Risk of prostate cancer diagnosis and mortality in men with a benign initial transrectal ultrasound-guided biopsy set: a population-based study

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Summary

Background The risk of missing prostate cancer in the transrectal ultrasound-guided systematic biopsies of the prostate in men with suspected prostate cancer is a key problem in urological oncology. Repeat biopsy or MRI-guided biopsies have been suggested to increase sensitivity for diagnosis of prostate cancer, but the risk of disease-specific mortality in men who present with raised prostate-specific antigen (PSA) concentration and a benign initial biopsy result remains unknown. We investigated the risk of overall and prostate cancer-specific mortality in men with a benign initial biopsy set.

Methods Data were extracted from the Danish Prostate Cancer Registry—a population-based registry including all men undergoing histopathological assessment of prostate tissue. All men who were referred for transrectal ultrasound-guided biopsy for assessment of suspected prostate cancer between Jan 1, 1995, and Dec 31, 2011, in Denmark were eligible for inclusion. Follow-up data were obtained on April 28, 2015. The primary endpoint was the cumulative incidence of prostate cancer-specific mortality, analysed in a competing risk setting, with death from other causes as the competing event.

Findings Between Jan 1, 1995, and Dec 31, 2011, 64 430 men were referred for transrectal ultrasound-guided biopsy, of whom 63 454 were eligible for inclusion. Median follow-up was 5·9 years (IQR 3·8–8·5) and the total follow-up time, from the enrolment of the first patient on Jan 1, 1995, until the extraction of causes of death on April 28, 2015, was 20 years. 10 407 (30%) of 35 159 men with malignant initial biopsy sets died from prostate cancer, compared with 541 (2%) of 27 181 men with benign initial biopsy sets. Estimated overall 20-year mortality was 76·1% (95% CI 73·0–79·2). In all men referred for transrectal ultrasound-guided biopsy, the cumulative incidence of prostate cancer-specific mortality after 20 years was 25·6% (24·7–26·5) versus 50·5% (47·5–53·5) for mortality from other causes. In men with benign initial biopsy sets, the cumulative incidence of prostate cancer-specific mortality was 5·2% (3·9–6·5) versus 59·9% (55·2–64·6) for mortality from other causes. In men with PSA concentrations 10 µg/L or lower and benign initial biopsy sets (2779 men), the cumulative incidence of prostate cancer-specific mortality was 0·7% (0·2–1·3). Cumulative incidence of prostate cancer specific mortality in men with benign initial biopsy sets was 3·6% (95% CI 0·1–7·2) for men with a PSA higher than 10 ng/mL but 20 ng/mL or less (855 men) and 17·6% (12·7–22·4) and for men with a PSA higher than 20 ng/mL (454 men).

Interpretation The first systematic transrectal ultrasound-guided biopsy set holds important prognostic information. The 20-year risk of prostate cancer-specific mortality in men with benign initial results is low. Our findings question whether men with low PSA concentration and a benign initial biopsy set should undergo further diagnostic assessment in view of the high risk of mortality from other causes.

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Introduction

Since the 1980s, transrectal ultrasound-guided systematic biopsies have been the standard of care in the diagnostic work-up of men judged to be at risk of prostate cancer,[1] but the prognostic implications of a benign first biopsy set are not well known. The detection rate of prostate cancer from the initial transrectal ultrasound-guided biopsy depends on several factors, such as prostate volume, number of biopsy cores, and prostate-specific antigen (PSA) concentration,[2–5] but prostate cancer can be missed because of sampling error or anterior location of the lesion.[6,7] Recent data suggest that MRI and subsequent MRI-guided biopsies can increase sensitivity and specificity of diagnosis, thus avoiding unnecessary biopsies.[8–10] However, although MRI-guided biopsy is able to detect prostate cancer that is initially missed by transrectal ultrasound-guided biopsy, the consequence of a benign initial result on later prostate cancer-specific mortality is not well described.

In 2010, the European Randomized Study of Screening for Prostate Cancer (ERSPC) reported that prostate cancer-specific mortality in 3056 men presenting with a benign biopsy set on the initial transrectal ultrasound-guided biopsy was 0·03% after 11 years of follow-up.[11] However,

Research in context

Evidence before this study

We searched PubMed with the terms "transrectal-guided biopsy", "prostate", "prostatic cancer", "benign", "negative", "prognosis", "PSA", and "mortality" for articles published in English between Jan 1, 1990, and May 15, 2016. This search retrieved one relevant trial assessing the risk of prostate cancer-specific death following a benign initial biopsy set. In 2010, the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed that the risk of prostate cancer-specific mortality in men randomly assigned to prostate-specific antigen (PSA) screening was 0·03% in those who presented with a benign initial biopsy set.

Added value of this study

Findings from our population-based study support the notion that the initial transrectal ultrasound-guided biopsy set holds important prognostic information. Men with a benign initial biopsy set have a low risk of prostate cancer-specific mortality and a high risk of mortality from other causes. These data should be interpreted with recognition that men in Denmark in the studied period are likely to have been underassessed by biopsy and underscreened compared with a contemporary setting due to the low uptake of PSA testing in the Danish general population during a large part of the studied period and the use of 6-core biopsy until early 2000s which is not standard of care today. Our data also show that the combination of a benign initial biopsy result and PSA concentration at biopsy could further substratify patients into risk groups in terms of disease-specific mortality.

Implications of all the available evidence

Overtreatment and overdiagnosis remain major problems in prostate cancer after the introduction of PSA testing. The need for repeat biopsy in men with benign initial biopsy results is questionable, and restricting these additional investigations to men with high PSA concentrations and other risk factors might lower the risk of overdiagnosis and the number of unnecessary biopsies. The optimum follow-up strategies in men who present with benign initial biopsy results is still unclear, and warrants further investigations, including use of imaging modalities and biomarkers.

the prognostic role of the first transrectal ultrasound-guided biopsy has not previously been described at a population-based level. We aimed to assess this role in an analysis of all men referred for transrectal ultrasound-guided biopsy in Denmark between 1995 and 2011.

Methods

Study design and participants

In this population-based analysis, we included all men undergoing transrectal ultrasound-guided biopsy between Jan 1, 1995, and Dec 31, 2011, in Denmark. Patient data were extracted from the Danish Prostate Cancer Registry (DaPCaR)—a population-based registry including all men undergoing histopathological assessment of prostate tissue. Methods for DaPCaR have been described in detail elsewhere;[12] the database includes integration of data from several national Danish registries. All initial biopsy sets registered in DaPCaR were used in the analysis. DaPCaR has been approved by the Danish Data Protection Agency and the Danish Health Authority. No ethics approval was required for the study.

Procedures

For the purpose of this study, all initial transrectal ultrasound-guided biopsy sets, repeat biopsy sets, age at biopsy, PSA concentrations, biopsy Gleason scores, and causes of death (prostate cancer *vs* other causes) were extracted. Patients were stratified by PSA concentration (≤10 μg/L *vs* >10 to ≤20 μg/L *vs* >20 μg/L) at referral. Gleason scores were divided into five groups (≤6, 7, 3+4, 4+3, or ≥8). Patients categorised as having a Gleason score of 7 included patients for whom only the score was available, and all patients for whom the Gleason score added up to 7—eg, 2+5. For causes of death, we combined information about vital status from the Central Person's Registry (updated daily) with causes of death from the national Cause of Death Register. If men were registered as dead, but did not have a death certificate as of April 28, 2015, or if the cause of death was unspecified, a manual review of medical records was done by the first author (NK) and coauthor JTH. Dates of deaths were obtained from the national Cause of Death Register.[12]

Prostate cancer was judged to be the cause of death if a patient had received androgen deprivation therapy, had evidence of metastatic disease, had received chemotherapy or palliative radiotherapy for prostate cancer, or had been referred for palliative care for prostate cancer. Metastatic disease was deemed to be present when positive bone scans or CT scans had been reported in the patient's chart. Docetaxel and cabazitaxel (either or both) were considered prostate cancer-specific chemotherapy. Radiotherapy was classed as prostate cancer-specific when aimed at the prostate or bony metastases. If a patient had been referred for palliative care, manual review was done to ensure that this referral was due to prostate cancer and not because of other malignancies.

Biopsy sets consisted of six cores until the early 2000s when guidelines were changed to a 10–12-core systematic biopsy scheme. PSA concentrations were obtained from laboratories across Denmark and were included in the analysis if taken a maximum of 2 years before and 3 months after the biopsy procedure. Biopsies containing adenocarcinoma, possible adenocarcinoma, dysplasia, or high-grade prostatic intraepithelial neoplasia, and neuroendocrine or small cell differentiation were judged to be malignant, and only biopsy sets containing