Original Article

Risk of prostate cancer and death after benign transurethral resection of the prostate—A 20-year population-based analysis

Maria Hilscher, MD[1]; Andreas Røder, MD, PhD[1,2]; J. Thomas Helgstrand, PhD, MD [1]; Nina Klemann, PhD, MD[1]; Klaus Brasso, PhD, MD[1,2]; Andrew Julian Vickers, PhD[3]; and Hein Vincent Stroomberg, PhD, MSc [1]

BACKGROUND: The oncological risks after benign histology on a transurethral resection of the prostate (TURP) remain largely unknown. Here, the risk of prostate cancer incidence and mortality following a benign histological assessment of TURP is investigated in a population-based setting. **METHODS:** Between 1995 and 2016, 64,059 men in Denmark underwent TURP without prior biopsy of the prostate; 42,558 of these men had benign histology. The risks of prostate cancer, prostate cancer with a Gleason score ≥ 3 + 4, and prostate cancer–specific death were assessed with competing risks. Specific risks for pre-TURP prostate-specific antigen (PSA) levels at 10 and 15 years were visualized by locally estimated scatterplot smoothing. **RESULTS:** The median age at TURP was 72 years (interquartile range [IQR], 65–78 years), and the median follow-up was 15 years (IQR, 10–19 years). The 10-year risks of any prostate cancer and prostate cancer with a Gleason score ≥ 3 + 4 and the 15-year risk of prostate cancer death showed clear visual relations with increasing PSA. The 15-year cumulative incidence of prostate cancer–specific death after benign TURP was 1.4% (95% confidence interval [CI], 1.3%–1.6%) for all men and 0.8% (95% CI, 0.6%–1.1%) for men with PSA levels <10 ng/ml. The primary limitation was exclusion due to missing PSA data. **CONCLUSIONS:** Men with low PSA levels and a benign TURP can be reassured about their cancer risk and do not need to be monitored differently than any other men. Patients with high PSA levels can be considered for further follow-up with prostate magnetic resonance imaging. These findings add to the literature suggesting that normal histology from the prostate entails a low risk of death from the disease. ***Cancer* 2022;128:3674-3680**.

LAY SUMMARY:

- There is little knowledge about the oncological risks after the surgical treatment of benign prostatic hyperplasia.
- This study shows a very low risk of adverse oncological outcomes in men with prostate-specific antigen (PSA) levels below 10 ng/ml at the time of transurethral resection of the prostate.
- Patients with higher PSA levels may need more extensive follow-up.

KEYWORDS: benign histology of the prostate, benign prostatic hyperplasia (BPH), disease-specific mortality, prostate cancer, prostate-specific antigen (PSA), transurethral resection of the prostate (TURP).

INTRODUCTION

Transurethral resection of the prostate (TURP) is the preferred surgical treatment option for men with lower urinary tract syndrome (LUTS) and bladder outlet obstructions due to benign prostatic hyperplasia.[1] Historically, TURP was also used to relieve obstructions in men with locally advanced prostate cancer when curative treatment was not possible and when histological confirmation of the disease could be achieved as a secondary goal. In Denmark, tissue resected during TURP has been routinely sent for histological analysis. This tradition was planned for documentation purposes, as pathological evaluations are stored in a nationwide pathology registry; thus, both histological evaluations and dates of treatment have been available for all TURP patients since 1995.

The value of benign TURP for excluding prostate cancer remains controversial. On the one hand, TURP is not a comprehensive or systematic sampling of the prostate. On the other hand, early studies did not find that TURP had a risk of missing clinically significant prostate cancer, and although later studies did observe an increased incidence of prostate cancer in a TURP cohort, this was attributed to surveillance bias.[2–7] Currently, guidelines recommend only a functional evaluation of the urinary tract 4–6 weeks after TURP for benign prostatic hyperplasia, and surveillance for cancer by routine prostate-specific antigen (PSA) testing is not routinely recommended.[8]

Correspondence Author: Hein Vincent Stroomberg, PhD, MSc, Copenhagen Prostate Cancer Center, Ole Maaløes Vej 24, 7521, DK-2200 Copenhagen, Denmark (hein.vincent.stroomberg@regionh.dk).

[1]Copenhagen Prostate Cancer Center, Department of Urology, Center for Cancer and Organ Disease, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [3]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York, USA

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.34407, **Received:** May 23, 2022; **Revised:** June 27, 2022; **Accepted:** June 28, 2022, **Published online** August 17, 2022 in Wiley Online Library (wileyonlinelibrary.com)

In recent years, we have seen controversy regarding the value of systematic transrectal ultrasound (TRUS)–guided biopsy for prostate cancer detection. For instance, although studies suggest that magnetic resonance imaging (MRI)–targeted biopsy finds a large number of Gleason score ≥ 7 cancers missed by systematic biopsy, there is also evidence that such cancers have an extremely low risk of a lethal outcome.[9,10]

The objective of this study was to estimate the probability of prostate cancer incidence and death following TURP with benign findings in previously unbiopsied men in the Danish population who underwent the operation in the years 1995–2016. Our aim was to address not only the clinical question of follow-up of men with benign TURP but also the biological question about the oncological aggressiveness of prostate tumors that are not readily detected with limited prostate sampling.

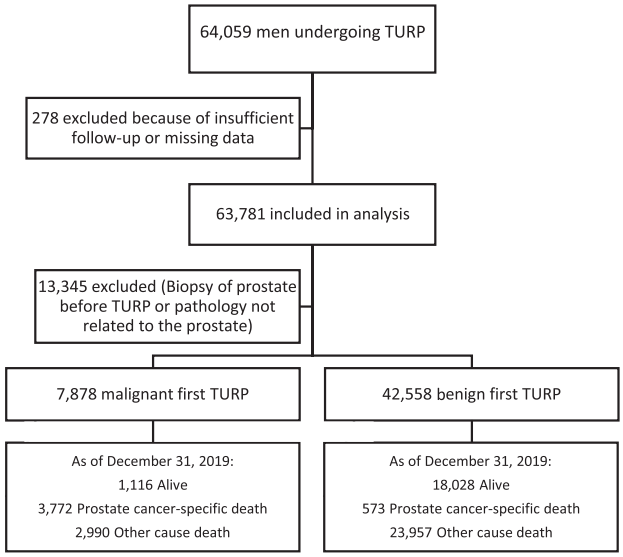

Figure 1. Flow chart of the men included in the study. TURP indicates transurethral resection of the prostate.

MATERIALS AND METHODS

All men who underwent TURP were identified in the Danish Prostate Cancer Registry (DaPCaR).[11] The study and the database were approved by the Danish Health and Medicines Authority (file number 3–3013-858/1/1) and the ethics committee of the Capital Region of Denmark (protocol number H4-2014-FSP). Data on the age at TURP, the pre-TURP prostate biopsy results, the histopathological evaluation of the TURP specimen, and the pre-TURP PSA levels were extracted. Pre-TURP PSA values were excluded if they were taken more than 182 days before TURP. Biopsies before TURP were categorized as malignant or benign; if the pathological diagnosis was registered as "suspicion of adenocarcinoma," the specimen was also considered benign. Men were excluded if follow-up data were missing, and they were further excluded from risk analysis if the patients had undergone TRUS biopsy before TURP and if other pathology results not related to the prostate (e.g., bladder cancer) were found on TURP. Causes of death were extracted from the Cause of Death Registry, and we further validated the causes of death by using a combination of the Danish Health Registries.[12] A flow diagram is depicted in Figure 1.

Statistics

The reported statistics followed the guidelines for statistics for clinical research in urology.[13] The cumulative incidence of subsequent histology (obtained by either TRUS biopsy or TURP sampling), prostate cancer, or prostate cancer with a Gleason score ≥ 7 was analyzed with the Aalen–Johansen estimator, with the competing event being any cause of death. Similarly, the cumulative incidence of cause-specific death was analyzed with prostate cancer–specific and other-cause deaths as competing events. Follow-up was defined as the time from the date of TURP to an event or censoring on the last day for which the vital status was known (December 31, 2020). The median follow-up time was defined as the median time to censoring by reverse Kaplan–Meier estimate. Predicted risks of death after TURP for PSA levels at the time of TURP were visualized by locally estimated scatterplot smoothing for the 10- and 15-year cumulative incidence. Subgroup analyses were performed for the incidence of Gleason scores ≥7 and cause-specific death in men who underwent TURP after 2004 and for the incidence of cause-specific death stratified by age groups (<60, 60–69, 70–79, and > 79 years at the time of TURP) in men with PSA levels below 10 ng/ml at the time of TURP. All statistical analyses were performed with R version 4.0.3 (R Development Core Team, Vienna, Austria) running on RStudio version 1.3.1093 (© 2009–2020 by RStudio, Inc), with statistical significance defined as a p value below .05. The data set is available upon request to the authors and the Danish data protection authorities.

RESULTS

Baseline characteristics

Between 1995 and 2016, a total of 63,781 individuals with at least one TURP were identified in DaPCaR, and 42,558 of these men had no history of pre-TURP biopsy of the

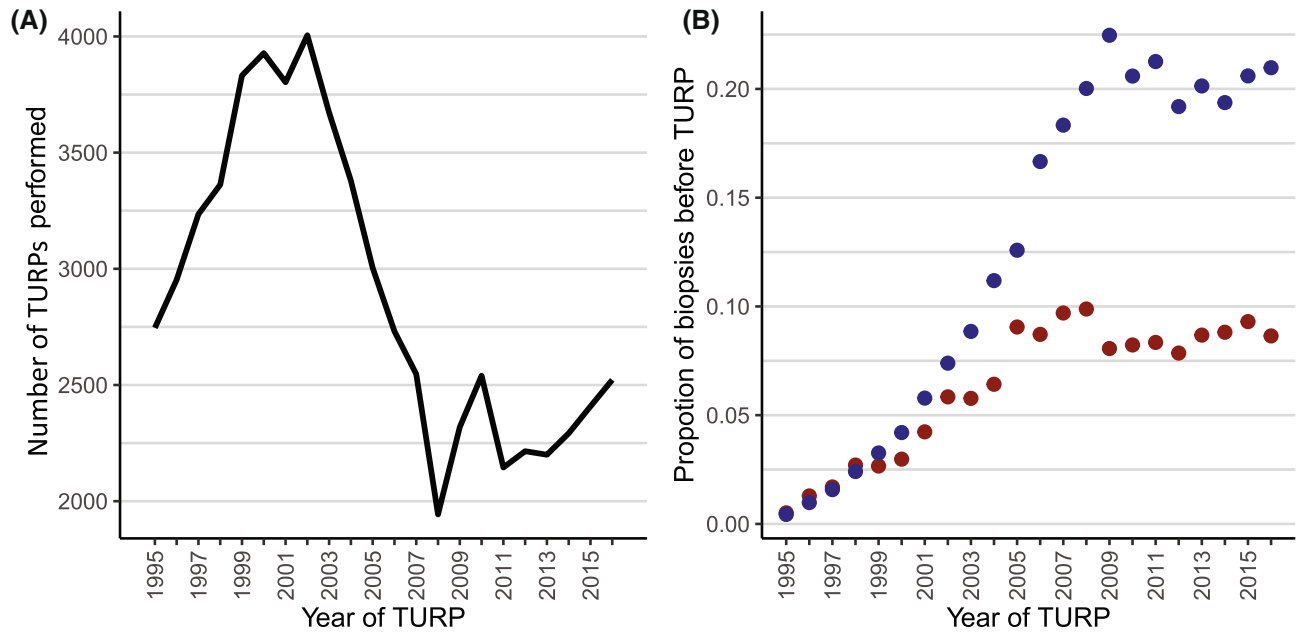

Figure 2. Absolute number of primary TURPs registered in Denmark and proportion of biopsies before TURP. (A) The line represents the absolute number of TURPs performed per year. (B) Proportions of benign (blue) and malign (red) histological assessments of TRUS-guided biopsy before TURP. TRUS indicates transrectal ultrasound; TURP, transurethral resection of the prostate.

prostate and benign histopathology on the initial TURP (Fig. 1). The median age was 72 years (interquartile range [IQR], 65–78 years). For the subset of patients with PSA data available (24%), the median PSA level was 3.7 ng/ml (IQR, 1.8–7.2 ng/ml). The crude number of initial TURPs and men with previous biopsies per year performed in Denmark is depicted in Figure 2. A total of 10,982 men underwent TRUS biopsy before the initial TURP, and 3774 of these men had malignant histopathology. According to a per-year analysis, 26 patients (12 benign) underwent biopsy of the prostate before TURP in 1995, and this number increased to 732 (523 benign) in 2010; after that, it stabilized (Fig. 2). A total of 7521 men underwent re-TURP during follow-up.

Risk of prostate cancer after benign TURP

A total of 6685 men had subsequent histology after a benign initial TURP. In 1986 men, prostate cancer was diagnosed after a benign initial TURP; 1465 of these men were diagnosed with a Gleason score ≥ 7. Overall, the 10-year cumulative incidences of subsequent histological evaluation, prostate cancer, and prostate cancer with a Gleason score ≥ 7 were 14.8% (95% confidence interval [CI], 14.4%–15.1%), 4.0% (95% CI, 3.8%–4.2%), and 2.9% (95% CI, 2.7%–3.0%), respectively. Higher PSA levels at TURP were observed to be associated with an increased risk of subsequent histology, an increased risk of prostate cancer, and an increased risk of prostate cancer with a Gleason score ≥ 7 (Fig. 3A). In men undergoing TURP after 2004, the 10-year cumulative incidence of a Gleason score ≥ 7 was 2.0% (95% CI, 1.8%–2.2%) (Table S2).

Analysis of death after initial TURP

The median follow-up for men without an event was 15 years (IQR, 10–19 years) after the benign initial TURP, with a total of 8513 men followed for more than 15 years. After the benign initial TURP, a total of 24,530 men died; 573 of these men died of prostate cancer. The cumulative incidence of prostate cancer–specific and other-cause death after 15 years was 1.4% (95% CI, 1.3%–1.6%) and 61% (95% CI, 60%–61%), respectively (Fig. S1). There was a clear relationship between a rising PSA level and prostate cancer–specific death and a small relationship with other-cause death (Fig. 3B,C). Moreover, the cumulative incidence of prostate cancer–specific death at 15 years for men with PSA levels of <10, 10–20, and > 20 ng/ml was 0.8% (95% CI, 0.6%–1.1%), 4.2% (95% CI, 2.9%–5.6%), and 6.5% (95% CI, 4.4%–8.7%), respectively (Fig. S1). As for the lower PSA levels, the 15-year risk was 0.6%, 0.9%, 1.7%, and 2.6% for PSA levels of 2.5, 5, 7.5, and 10 ng/ml, respectively (Fig. 3B,C and Table S1). No clear relationship between age and prostate cancer–specific mortality was found in men with PSA levels below

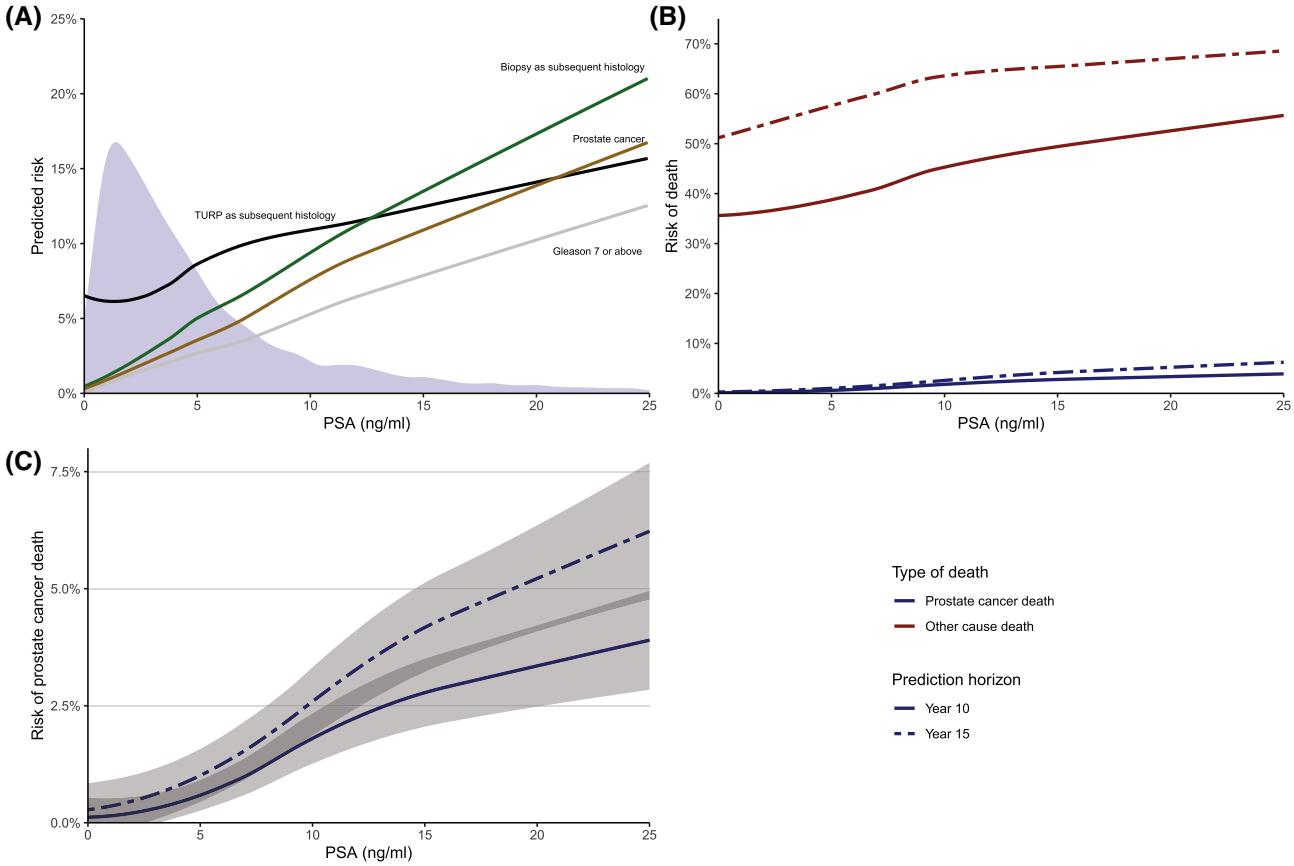

Figure 3. Predicted risks after benign pathology in initial TURP. (A) Predicted risk at 10 years of subsequent histology by TURP (black line), subsequent histology by biopsy (green line), prostate cancer (golden line) and a Gleason score ≥ 7 diagnosis (gray line) according to the PSA level and median age at TURP. Visualization is provided by LOESS. Density is indicated by the light blue color and shows the spread of the PSA values; note that the axis for the density is shown on the right side of the plot. (B) The 10- and 15-year cause-specific risks of prostate cancer–specific death (blue line) and other-cause death (red line) by PSA at TURP as visualized by LOESS. (C) Magnification of the risk of prostate cancer–specific death. The gray field behind the lines represents the prediction interval. LOESS indicates locally estimated scatterplot smoothing; PSA, prostate-specific antigen; TURP, transurethral resection of the prostate.

10 ng/ml and a benign initial TURP (Table S3). The risk of other-cause death after 15 years was 56% (95% CI, 55%–57%), 64% (95% CI, 61%–67%), and 69% (95% CI, 65%–73%) for men with PSA levels of <10, 10–20, and > 20 ng/ml, respectively. The cumulative incidence of prostate cancer–specific and other-cause death after 15 years in men with a malignant initial TURP was 50% (95% CI, 49%–51%) and 40% (95% CI, 39%–41%), respectively. The 15-year cumulative incidence of prostate cancer–specific death was not markedly different for men undergoing TURP after 2004 in comparison with the entire cohort; however, the incidence of other-cause death was lower (Table S2).

DISCUSSION

In this study, we have demonstrated that in men with a low PSA level at TURP, the incidence of the diagnosis of prostate cancer after 10 years is 4%, and the incidence of dying of prostate cancer after 15 years following a benign TURP is 1%, which can be considered low. This study is the largest contemporary study of TURP patients in which the pathological results of TURP and the diagnostic activity before and after TURP are known. Also, the follow-up was long, with nearly 9000 men followed for more than 15 years (including an overall mortality rate of 60%); this makes the data far more mature than those of previous publications.

An interesting decrease in TURP activity coincided with an increase in the number of TRUS biopsies performed before TURP; this points to men being PSA-tested while being evaluated for LUTS. Of course, selection and better medical treatment of LUTS play a role in the decreased TURP activity. Preoperative selection and increased pre-TURP PSA testing are the most likely explanations for

the decreased percentage of men with prostate cancer at the first TURP without previous invasive diagnostic activity. A total of 7521 men underwent re-TURP after the initial procedure. Unfortunately, no clinical information on the decision to perform re-TURP was available. The risk of re-TURP is not well described in the literature, but a Cochrane review based on six studies and a limited number of patients (652) suggests that the rate is 1 per 1000 patients.[14]

A total of 1986 patients were diagnosed with prostate cancer after a benign initial TURP, and 1465 of these patients were diagnosed with prostate cancer with a Gleason score ≥ 7. There have been previous theoretical speculations suggesting that the TURP procedure itself imposes a risk of developing prostate cancer as a result of inflammation, but the results are inconsistent, and the association is weak.[3,15] Our study shows that the cumulative incidence of prostate cancer after a benign TURP with PSA < 10 ng/ml before the TURP was 3%, which seems low, yet it is in concordance with another population-based study.[16] However, a recent review found that the incidence of prostate cancer ranged from 6% to 23% after holmium laser enucleation of the prostate. In that regard, our findings can be considered low, yet PSA levels were considerably higher in most studies—a finding shown here to be highly correlated with a prostate cancer diagnosis after a benign TURP.[17] A Swedish cohort study found that the mean time from a benign TURP to a diagnosis of prostate cancer was 7.5 years, and this was consistent with our data, according to which the median time to a prostate cancer diagnosis after a benign TURP was 6.3 years.[5]

Importantly, the risk of dying of prostate cancer was only 1.4% 15 years after a benign TURP. There are currently no recommendations for specific follow-up schedules after TURP beyond a functional evaluation of the urinary tract. Our data show that the risk of prostate cancer–specific death is almost identical to the risk of prostate cancer–specific death in men with benign systematic TRUS biopsies. A recent review reported that the risk of prostate cancer–specific death after benign TRUS biopsies ranged from 0.5% to 5.2% after 10–20 years of follow-up, and there was a strong association with PSA.[18,19] The current study shows that the cumulative incidence of prostate cancer mortality was up to 0.8% after 15 years in men with PSA levels <10 ng/ml; this was an even lower incidence than the incidence of 1.3% after a benign initial biopsy.[20,21] This difference may be explained by the selection of patients for TURP; specifically, patients who undergo TURP have lower PSA levels than men with a negative first biopsy. Hence, absent red flags such as a high PSA level, men with benign histology after TURP can be reassured that, despite a limited sampling of the prostate, they are at very low risk of aggressive prostate cancer and do not require extensive monitoring. Research into other potential red flags such as age is warranted in this population.

The use of MRI of the prostate and targeted biopsies of the prostate has become increasingly widespread since the publication of data showing the superiority of targeted biopsies in the ability to identify Gleason score ≥ 7 cancers missed by systematic TRUS biopsy.[9,22] However, doubt has been cast on whether these cancers are oncologically aggressive. We and other groups have shown that the long-term risk of prostate cancer death in men with benign systematic biopsies is very low[18,21]; if MRI targeting identifies many histologically defined Gleason score ≥ 7 tumors in a group of men with low prostate cancer mortality, it is clear that most of the tumors are in fact indolent despite their histology.[10] This suggests that current guidelines on how to histologically evaluate and grade MRI-targeted biopsies may need revision. Our findings support the hypothesis that prostate tumors that are not easily identified on limited sampling of the prostate are unlikely to be aggressive, and they cast doubt on the value of the suggested use of targeted biopsy approaches in men without other indications for prostate cancer, such as men with asymptomatic, elevated PSA levels.

The strengths of this study include the large DaPCaR data set, a population-based registry with high validity and a national scale, as well as the ability to cross-reference data from different registries because of the unique Danish central person registry. Limitations of the study include more limited data on PSA due to a lack of electronic storage in local and regional databases.[11] Because no data on drug use before TURP were available, no adjustments for the potential influence of 5-alpha-reductase inhibitors on PSA could be performed; therefore, the PSA levels of individual patients in the clinic need to be interpreted with caution. Furthermore, studies have suggested an association of 5-alpha-reductase inhibitors with reduced prostate cancer–specific death; as such, the estimates shown here can potentially be explained in part by the intake of these drugs.[23] Further studies on causal relations are thus needed. Another limitation is the lack of predictors known to be associated with a poor prognosis in prostate cancer; for example, a family history of prostate cancer, urine and blood markers, and imaging findings should not be ignored on the basis of the research shown here. Future research should elucidate the value of these predictors in this patient group. The Gleason grading system was reclassified by the International Society of Urological Pathology in 2005, and this has led to

a grade migration in which prostate cancers diagnosed after 2005 are graded higher.[24,25] Subgroup analyses for men undergoing TURP after 2004 showed a decreased incidence at 10 years of Gleason scores ≥7 in comparison with the entire cohort; this can likely be explained by the decrease in the use of TURP as a diagnostic tool (Table S2). Furthermore, a decreased 15-year incidence of other-cause death but not prostate cancer–specific death was observed in men undergoing TURP after 2004 in comparison with the entire cohort. As the decrease in other-cause death coincided with increased life expectancy, it is unlikely that the grade shift substantially influenced mortality. However, we cannot fully account for the grade migration in the database, and future studies of the true effect are warranted.

The risk of prostate cancer and prostate cancer–specific death following a TURP with a benign histology is very low and comparable to the risk for men with a negative prostate biopsy. Men with low PSA levels (<7.5 ng/ml) and a benign TURP can be reassured about their cancer risk and do not need to be monitored differently than any other men. Patients with high PSA levels can be considered for advanced imaging techniques such as prostate MRI. Our findings add to a body of literature suggesting that extensive investigation of the prostate is unnecessary: Prostate tumors that are hard to find are highly unlikely to lead to mortality.

ACKNOWLEDGMENTS

This work was supported by a Cancer Center Support Grant to the Memorial Sloan Kettering Cancer Center (P30 CA008748), a Specialized Program of Research Excellence grant for prostate cancer to Dr H. Scher (P50 CA92629), the Sidney Kimmel Center for Prostate and Urologic Cancers, and David H. Koch through the Prostate Cancer Foundation.

CONFLICTS OF INTEREST

Andreas Røder reports acting as a consultant for Astellas Pharma, AstraZeneca, Bayer, Merck, Janssen Biotech, and Pfizer Pharma. Andrew Julian Vickers is named on a patent for a statistical method to detect prostate cancer that has been licensed to and commercialized by OPKO Health as the 4Kscore; he receives royalties from sales of the test and has stock options in OPKO Health. Hein Vincent Stroomberg reports support for attending meetings or other travel from Merck. The other author made no disclosures.

AUTHOR CONTRIBUTIONS

Maria Hilscher: Data curation, formal analysis, visualization, and writing–original draft. **Andreas Røder:** Conceptualization, methodology, project administration, supervision, and writing–review and editing. **J. Thomas Helgstrand:** Conceptualization, data curation, resources, supervision, and writing–review and editing. **Nina Klemann:** Conceptualization, resources, supervision, and writing–review and editing. **Klaus Brasso:** Conceptualization, project administration, supervision, and writing–review and editing. **Andrew Julian Vickers:** Methodology, supervision, visualization, and writing–review and editing. **Hein Vincent Stroomberg:** Conceptualization, data curation, formal analysis, supervision, visualization, and writing–review and editing.

FUNDING INFORMATION

National Cancer Institute, Grant/Award Numbers: P30 CA008748 and P50 CA92629; Sidney Kimmel Center for Prostate and Urologic Cancers; Prostate Cancer Foundation.

REFERENCES

1. Nickel JC, Méndez-Probst CE, Whelan TF, Paterson RF, Razvi H. 2010 update: guidelines for the management of benign prostatic hyperplasia. *J Can Urol Assoc*. 2010;4(5):310-316. doi:10.5489/cuaj.10124
2. Greenwald P, Kirmss V, Polan AK, Dick VS. Cancer of the prostate among men with benign prostatic hyperplasia. *J Natl Cancer Inst*. 1974;53(2):335-340. doi:10.1093/jnci/53.2.335
3. Hammarsten J, Andersson S, Peeker R, Holmén A, Högstedt B. Does transurethral resection of a clinically benign prostate gland increase the risk of developing clinical prostate cancer? A 10-year follow-up study. *Cancer*. 1994;74(8):2347-2351. doi:10.1002/1097-0142(19941015)74:8<2347::AID-CNCR2820740820>3.0.CO;2-6
4. Chokkalingam AP, Nyrén O, Johansson JE, et al. Prostate carcinoma risk subsequent to diagnosis of benign prostatic hyperplasia: a population-based cohort study in Sweden. *Cancer*. 2003;98(8):1727-1734. doi:10.1002/cncr.11710
5. Karlsson CT, Wiklund F, Grönberg H, Bergh A, Melin B. Risk of prostate cancer after trans urethral resection of BPH: a cohort and nested case-control study. *Cancers (Basel)*. 2011;3(4):4127-4138. doi:10.3390/cancers3044127
6. Ørsted DD, Bojesen SE, Nielsen SF, Nordestgaard BG. Association of clinical benign prostate hyperplasia with prostate cancer incidence and mortality revisited: a nationwide cohort study of 3 009 258 men. *Eur Urol*. 2011;60(4):691-698. doi:10.1016/j.eururo.2011.06.016
7. Dai X, Fang X, Ma Y, Xianyu J. Benign prostatic hyperplasia and the risk of prostate cancer and bladder cancer a meta-analysis of observational studies. *Medicine (Baltimore)*. 2016;95(18):e3493. doi:10.1097/MD.0000000000003493
8. Gravas S, Cornu JN, Gacci M, et al. EAU Guidelines on Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), Incl. Benign Prostatic Obstruction (BPO). EAU Guidelines Office; 2022.
9. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med*. 2018;378(19):1767-1777. doi:10.1056/nejmoa1801993
10. Vickers AJ. Effects of magnetic resonance imaging targeting on overdiagnosis and overtreatment of prostate cancer. *Eur Urol*. 2021;80(5):567-572. doi:10.1016/j.eururo.2021.06.026
11. Helgstrand JT, Klemann N, Røder MA, et al. Danish Prostate Cancer Registry—methodology and early results from a novel national database. *Clin Epidemiol*. 2016;8:351-360. doi:10.2147/CLEP.S114917
12. Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health*. 2011;39(7):26-29. doi:10.1177/1403494811399958
13. Assel M, Sjoberg D, Elders A, et al. Guidelines for reporting of statistics for clinical research in urology. *Eur Urol*. 2019;75(3):358-367. doi:10.1016/j.eururo.2018.12.014
14. Alexander CE, Scullion MMF, Omar MI, Yuan Y, Mamoulakis C, N'Dow JMO, Chen C, Lam TBL, Cochrane Urology Group Bipolar versus monopolar transurethral resection of the prostate for lower urinary tract symptoms secondary to benign prostatic obstruction. *Cochrane Database Syst Rev* 2019;12(12):CD009629. doi:10.1002/14651858.CD009629.pub4
15. Armenian HK, Lilienfeld AM, Diamond EL, Bross IDJ. Relation between benign prostatic hyperplasia and cancer of the prostate. *A prospective and retrospective study Lancet*. 1974;304(7873):115-117. doi:10.1016/S0140-6736(74)91551-7
16. Holman CDJ, Wisniewski ZS, Semmens JB, Rouse IL, Bass AJ. Mortality and prostate cancer risk in 19,598 men after surgery for benign prostatic hyperplasia. *BJU Int*. 1999;84(1):37-42. doi:10.1046/j.1464-410x.1999.00123.x
17. Yilmaz M, Toprak T, Suarez-Ibarrola R, Sigle A, Gratzke C, Miernik A. Incidental prostate cancer after holmium laser enucleation of the prostate—a narrative review. *Andrologia*. 2022;54(3):e14332. doi:10.1111/and.14332

18. Kawa SM, Benzon Larsen S, Helgstrand JT, Iversen P, Brasso K, Røder MA. What is the risk of prostate cancer mortality following negative systematic TRUS-guided biopsies? A systematic review. *BMJ Open*. 2020;10(12):e040965. doi:10.1136/bmjopen-2020-040965
19. Palmstedt E, Månsson M, Frånlund M, et al. Long-term outcomes for men in a prostate screening trial with an initial benign prostate biopsy: a population-based cohort. *Eur Urol Oncol*. 2019;2(6):716-722. doi:10.1016/j.euo.2019.01.016
20. Klemann N, Røder MA, Helgstrand JT, et al. Risk of prostate cancer diagnosis and mortality in men with a benign initial transrectal ultrasound–guided biopsy set: a population-based study. *Lancet Oncol*. 2017;18(2):221-229. doi:10.1016/S1470-2045(17)30025-6
21. Kawa SM, Stroomberg HV, Larsen SB, et al. A nationwide analysis of risk of prostate cancer diagnosis and mortality following an initial negative TRUS-biopsy with long-term follow-up. *J Urol*. 2022;208(1):100-108. doi:10.1097/ju.0000000000002491
22. 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. doi:10.1056/nejmoa1910038
23. Björnebo L, Nordström T, Discacciati A, et al. Association of 5α-reductase inhibitors with prostate cancer mortality. *JAMA Oncol Published online May*. 2022;19:1019-1026. doi:10.1001/jamaoncol.2022.1501
24. Uemura H, Hoshino K, Sasaki T, et al. Usefulness of the 2005 International Society of Urologic Pathology Gleason grading system in prostate biopsy and radical prostatectomy specimens. *BJU Int*. 2009;103(9):1190-1194. doi:10.1111/j.1464-410X.2008.08197.x
25. Berg KD, Thomsen FB, Nerstrøm C, et al. The impact of the 2005 International Society of Urological Pathology consensus guidelines on Gleason grading—a matched-pair analysis. *BJU Int*. 2016;117(6):883-889. doi:10.1111/bju.13439