Increasing rates of NCCN high and very high-risk prostate cancer versus number of prostate biopsy cores

Mike Wenzel MD, BSc1,2 | Christoph Würnschimmel MD2,3 | Claudia C. Ruvolo MD2,4 | Luigi Nocera MD2,5 | Zhe Tian MSc2
Fred Saad MD, PhD2 | Alberto Briganti MD, PhD5 | Derya Tilki MD, PhD3,6 | Markus Graefen MD, PhD3 | Luis A. Kluth MD, PhD1 | Philipp Mandel MD, PhD1 | Felix K.H. Chun MD, PhD1 | Pierre I. Karakiewicz MD, PhD2

1Department of Urology, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany
2Cancer Prognostics and Health Outcomes Unit, Division of Urology, University of Montréal Health Center, Montréal, Québec, Canada
3Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany
4Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, Naples, Italy
5Department of Urology and Division of Experimental Oncology, IBCAS San Raffaele Scientific Institute, Milan, Italy
6Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Abstract
Background: Recently, an increase in the rates of high-risk prostate cancer (PCa) was reported. We tested whether the rates of and low, intermediate, high and very high-risk PCa changed over time. We also tested whether the number of prostate biopsy cores contributed to changes rates over time.

Methods: Within the Surveillance, Epidemiology and End Results (SEER) database (2010–2015), annual rates of low, intermediate, high-risk according to traditional National Comprehensive Cancer Network (NCCN) and high versus very high-risk PCa according to Johns Hopkins classification were tabulated without and with adjustment for the number of prostate biopsy cores.

Results: In 119,574 eligible prostate cancer patients, the rates of NCCN low, intermediate, high-risk PCa were, respectively, 29.7%, 47.8%, and 22.5%. Of high-risk patients, 39.6% and 60.4% fulfilled high and very high-risk criteria. Without adjustment for number of prostate biopsy cores, the estimated annual percentage changes (EAPC) for low, intermediate, high and very high-risk were respectively −5.5% (32.4%–24.9%, p < .01), +0.5% (47.6%–48.4%, p = .09), +4.1% (8.2%–9.9%, p < .01), and +8.9% (11.8%–16.9%, p < .01), between 2010 and 2015. After adjustment for number of prostate biopsy cores, differences in rates over time disappeared and ranged from 29.8%–29.7% for low risk, 47.9%–47.9% for intermediate risk, 8.9%–9.0% for high-risk, and 13.6%–13.6% for very high-risk PCa (all p > .05).

Conclusions: The rates of high and very high-risk PCa are strongly associated with the number of prostate biopsy cores, that in turn may be driven by broader use magnetic resonance imaging (MRI).

Keywords
Gleason grade group, intermediate risk, low risk, NCCN, stage, very high risk
INTRODUCTION

Several publications have shown an adverse stage migration toward higher rates of locally advanced or more aggressive prostate cancer (PCA) at initial diagnosis, especially after the 2012 Update of the United States Preventive Service Task Force (USPSTF) grade D recommendation against prostate-specific antigen (PSA)-based screening for PCA.\(^1\text{-}^4\) Contemporary trend analyses of newly diagnosed PCAs indicated increasing rates of high-risk PCAs according to the traditional National Comprehensive Cancer Network (NCCN) criteria, especially from 2010 onwards.\(^7\text{-}^8\) However, no previous study examined the rates of high-risk versus very high-risk according to the Johns Hopkins classification that can be applied to the traditional NCCN high-risk patients, due to unavailable biopsy core information.\(^9\text{-}^{10}\)

We addressed this unmet need and relied on the Surveillance, Epidemiology and End Results (SEER) registries database (2010–2015). Specifically, we tested whether the rates of low, intermediate high-risk, and very high-risk PCAs changed over time. We also tested whether more extensive prostate sampling may have contributed to changes in low, intermediate, high and/or very-high risk PCAs rates over time.\(^11\text{-}^{13}\) We hypothesized that a diagnostic bias resulting from more detailed sampling at prostate biopsy may result in higher rates of high and very high-risk PCAs, especially since the diagnosis of very high-risk PCA requires ≥5 biopsy cores with either GGG (Gleason grade group) 4 or 5 cancer.

MATERIAL AND METHODS

2.1 Study population

Within SEER database 2010–2015, we identified all patients ≥18 years old with histologically confirmed adenocarcinoma of the prostate, diagnosed at biopsy (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9).\(^14\) Cases that were identified only at autopsy or death certificate or with unknown histology were excluded. Moreover, patients with unavailable PSA value, unknown cT-stage, unknown biopsy GGG, and metastatic PCAs were also excluded in addition to patients with fewer than 8 cores and more than 24 cores at prostate biopsy, as well as patients with unknown number of obtained cores at biopsy or unknown number of positive cores at biopsy.\(^15\text{-}^{16}\) All patients were stratified according to traditional NCCN low, intermediate, and high-risk criteria.\(^8\) The Johns Hopkins classification defines high-risk as at least one of the following features: \(c\)T3a or GGG 4/5 or PSA > 20 ng/mL. Additionally, the Johns Hopkins classification defines very high-risk PCAs according to the presence of at least one of the following criteria: \(c\)T3b-cT4 and/or primary Gleason pattern 5 and/or 2–3 high risk features and/ or ≥5 positive biopsy cores and biopsy pathology of GGG 4-5. These selection criteria resulted in 119,574 PCA patients, of whom 35,535, 57,184, 26,855 harbored low risk versus intermediate risk versus high-risk PCAs according to traditional NCCN criteria, respectively. Within the traditional NCCN 26,855 high-risk patients, the use of the Johns Hopkins sub-groupings identified 10,674 and 16,181 high and very high-risk individuals.

2.2 Statistical analyses

The first set of the analyses focused on 119,574 patients who were stratified according to the three traditional NCCN risk groups. Here, we tabulated trends over time in low, intermediate, and high-risk PCAs between 2010 and 2015, without accounting for the number of prostate biopsy cores. Subsequently, we repeated the tabulations after adjustment for the number of obtained prostate biopsy cores in a multinomial model, as previously reported.\(^19\) Hereby, a predicted probability was calculated for each patient. Afterwards, probabilities of each patient were averaged for all PCAs risk categories for each year separately.

In the second set of analyses, we exclusively focused on NCCN high-risk subgroup of 26,855 patients who were further stratified according to the Johns Hopkins classification between high \((n = 10,674)\) versus very high-risk \((16,181)\) PCAs. Here we also tabulated the rates over time of Johns Hopkins high and very high-risk PCAs patients, without accounting for the number of prostate biopsy cores. Subsequently, we repeated the tabulations after adjustment for the number of prostate biopsy cores, as explained above.

In the third set of analyses, we performed a detailed tabulation of PCA characteristics (GGG, PSA, and \(c\)T-stage) in patients within the NCCN high-risk stratification. Similarly, we also performed the same tabulations within high and very high-risk groups, according to Johns Hopkins classification.

In all tabulations, differences in rates over time were estimated with estimated annual percent change (EAPC) that relied on log linear methodology, which used the \(t\)-test, as an established methodology.\(^19\text{-}^{20}\) All tests were two sided with a level of significance set at \(p < .05\) and R software environment for statistical computing and graphics (version 3.4.3) was used for all analyses.

RESULTS

3.1 Descriptive characteristics of the study population

Of 119,574 eligible PCA patients, respectively, 35,535 (29.7%), 57,184 (47.8%), and 26,855 (22.5%) harbored NCCN low, intermediate, and high-risk PCAs. In the subgroup of NCCN high-risk patients, the application of the Johns Hopkins classification resulted in respectively 10,674 (39.6%) and 16,181 (60.4%) high and very high-risk patients (Table 1).

According to the traditional NCCN stratification, number of prostate biopsy cores and number of positive prostate biopsy cores were respectively 12 (interquartile range [IQR]: 12–13) and 2 (IQR: 1–4) for low-risk versus 12 (IQR: 12–13) and 4 (IQR: 2–6) for intermediate-risk versus 12 (IQR: 12–13), and 6 (IQR: 8–10) for high-risk PCAs (both \(p < .001\)). Although the median and IQR values for prostate biopsy cores were the same within the groups, an increase in the number of prostate cores taken occurred between 2010 and 2015 (Figure 1). Specifically, the rates of patients with >10 cores...
obtained at prostate biopsy increased across all groups and also specifically in NCCN high-risk PCa (both \( p < .001 \)).

According to the Johns Hopkins classification, the number of prostate biopsy cores and number of positive prostate biopsy cores were 12 (IQR: 12–13) and 3 (IQR: 2–6) for high-risk versus 12 (IQR: 12–13) and 8 (IQR: 6–11) for very high-risk PCa (both \( p < .001 \)). Although the median and IQR values for prostate biopsy cores were the same in high and very high-risk PCa, an increase in the number of prostate biopsy cores taken occurred between 2010 and 2015 (Figure 1). Specifically, rates of individuals with >10 cores obtained at prostate biopsy increased in respectively Johns Hopkins high and very high-risk PCa (both \( p < .001 \)).

### TABLE 1

Descriptive characteristics of 26 855 NCCN high-risk prostate cancer (PCa) patients, stratified according to Johns Hopkins high versus very high-risk PCa, diagnosed within the Surveillance, Epidemiology, and End Results database from 2010 to 2015

| Variables                                      | Overall, \( n = 26 \, 855 \) | High-risk PCa, \( N = 10 \, 647 (39.6\%) \) | Very high-risk PCa, \( N = 16 \, 181 (60.4\%) \) | \( p \) value |
|------------------------------------------------|------------------------------|-----------------------------------------------|-----------------------------------------------|--------------|
| Age at diagnosis, median (IQR)                 | 67 (62–73)                   | 67 (61–73)                                    | 68 (62–74)                                    | <.001        |
| PSA, in ng/ml, median (IQR)                    | 12.1 (6.7–27.4)              | 16.2 (6.7–29.3)                               | 11.3 (6.7–25.4)                               | <.001        |
| Number of prostate biopsy cores, median (IQR), Mean (Range) | 12 (12–13), 12.6 (8–24)     | 12 (12–13), 12.6 (8–24)                       | 12 (12–13), 12.7 (8–24)                       | <.001        |
| Number of positive prostate biopsy cores, median (IQR) | 6 (4–10)                    | 4 (2–6)                                       | 8 (6–11)                                      | <.001        |
| Percentage of positive biopsy cores, median (IQR) | 50 (30–80)                   | 30 (20–50)                                    | 70 (50–90)                                    | <.001        |
| PSA stratification                             |                              |                                               |                                               |              |
| <10 ng/ml                                      | 11 460 (42.7)                | 4 277 (40.1)                                  | 7 183 (44.4)                                  | <.001        |
| 10–20 ng/ml                                    | 5 241 (19.5)                 | 1 347 (12.6)                                  | 3 894 (24.1)                                  |              |
| >20 ng/ml                                      | 10 154 (37.8)                | 5 050 (47.3)                                  | 5 104 (31.5)                                  |              |
| cT stage                                       |                              |                                               |                                               |              |
| cT1                                            | 13 947 (51.9)                | 6 586 (61.7)                                  | 7 361 (45.5)                                  | <.001        |
| cT2                                            | 9 477 (35.3)                 | 3 372 (31.6)                                  | 6 105 (37.7)                                  |              |
| cT3a                                           | 1 844 (6.9)                  | 716 (6.7)                                     | 1 128 (7.0)                                   |              |
| cT3b                                           | 1 253 (4.7)                  | 0 (0)                                         | 1 253 (7.7)                                   |              |
| cT4                                            | 334 (1.2)                    | 0 (0)                                         | 334 (2.1)                                     |              |
| Gleason Score at biopsy                         |                              |                                               |                                               |              |
| 3 + 3                                          | 1 529 (5.7)                  | 1 453 (13.6)                                  | 76 (0.5)                                      | <.001        |
| 3 + 4                                          | 2 551 (9.5)                  | 2 272 (21.3)                                  | 279 (1.7)                                     |              |
| 4 + 3                                          | 2 363 (8.8)                  | 2 041 (19.1)                                  | 322 (2)                                       |              |
| 3 + 5                                          | 980 (3.6)                    | 224 (2.1)                                     | 756 (4.7)                                     |              |
| 4 + 4                                          | 10 713 (39.9)                | 3 647 (34.2)                                  | 7 066 (43.7)                                  |              |
| 5 + 3                                          | 236 (0.9)                    | 0 (0)                                         | 236 (1.5)                                     |              |
| 4 + 5                                          | 6 218 (23.2)                 | 1 037 (9.7)                                   | 5 181 (32)                                    |              |
| 5 + 4                                          | 1 520 (5.7)                  | 0 (0)                                         | 1 520 (9.4)                                   |              |
| 5 + 5                                          | 745 (2.8)                    | 0 (0)                                         | 745 (4.6)                                     |              |
| cN stage                                       |                              |                                               |                                               |              |
| cN0                                            | 24 412 (90.9)                | 10 186 (95.4)                                 | 14 226 (87.9)                                 | <.001        |
| cN1                                            | 2 148 (8)                    | 397 (3.7)                                     | 1 751 (10.8)                                  |              |
| cNx                                            | 295 (1.1)                    | 91 (0.9)                                      | 204 (1.3)                                     |              |

Abbreviations: BT, brachytherapy; EBRT, external beam radiotherapy; IQR, inter quartile range; NLT, no local treatment; PCa, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy.
3.2 | Rates of traditional NCCN low versus intermediate versus high-risk PCa without and with adjustment for number of prostate biopsy cores

The rates of low risk PCa decreased over time (EAPC: −5.5%, \(p = .01\)) from 32.4% to 24.9% (Figure 1A). Conversely, high-risk PCa rate increased over time from 20.0% to 26.7% (EAPC: +6.9%, \(p < .01\)). Intermediate risk rate did not change between 2010 and 2015 and represented the most prevalent risk category (47.6%–48.4%, \(p = .09\)), across the study period.

After adjustment for number of prostate biopsy cores (Figure 1B), differences in trends over time disappeared. Specifically, no increase or decrease in EAPCs was recorded for low, intermediate, or high-risk NCCN PCa, between 2010 and 2015 (all \(p > .05\)). The absolute rates ranged from 29.8% to 29.7%, 47.9% to 47.9%, and 29.8% to 29.7% for respectively low, intermediate, and high-risk PCa.

3.3 | Rates of Johns hopkins high versus very high-risk PCa without and with adjustment for number of prostate biopsy cores

The rates of high-risk increased over time (EAPC: +4.1%, \(p = .01\)) from 8.2% to 9.9% (Figure 2A). Moreover, the rates of very high-risk PCa increased even stronger from 11.8% to 16.9% (EAPC: +8.9%, \(p < .01\)) between 2010 and 2015.

After adjustment for number of prostate biopsy cores (Figure 2B), differences in trends over time disappeared. Specifically,
no increase or decrease in EAPCs were recorded for high and very high-risk NCCN PCa between 2010 and 2015 (all \( p > .05 \)). The absolute rates ranged from 8.9% to 9.0% and 13.6% to 13.6% for respectively high and very high-risk PCa.

3.4 | Detailed tabulation of PCa characteristics in traditional NCCN high-risk PCa without and with adjustment for number of prostate biopsy cores

In traditional NCCN high-risk PCa patients, GGG5 rates significantly increased over time (EAPC: +3.3%, \( p < .01 \)) from 29.7% to 34.1%, between 2010 and 2015 (Figure 3A). Conversely, in the same time period, GGG1 and GGG2 rates decreased (~6.6% and ~3.3%, both \( p \leq .03 \)) from 6.6% to 10.6% to 5.0% and 9.0%. GGG3 and 4 rates did not change over time.

Analyses of PSA (<10 vs. 10–20 vs. >20 ng/ml) and cT-stage did not reveal significant or clinically meaningful changes in rates over time. The exceptions consisted of an increase in cT1-stage and of a decrease in cT2-stage over time (all \( p < .05 \)) in both high and very high-risk PCa.

After adjustment for the number of prostate biopsy cores (Figure 3D), differences in rates over time disappeared in all GGG groups. Specifically, after adjustment for number of prostate biopsy cores, the absolute GGG5 rates ranged from 9.6% to 9.6% and 46.4% to 46.1% for Johns Hopkins high and very high-risk PCa (Figure 4).

4 | DISCUSSION

We hypothesized that in patients at risk of more aggressive PCa, a diagnostic bias resulting from more detailed biopsy schemes, with higher numbers of cores may result in higher proportions of high-risk PCa according to the traditional NCCN criteria, as well as in higher proportions of high and/or very high-risk PCa, according to the Johns Hopkins classification. Our analyses resulted in several noteworthy observations.

First, according to traditional NCCN criteria, we observed an increase of high-risk PCa rates, over time. This observation is consistent with previous reports, which originated from the National Cancer Database (NCDB).\(^7\) The concordance of findings between the SEER and NCDB validates the increase in high-risk prostate cancer. It is especially noteworthy that the highest increase of high-risk prostate cancer occurred after 2012 and may be linked to the change in screening guidelines.

Second, unlike previous analyses, we focused on the rates of high versus very high-risk PCa, according to the Johns Hopkins stratification. The rationale for this analysis was based on the absence of epidemiological data that addressed high and very high-risk patients,
due to unavailable information about number of positive prostate biopsy cores, in previous analyses. Our findings demonstrated that high and very high-risk PCa rates increased over time from 8% to 10% (EAPC: +4.1%) and 12% to 17% (EAPC: +8.9%), respectively. These observations concur with previously reported traditional NCCN high-risk PCa rates. Since the observed increases over time may be related to magnetic resonance imaging (MRI) driven increases in the extent of prostate sampling, we repeated the tabulations after adjustment for number of prostate biopsy cores. Analyses of rates of traditional NCCN high-risk (EAPC: 0.1%, range 22.3%–22.4%) and of rates of Johns Hopkins high (EAPC: 0.07%, range 8.9%–9.0%) and very high-risk PCa (EAPC: −0.03%, range 13.6%–13.6%), after adjustment for number of prostate biopsy cores revealed stable rates over time. This observation validates our initial hypothesis about the association between more detailed biopsy schemes and unadjusted rates of traditional high-risk and Johns Hopkins high and very high-risk PCa, over time. In consequence, previously reported increases in traditional NCCN high-risk PCa rates appear to be driven by a biopsy extent-related diagnostic bias, since adjustment for the number of prostate biopsy cores entirely eliminated differences in rates over time.

Interestingly, we also reported an increase in GGG5 rates over time, when adjustment for prostate biopsy number of cores was not made. However, this increase also disappeared after adjustment for number of prostate biopsy cores. This observation further validates the hypothesis postulating that the unadjusted increase in rates of high and very high-risk PCAs is artificial and is related to increased extent of sampling.

In summary, our analyses tested for changes in rates of traditional NCCN high risk, as well as Johns Hopkins high and very-high risk PCa rates over time. Moreover, we tested whether these rates are potentially influenced by biopsy schemes that may be based on larger numbers of cores obtained at prostate biopsy within the recent years. Our analyses demonstrated that after adjustment for the number of prostate biopsy cores, no changes in either traditional NCCN high-risk or Johns Hopkins high or very high-risk rates were recorded over time. The same phenomenon applies to GGG5. Taken together our observations that rely on traditional NCCN high risk, as well as Johns Hopkins high and very-high risk PCa definitions and GGG5 demonstrated that the apparent increase in rates over time can be, despite other influencing factors such as changes in diagnostics and technically improvement, explained by the numbers of cores taken at biopsy.

Our work has limitations and should be interpreted in the context of its retrospective and population-based design. Second, the distribution between high and very high-risk according to Johns Hopkins stratification classically relies on the presence of ≥5 positive cores with GGG4 or GGG5 in those cores. Unfortunately, the SEER database does not provide this amount of detail. Therefore, we relied on ≥5 positive cores in patients with GGG4 or 5 in final biopsy results. In consequence, ideally our observations should be validated in databases that provide this additional detail. Unfortunately, the NCDB cannot provide this information either. Conversely, institutional databases hold this information. However, epidemiological trends addressing high-risk and very high-risk PCa patients may be
difficult to assess within institutional or even multi-institutional databases, due to insufficient numbers of observations. For example, in Johns Hopkins original publication consisted of only 114 very high-risk patients. 9 Similarly, the European validation of very high-risk patients relied on only 1369 very high-risk patients, during an observation period of 25 years.10 Moreover, although we attribute the increasing number of cores due to increasing rates of MRI-derived targeted biopsy, MRI findings are not available in the SEER database. Therefore, the proposed explanation cannot be validated based on factual information from within the SEER database. However, it can be substantiated with observations made from institutional databases, where this link has been previously observed and reported.12-21 Finally, other factors such as changes PCA screening may have also influenced changes in rates over time, which cannot be explained only by number of cores taken at biopsy. Especially the Update of the USPSTF grade D recommendation against PSA-based screening for PCa may also significantly contributed the occurrence of increasing rates of high-risk PCa and needs to be considered when the current study is interpreted.

5 | CONCLUSIONS

Our analyses demonstrated that after adjustment for the number of prostate biopsy cores, no changes in either traditional NCCN high-risk or Johns Hopkins high or very high-risk rates were recorded over time. The same phenomenon applies to GGG5. In consequence, our observations robustly and convincingly demonstrated that the apparent increase in rates over time is artificial and related to more detailed biopsy schemes.

ACKNOWLEDGMENT

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

All analyses and their reporting followed the SEER reporting guidelines. Due to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval was not required.

AUTHOR CONTRIBUTIONS

Conceptualization: Mike Wenzel, Christoph Würnschimmel, Claudia Collà Ruvolo, Felix K.H. Chun, Pierre I. Karakiewicz. Data curation: Mike Wenzel, Christoph Würnschimmel, Claudia Collà Ruvolo, Luigi Nocera, Zhe Tian. Formal analysis: Mike Wenzel, Zhe Tian. Funding acquisition. Investigation: Mike Wenzel, Christoph Würnschimmel, Claudia Collà Ruvolo, Luigi Nocera. Methodology: Mike Wenzel, Zhe Tian. Project administration. Resources: SEER database software R system. Supervision: Pierre I. Karakiewicz, Felix K.H. Chun, Fred Saad. Validation: Zhe Tian, Pierre I. Karakiewicz, Fred Saad, Alberto Briganti, Derya Tilki, Markus Graeven, Luis A. Kluth, Philipp Mandel, Felix K.H. Chun.

DATA AVAILABILITY STATEMENT

The statistical code for the analyses will be made available on request to bona fide researchers.

ORCID

Mike Wenzel http://orcid.org/0000-0002-4338-0889
Christoph Würnschimmel http://orcid.org/0000-0001-7891-4791
Claudia C. Ruvolo http://orcid.org/0000-0001-8110-7341
Luigi Nocera http://orcid.org/0000-0003-3354-8139
Derya Tilki http://orcid.org/0000-0001-7033-1380

REFERENCES

1. Moyer VA. U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157(2):120-134.
2. Leyh-Bannurah S-R, Karakiewicz PI, Pompe RS, et al. Inverse stage migration patterns in North American patients undergoing local prostate cancer treatment: a contemporary population-based update in light of the 2012 USPSTF recommendations. World J Urol. 2019;37(3):469-479.
3. Wallis CJD, Klaassen Z. ‘Reverse stage migration’: what can population-based data tell us about trends in prostate cancer presentation? Eur Urol Oncol. 2018;1(4):321-322.
4. Reese AC, Wessel SR, Fisher SG, Myldjo JH. Evidence of prostate cancer ‘reverse stage migration’ toward more advanced disease at diagnosis: data from the Pennsylvania Cancer Registry. Urol Oncol. 2016;34(8):335.e21-28.
5. Butler SS, Muralidhar V, Zhao SG, et al. Prostate cancer incidence across stage, NCCN risk groups, and age before and after USPSTF Grade D recommendations against prostate-specific antigen screening in 2012. Cancer. 2020;126(4):717-724.
6. Budäus L, Spethmann J, Isbarn H, et al. Inverse stage migration in patients undergoing radical prostatectomy: results of 8916 European patients treated within the last decade. BJU Int. 2011;108(8):1256-1261.
7. Fletcher SA, von Landenberg N, Cole AP, et al. Contemporary national trends in prostate cancer risk profile at diagnosis. Prostate Cancer Prostatic Dis. 2020;23(1):81-87.
8. Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, version 1.2020. NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2020.
9. Sundi D, Wang VM, Pierorazio PM, et al. Very-high-risk localized prostate cancer: definition and outcomes. Prostate Cancer Prostatic Dis. 2014;17(1):57-63.
10. Pompe RS, Karakiewicz PI, Tian Z, et al. Oncologic and functional outcomes after radical prostatectomy for high or very high risk prostate cancer: European validation of the current NCCN® guideline. J Urol. 2017;198(2):354-361.
11. Kasivisvanathan V, Rannikko AS, Borgh R, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018;378(19):1767-1777.
12. Zhang M, Milot L, Khalvati F, et al. Value of increasing biopsy cores per target with cognitive MRI-targeted transrectal US prostate biopsy. Radiology. 2019;291(1):83-89.
13. Kim SP, Karnes RJ, Mwangi R, et al. Contemporary trends in magnetic resonance imaging at the time of prostate biopsy: results from a large private insurance database. Eur Urol Focus. 2019;7(1):86-94.
14. About the SEER Program [Internet]. SEER. [cited]. 2021. https://seer.cancer.gov/about/overview.html


15. Tu X, Lin T, Cai D, Liu Z, Yang L, Wei Q. The optimal core number and site for MRI-targeted biopsy of prostate? A systematic review and pooled analysis. *Minerva Urol Nefrol*. 2020;72(2):144-151.

16. Ghani KR, Dundas D, Patel U. Bleeding after transrectal ultrasonography-guided prostate biopsy: a study of 7-day morbidity after a six-, eight- and 12-core biopsy protocol. *BJU Int*. 2004;94(7):1014-1020.

17. Brossner C, Madersbacher S, de Mare P, Ponholzer A, Al-Ali B, Rauchenwald M. Follow-up of men obtaining a six-core versus a ten-core benign prostate biopsy 7 years previously. *World J Urol*. 2005;23(6):419-421.

18. Scattoni V, Raber M, Abdollah F, et al. Biopsy schemes with the fewest cores for detecting 95% of the prostate cancers detected by a 24-core biopsy. *Eur Urol*. 2010;57(1):1-8.

19. Wenzel M, Nocera L, Ruvolo CC, et al. Racial/ethnic disparities in tumor characteristics and treatments in favorable and unfavorable intermediate risk prostate cancer. *J Urol*. 2021;206(1):69-79. https://doi.org/10.1097/JU.0000000000001695

20. Wenzel M, Nocera L, Collà Ruvolo C, et al. Incidence rates and contemporary trends in primary urethral cancer. *Cancer Causes Control*. 2021;32(6):627-634. https://doi.org/10.1007/s10552-021-01416-2

21. Preissler F, Theyssen L, Wenzel M, et al. Performance of combined magnetic resonance imaging/ultrasound fusion-guided and systematic biopsy of the prostate in biopsy-naive patients and patients with prior biopsies. *Eur Urol Focus*. 2019;7(1):39-46.

22. Tracy CR, Flynn KJ, Sjoberg DD, Gelhaus PT, Metz CM, Ehrdaie B. Optimizing MRI-targeted prostate biopsy: the diagnostic benefit of additional targeted biopsy cores. *Urol Oncol*. 2020;39(3):193.e1-193.e6.

23. Hakozaki Y, Matsushima H, Kumagai J, et al. A prospective study of magnetic resonance imaging and ultrasonography (MRI/US)-fusion targeted biopsy and concurrent systematic transperineal biopsy with the average of 18-cores to detect clinically significant prostate cancer. *BMC Urol*. 2017;17(1):2-12.

24. Dimitroulis P, Rabenalt R, Nini A, et al. Multiparametric magnetic resonance imaging/ultrasound fusion prostate biopsy—are 2 biopsy cores per magnetic resonance imaging lesion required? *J Urol*. 2018;200(5):1030-1034.

25. Pepe P, Cimino S, Garufi A, et al. Detection rate for significant cancer at confirmatory biopsy in men enrolled in Active Surveillance protocol: 20 cores vs 30 cores vs MRI/TRUS fusion prostate biopsy. *Arch Ital Urol Androl*. 2016;88(4):300-303.

26. Kenigsberg AP, Renson A, Rosenkrantz AB, et al. Optimizing the number of cores targeted during prostate magnetic resonance imaging fusion target biopsy. *Eur Urol Oncol*. 2018;1(5):418-425.

27. Ahdoot M, Wilbur AR, Reese SE, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. *N Engl J Med*. 2020;382(10):917-928.

28. Stabile A, Giganti F, Rosenkrantz AB, et al. Multiparametric MRI for prostate cancer diagnosis: current status and future directions. *Nat Rev Urol*. 2020;17(1):41-61.

**How to cite this article:** Wenzel M, Würnschimmel C, Ruvolo CC, et al. Increasing rates of NCCN high and very high-risk prostate cancer versus number of prostate biopsy cores. *Prostate*. 2021;1-8. https://doi.org/10.1002/pros.24184