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

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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, and 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

1 | 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.[1–6] Contemporary trend analyses of newly diagnosed PCa indicated increasing rates of high-risk PCa according to the traditional National Comprehensive Cancer Network (NCCN) criteria, especially from 2010 onwards.[7,8] 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.[9,10]

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 PCa 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 PCa rates over time.[11–13] 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 PCa, especially since the diagnosis of very high-risk PCa requires ≥5 biopsy cores with either GGG (Gleason grade group) 4 or 5 cancer.

2 | 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 PCa 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.[15–18] 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[9]: cT3a or GGG 4/5 or PSA > 20 ng/ml. Additionally, the Johns Hopkins classification defines very high-risk PCa according to the presence of at least one of the following criteria: cT3b-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 PCa according to traditional NCCN criteria, respectively. Within the traditional NCCN 26,855 high-risk patients, the use of the Johns Hopkins subgroupings 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 PCa 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 PCa 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) PCa. Here we also tabulated the rates over time of Johns Hopkins high and very high-risk PCa 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 cT-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.[19,20] 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.

3 | 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 PCa. 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 PCa (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

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.

obtained at prostate biopsy increased across all groups and also specifically in NCCN high-risk PCa (both $p < .001$).

According to the Johns Hopkin classification, the number of prostate biopsy cores and number of positive prostate biopsy cores were 12 (IQR: 12–12) 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 $p < .001$).

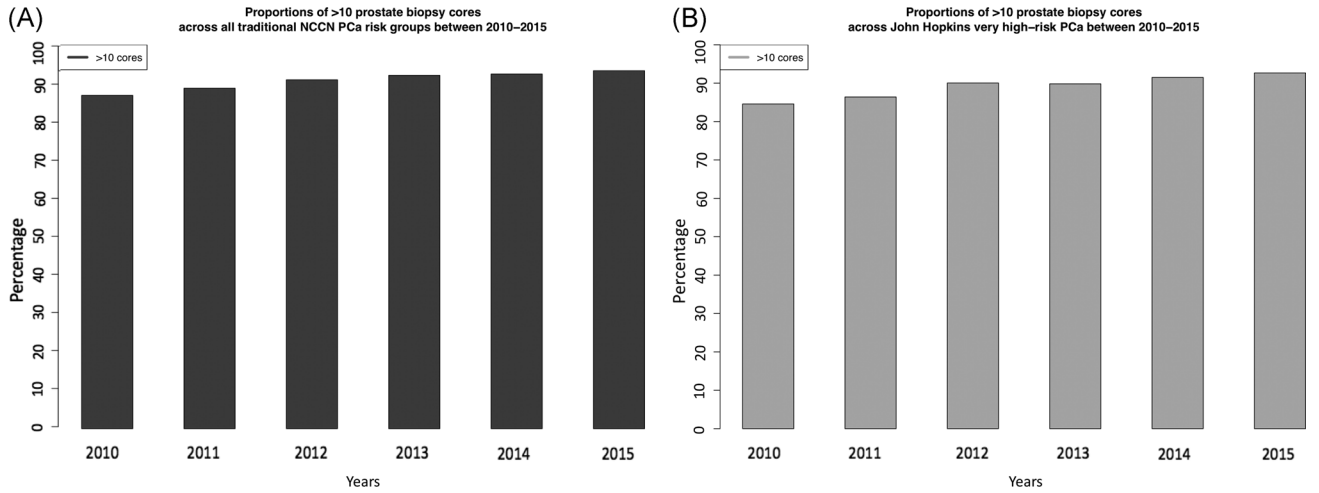

FIGURE 1 Rates over time according to number of prostate biopsy cores obtained between 2010 and 2015. Rates over time according to >10 prostate biopsy cores obtained between 2010 and 2015 for (A) all combined traditional NCCN low, intermediate, and high-risk prostate cancer (PCa) patients and (B) Johns Hopkins very high-risk PCa patients

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,

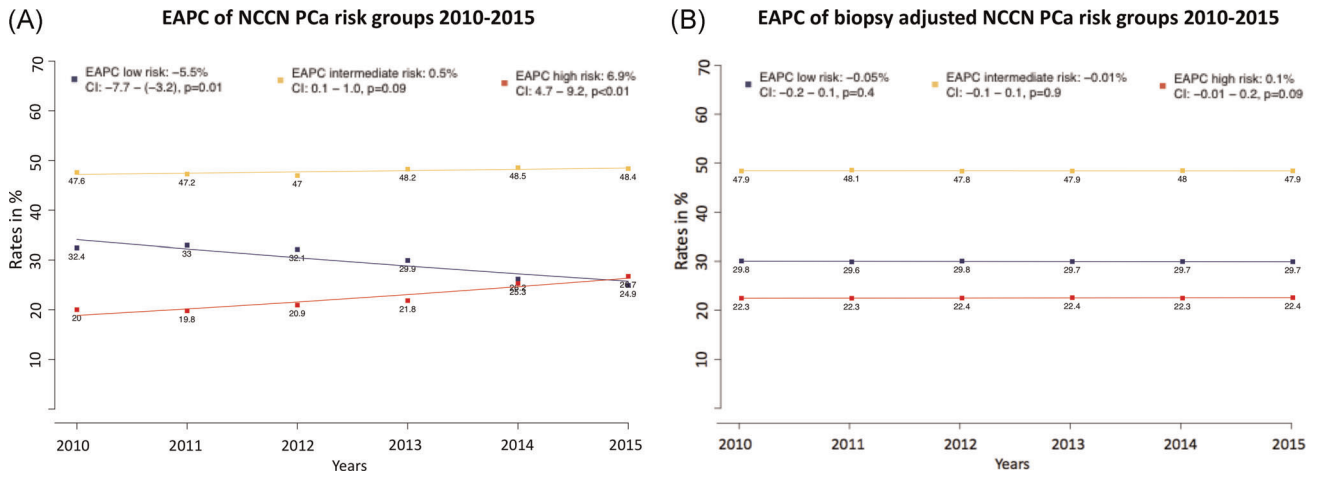

FIGURE 2 Unadjusted and adjusted rates over time for traditional NCCN low, intermediate, and high-risk prostate cancer (PCa) between 2010 and 2015. Log linear regression analyses were used to compute estimated annual percent change (EAPC) for (A) unadjusted observed rates between 2010 and 2015 and (B) adjusted rates for number of prostate biopsy cores between 2010 and 2015. CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

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, GGG 5 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, GGG 1 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%. GGG 3 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 (+2.3%, 47.4%–53.3%, $p = .03$) and of a decrease in cT2-stage over time (−3.7%, 38.6%–32.5%, $p < .01$).

After adjustment for number of prostate biopsy cores (Figure 3D), differences in rates over time disappeared in all GGG groups. Specifically, in GGG5 subgroup, the rate adjusted for number of prostate biopsy cores ranged from 31.8% to 31.8% (EAPC: −0.1%, $p \geq .4$). Similarly, differences in rates over time in cT-stage disappeared after adjustment.

3.5 | Detailed tabulation of PCa characteristics according to Johns hopkins high versus very high-risk PCa classification without and with adjustment for number of prostate biopsy cores

In analyses of patients that qualified for Johns Hopkins high or very high-risk PCa profile (Figure 3B,C), GGG5 rates also significantly increased over time in high-risk (EAPC + 3.9%, $p = .02$, 8.3%–10.4%), as well as in very high-risk PCa (EAPC + 1.9%, $p = .01$, 44.6%–48.0%).

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 3E,F), 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 PCa. 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,

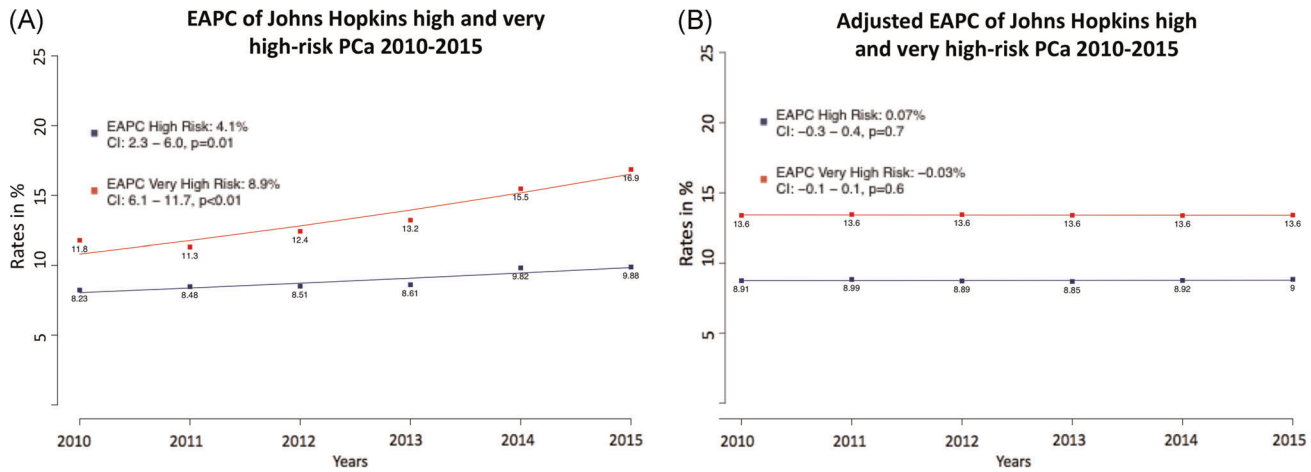

FIGURE 3 Unadjusted and adjusted rates over time for Johns Hopkins high and very high-risk prostate cancer (PCa) between 2010 and 2015. Log linear regression analyses were used to compute estimated annual percent change (EAPC) for (A) Johns Hopkins high and very high-risk unadjusted rates between 2010 and 2015 and (B) Johns Hopkins high and very high-risk rates after adjustment for number of prostate biopsy cores between 2010 and 2015. CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

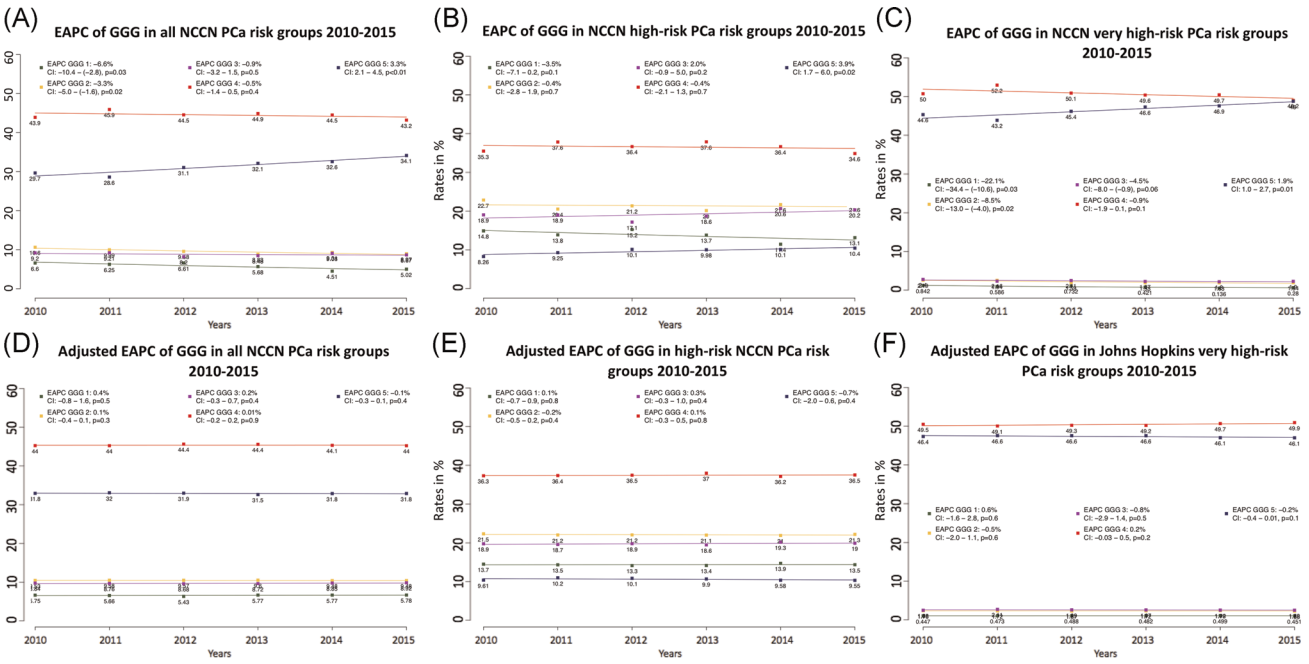

FIGURE 4 Unadjusted and adjusted rates of Gleason grade group (GGG) in traditional NCCN high-risk and Johns Hopkins high and very high-risk prostate cancer (PCa) between 2010 and 2015. Log linear regression analyses were used to compute estimated annual percent change (EAPC) for (A) GGG in all traditional NCCN high risk PCa patients, (B) Johns Hopkins high-risk PCa patients, (C) Johns Hopkins very high-risk PCa patients. (D-F) Similar stratifications were performed after adjustment for number of prostate biopsy cores. CI, confidence interval, GGG, Gleason grade group; PCa, prostate cancer [Color figure can be viewed at wileyonlinelibrary.com]

due to unavailable information about number of positive prostate biopsy cores, in previous analyses.[7] 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.[7] 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.[7]

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 PCa 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.[12,21–28] 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.

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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 Graefen, 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.

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