group corresponding to high-grade disease. Major Gleason scoring revisions were adopted in 2005 (7). However, in 2013, a new grading system was proposed by the group from Johns Hopkins Hospital (14). The grading system includes five distinct Grade Groups based on the modified GS groups. These Grade Groups were shown to be more accurate in predicting progression than the Gleason risk stratification groups (≤6, 7, 8–10) (15). It has been reported that high-grade tumours are significantly larger than tumours which are low/intermediate grade. Our results are in agreement with these findings by showing a higher number of positive biopsies and more average percentage of cancer in biopsy in patients with high-grade disease.

Due to a lack of serum PSA specificity many authors have advocated normalizing the PSA by the volume of the prostate gland, yielding a PSAD (16). The use of PSAD for cancer diagnosis is controversial with studies both confirming and refuting the use of PSAD. In our analysis PSAD was the strongest predictor of tumour grade and review of the ROC curves indicates that its sensitivity and specificity are sufficiently good to be used as a single threshold test. However, given the complexity of prostate cancer risk assessment, model that incorporates data on multiple independent variables, including PSAD, is likely to be both more useful and appropriate. Although previous studies suggested an inverse relationship between prostate volume at diagnosis and the probability of high GS (17, 18), we did not confirm these findings. There are some hypoteses to explain this relation. Various authors stated that this was a result of sampling error of prostate biopsy in larger prostates. However, in some studies it has been shown that the correlation of prostate volume and GS depends on the stage of the disease (19). Futhermore, definitive prostate volume values can only be calculated with RP specimens and also a Gleason upgrade can be expected at radical prostatectomy pathology in some patients (20).

The adoption of PSA for PCa screening resulted in profound stage migration toward earlier stage, less aggressive disease, and a correspondent decrease in prostate cancer-specific mortality. However, PCa screening using serum PSA is a controversial subject. The European Association of Urology recommends screening for men with at least 10 to 15 years' life expectancy (21). In addition, they recommend a baseline PSA level at age 40 to 45 followed by screening at intervals based on the baseline PSA (22). Concerns about overscreening and overdiagnosis subsequently led professional guidelines (circa 2000 and later) to recommend against routine PSA testing (2). On the other hand, contemporary epidemiological data from the Pennsylvania Cancer Registry demonstrated that over the past 2 decades, PCa incidence rates have decreased, primarily because of the decreased detection of early-stage disease, and contrarily a corresponding shift toward more advanced disease at diagnosis (23). Unlike population screening, in this study we analyzed opportunistic testing that consists of individual case finding, which are initiated by the patient being tested and/or his physician. In the European Randomized Study of Screening for Prostate Cancer, the incidence of men with Gleason grade at least 8 was 10.6% in the nonscreened arm vs. 6.1% in the screened arm (24). Also, a SEER analysis demonstrates that a significant grade migration has occurred from the period just before the widespread of PSA screening (1984–2003) to more recent periods and high-grade disease accounted for 21% of all tumours (8, 25). However, in this regional-level cohort we found the worrying frequency of high-grade PCa (35%) at the present time, older age and higher median PSA compared to previous reports (3, 8). These results suggest that screening with serum PSA can allow early detection of disease, thereby reducing the proportion of men found to have high-risk disease at diagnosis.

The study is limited by the retrospective design, in a single tertiary centre with a relatively small patient cohort. Next, the higher percentage of older men with GS ≥ 8 could be biased by the selection criteria for biopsy (i.e. higher PSA values, suspicious DRE). Futhermore, we have not investigated the frequency and clinical factors affecting the under grading of biopsy Gleason sum, observed in other studies in about half of patients with radical prostatectomy (20). In addition, the accuracy of TRUS volumes is very user dependent. Finally, a targeted magnetic resonance/ultrasound fusion–guided biopsy technique produced better results than a standard biopsy in the detection of high-risk PCa (26). These data were not available in our cohort. Our results should be interpreted with caution given that our study design did not allow us to determine whether PSA screening in older, healthier men may improve their outcomes. Nevertheless, to our best knowledge, up to now, regional-level data that characterize contemporary PCa patients are limited. These parameters are crucial not only for monitoring on epidemiological situation regarding malignant diseases, but also for the evaluation of various preventive measures and programs implemented with the aim to prevent and reduce the burden of these diseases in our population. Physicians and patients should take into account the higher risk of more aggressive or advanced disease in older men when discussing the risks and benefits of PSA screening with healthy older men with a substantial life expectancy (10). These data highlight the continued need for nationwide monitoring of PCa incidence and trends by demographic and tumor characteristics and refinements in PCa screening and treatment.

CONCLUSION

In this regional-level cohort we found the worrying frequency of high-grade PCa at the present time in the circumstances of opportunistic testing. Our study has shown that older men have a higher probability of being diagnosed with high-grade disease. A more aggressive disease may be predicted using PSAD and age. Although our results do not imply that older men should receive more screening than they currently do, the striking correlation between older age and higher-grade disease could be considered when counseling healthy older men about the pros and cons of PSA screening.

CONFLICT OF INTEREST

None.

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