BMJ Open  What is the risk of prostate cancer mortality following negative systematic TRUS-guided biopsies? A systematic review

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ABSTRACT

Objective  To investigate the risk of prostate cancer-specific mortality (PCSM) following initial negative systematic transrectal ultrasound-guided (TRUS) prostate biopsies.

Design  Systematic review.

Data sources  PubMed and Embase were searched using a string combination with keywords/Medical Subject Headings terms and free text in the search builder. Date of search was 13 April 2020.

Study selection  Studies addressing PCSM following initial negative TRUS biopsies. Randomised controlled trials and population-based studies including men with initial negative TRUS biopsies reported in English from 1990 until present were included.

Data extraction  Data extraction was done using a predefined form by two authors independently and compared with confirm data; risk of bias was assessed using the Newcastle–Ottawa Scale for cohort studies when applicable.

Results  Four eligible studies were identified. Outcomes were reported differently in the studies as both cumulative incidence and Kaplan-Meier estimates have been used. Regardless of the study differences, all studies reported low estimated incidence of PCSM of 1.8%–5.2% in men with negative TRUS biopsies during the following 10–20 years. Main limitation in all studies was limited follow-up.

Conclusion  Only a few studies have investigated the risk of PCSM following initial negative biopsies and all studies included patients before the era of MRI of the prostate. However, the studies point to the fact that the risk of PCSM is low following initial negative TRUS biopsies, and that the level of prostate-specific antigen before biopsies holds prognostic information. This may be considered when advising patients about the need for further diagnostic evaluation.

PROSPERO registration number  CRD42019134548.

INTRODUCTION

Systematic transrectal ultrasound-guided biopsies (TRUS biopsies) of the prostate have been gold standard for prostate cancer (PCa) detection since 1989 when Hodge et al demonstrated that the sextant biopsy technique detected 9% more cancers than targeted TRUS biopsies from hypoechoic areas in men with abnormal digital rectal examination. Sextant biopsies were routinely used until early 2000s where studies showed an increase of 19%–50% in PCa detection rates on TRUS biopsies by adding four cores from the lateral peripheral zone. This 10-core biopsy scheme is considered standard procedure. In the past decades, improved treatment modalities and prostate-specific antigen (PSA) testing have fuelled the interest in early and accurate diagnosis of PCa. Today, PCa has become the most frequently diagnosed cancer among men in the Western world. Undoubtedly, the increment in incidence of PCa worldwide is primarily a result of more frequent use of PSA as an early test for the disease in asymptomatic men, which has also led to increased diagnostic activity with TRUS biopsies. More men undergo systematic TRUS biopsies where biopsies turn out to be without cancer, that is, negative. The reported rate of false-negative systematic TRUS biopsies is 10%–34%, but the clinical significance of these missed cancers is not well described. Many may be low grade, low volume and consequently of low risk to the patient. Moreover, the term clinical significance may have several definitions or endpoints. Recently, clinical significance in PCa has emerged as a pathological definition rather than a prognostic endpoint such as death from the disease. Clinical significance,
as a prognostic definition in men with initial negative systematic TRUS biopsies, is not well studied.

Recent advancements in technology, such as multi-parametric MRI (mpMRI) of the prostate, have led to an increased understanding of how and where systematic TRUS biopsies miss cancers and question the future role of this diagnostic strategy. All MRI studies define clinical significance according to prostate biopsy histology. Several studies have questioned the accuracy of PSA and TRUS biopsies in diagnosing clinically significant PCAs, especially in the re-biopsy setting in men with initial negative systematic TRUS biopsies. Clinically significant as a histological concept was originally introduced by Epstein et al as a tumour with a volume >0.2 cm³, presence of Gleason pattern 4 or 5, and a PSA density >0.15 µg/L/g. Few studies use this definition strictly. MRI studies have shown that when mpMRI and targeted biopsy techniques are used in a re-biopsy setting in men with initial negative systematic TRUS biopsies, up to 50% are subsequently diagnosed with csPCa, defined by biopsy histology. Optimistically, the increased sensitivity results in more csPCa being diagnosed and because of an improved specificity, the rate of insignificant PCAs (and thereby overdiagnosis) is reduced. Rapidly, guidelines have recommended that diagnostic work-up for PCa include use of mpMRI both pre-biopsy and before re-biopsy after initial negative systematic TRUS biopsies. However, there is a potential gap between the histological definition of csPCa and prognosis. It remains questionable if all men with initial negative TRUS biopsies need MRI, or men can be safely omitted for further follow-up after negative TRUS biopsies. This paper systematically reviews the current evidence on the prognostic role of initial negative TRUS biopsies.

METHODS

This review was registered in Prospero (registration number CRD42019134548) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (see online supplemental appendix). Studies included should be randomised controlled trials or population-based cohort studies including men with initial negative systematic TRUS biopsies and should present data on prostate cancer-specific mortality (PCSM). Studies reported in English in peer-reviewed journals from 1990 (when the use of TRUS biopsies was introduced) until present were included.

Searches were performed in PubMed and Embase databases using a search string combination with both keywords/Medical Subject Headings terms and free text in the advanced search builder (see online supplemental appendix for the full search string). Primary search string included: 1. Prostatic Neoplasm OR prostate cancer 2. Biopsy OR Image-guided biopsy OR transrectal ultrasound biopsy

3. Negative prostate biopsy OR benign initial
4. 1 AND 2 AND 3

Time of search was 13 April 2020. Based on titles, all relevant abstracts were screened independently by two authors (SMK, SBL) using Covidence, an online systematic review program, to identify studies that potentially met the described inclusion criteria. The selected full-text articles were evaluated by the two authors (SMK, SBL) for eligibility. Any disagreement was resolved by discussion with a third author (MAR). Data extraction was done using a predefined form by the same two authors independently and compared with confirm data.

To evaluate the quality of the included studies, two authors (SMK, SBL) independently and blindly to each other used the Newcastle–Ottawa Scale (NOS) for cohort studies when applicable (table 1). Risk of bias across studies was not assessed.

Patient and public involvement

No patient involvement.

RESULTS

In all, 523 records were identified, hereof 42 duplicates. Among the remaining 481 records screened by titles or abstract, 9 records were deemed relevant to the review. All records were assessed for eligibility, and five were excluded as they did not meet the inclusion criteria; either being a conference abstract only or with non-eligible outcome or design. A flow chart for the inclusion of studies is shown in figure 1.

Two of the included studies originated from North America and two from Europe (see extracted information in table 2). One from each continent was based on a screening trial, the Rotterdam cohort of the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the American Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. The two remaining studies originated from Canada and Denmark and were based on registry data. In total, the studies included 126 672 men with initial negative TRUS biopsies.

The focus of this review was to determine PCSM reported on men with initial negative TRUS biopsies in the included studies.

Cancer-specific mortality

The risk of subsequent PCSM among men with initial negative TRUS biopsies ranged from 0.03% to 2% in the studies with a median follow-up ranging from 5.9 to 11 years (see table 2).

Three of the included studies calculated the cumulative incidence of PCSM. The 20-year cumulative incidence of PCSM was 5.2% (95% CI 3.9% to 6.5%) in the Danish study by Klemann et al. Of special interest, the study demonstrated that in men with PSA <10 µg/L prior to negative TRUS biopsies, the cumulative incidence of PCSM at 15 years was only 0.7% (95% CI 0.2% to 1.3%). The median follow-up time was 5.9 years (IQR 3.8–8.5)
but a large number of men had more than 15 years of follow-up. The 20-year cumulative incidence of PCSM was 1.8% (95% CI 1.6% to 2.0%) in the Canadian study by Sayyid et al.20 The American study by Lewicki et al.19 found an 11-year cumulative incidence of PCSM of about 1.8% (95% CI not reported). Among men with initial negative TRUS biopsies in the ERSPC trial, Schröder et al. reported a 3% risk of PCa death at 11 years.9

Quality of studies
None of the included studies presents a description of the derivation of their cohort including more detailed information on patient inclusion and exclusion apart from ‘no prior diagnosis of PCa’, and risk of bias due to patient selection can therefore not be eliminated. Two of the studies9 19 were based on trials from which the inclusion and exclusion information could be retrieved.22 23 The cohorts were from a secure record indicating low risk of bias, and the assessment of outcome was all linked to a record except for the cohort in the American study by Lewicki et al.19 which was based on self-reports presenting intermediate risk of bias. The study by Klemann et al.21 stated a complete follow-up. The other studies did not state their loss to follow-up. For the studies, the quality scores on the NOS ranged from 5 to 7, but for one study the NOS was non-applicable and therefore a minimum score is stated (see table 3). Risk of publication bias has not been assessed.

DISCUSSION
We identified four studies where risks of PCSM following initial negative TRUS biopsies have been reported. Despite interstudy differences, differences in other-cause mortality, follow-up time and re-biopsy strategies, the studies find an almost identical low risk of subsequent PCSM at 10–20 years following initial negative systematic TRUS biopsies.

Two of the studies originated from randomised trials investigating the effect of systematic PSA-based screening to reduce the risk of PCSM and thus the primary endpoint was not to investigate the cohort of men in which the TRUS biopsies were negative. Furthermore, differences in pre-biopsy strategies may affect PCSM. Men in the Canadian and Danish population did not undergo systematic PSA testing, and the median PSA from the American screening trial was 4.89 µg/L (IQR 1.88–6.36)19 and the median PSA from a non-screened population-based cohort was 7.7 µg/L (IQR 5.5–12.0).21
Danish and Canadian studies\(^9\) \(^{20}\) \(^{21}\) were register-based which introduce a risk of bias due to the inherent risk of misclassification of the cause of death, correct diagnosis and so on. All studies included information on the risk of bias for the cause of death. The Danish Cause of Death Registry has been reported to have >93\% concordance between the cause of death registered in the registry and cause of death based on information from patient files.\(^{24}\) PCSM as the outcome was retrieved from a national registry in the Danish study\(^{21}\) and in the screening trials, this was evaluated by a cause-of-death committee for each death.\(^9\) \(^{19}\) In the American study, deaths were confirmed from death certificates.\(^{19}\)

During the past decade, an intense interest in the use of MRI and MRI–TRUS fusion targeted biopsies to diagnose and to reduce the risk of missing csPCa has evolved—also in men with initial negative systematic TRUS biopsies. The potential to diagnose more csPCa and at the same time keep the detection of insignificant PCa low has led to a large number of studies on the subject.

A systematic review by Fütterer \textit{et al} showed that the use of MRI-targeted biopsies found a median of 50\% (IQR 48\%–53\%) csPCa in men aged 60–80 years with previous negative biopsies.\(^{25}\) The included studies in the review used histology of TRUS biopsies as the reference standard. The very high prevalence of csPCa is noteworthy as it is higher than what is reported in a recent systematic review of PCa in autopsies, where the prevalence of autopsy-detected PCa in the same age group was 30\%–40\%.\(^{26}\) However, caution is called for when comparing prevalence of PCa in autopsy studies with prevalence in biopsy materials, respectively, as several biases with selection as the most obvious, may play a role. In the papers included in the review by Fütterer \textit{et al}, various definitions of csPCa were used including different biopsy Gleason scores (GS), number and length of positive cores and PSA levels.\(^{25}\) The studies primarily included re-biopsies in men with positive mpMRIs and disregarded the negative mpMRIs which could bias the true negative and false negative values. Most of the included studies used radical prostatectomy specimen as the reference standard, which also represents an important bias as only MRI-positive men went on to undergo surgery.

A recent Cochrane review by Drost \textit{et al} demonstrated that csPCa (GS 3+4 or higher) was found in 22.8\% (95\% CI 20.0\% to 26.2\%) of men with initial negative biopsies in a re-biopsy setting with a combination of both an MRI pathway and TRUS biopsies using template biopsies as the reference standard.\(^27\) The differences in detection of csPCa in the reviews by Fütterer \textit{et al} and Drost \textit{et al}, respectively, are probably caused by the different reference standards. Template biopsies are more likely to represent the true pathology of the prostate than systematic TRUS biopsies. Drost \textit{et al} found the detection ratio of MRI pathway versus TRUS biopsies in men with initial negative TRUS biopsies to be 1.44 (95\% CI 1.19 to 1.75). In men with initial negative TRUS biopsies and a negative mpMRI, Drost \textit{et al} also showed that 5.3\% (95\% CI
### Table 2  
Extracted information from the studies included in the systematic review

| Reference      | Country/ethnicity/inclusion period | Screened population (positive screening criteria) | Number of participants (initial negative biopsies/total biopsies) | PCSM when initial negative biopsies | Mortality when initial negative biopsies | Primary findings on mortality when initial negative biopsies | Age interval (years) | Median PSA when biopsied with negative result (µg/L) | Median follow-up (years) |
|----------------|-----------------------------------|--------------------------------------------------|---------------------------------------------------------------|------------------------------------|----------------------------------------|----------------------------------------------------------|----------------------|--------------------------------------------------|--------------------------|
| Schröder et al | The Netherlands (ERSPC) Ethnicity not described but mainly Caucasian November 1993-December 1999 | Yes (PSA of >4 µg/L or an abnormal digital rectal examination (DRE) up until November 1997 when DRE was excluded as a screening test and biopsies were recommended if PSA was >3 µg/L) | 3056/4 133 | 7/3056 (0.03%) | 153/3056 (5%) all-cause mortality 146/3056 (4.8%)* | Kaplan-Meier estimate 80% progression-free survival 97% PCa-specific survival | 55–74 at inclusion (no age shown) | Not shown | 11 (IQR: 8–14) |
| Lewicki et al  | USA Caucasian 92%+ Afro-American 4%+ other 1993-2001 | Yes (PSA >4 µg/L or an abnormal DRE) | 760/1233 | 8/760 (1.1%) | 18.5% all-cause mortality 133/760 (17.5%)* | 11-year PCSM cumulative incidence 1.8% Proportional sub-HR PCSM 2.93 (95% CI 1.44 to 5.99) | Median 63 (IQR: 60–68) | 4.89 (IQR: 1.88–6.36) | 12.9 (IQR: not shown) |
| Klemann et al  | Denmark Ethnicity not described but mainly Caucasian January 1995–December 2011 | No | 27 181/63 454 | 541/27 181 (2%) | 615/4 27 181 (2.3%) Other-cause mortality | 20-year cumulative incidence for PCSM 5.2% (95% CI 3.9% to 6.5%) 20-year cumulative incidence for other-cause mortality 59.9% (95% CI 55.2% to 64.6%) | Median 67 (IQR: 62–73) | 7.7 (IQR: 5.5–12.0) | 5.9 (IQR: 3.8–8.5) |
| Sayyid et al   | Canada Ethnicity not described but probably mainly Caucasian 1994–2014 | No | 95 675/95 675 | 620/95 675 (0.66%) | 16 153/95 675 (16.9%) all-cause mortality 15 924/95 675 (16.2%)* | 10-year cumulative incidence for PCSM 0.57% (95% CI 0.51% to 0.63%) 20-year cumulative incidence for PCSM 1.8% (95% CI 1.6% to 2.0%), and for other-cause mortality 45.9% (95% CI 45.0% to 46.8%) | 40–80-included, median 63 (IQR: 57–69) | Not shown | 8.1 (IQR: 4.5–12.3) |

*Calculated other-cause mortality.

ERSPC, European Randomized Study of Screening for Prostate Cancer; PCa, prostate cancer; PCSM, prostate cancer-specific mortality; PSA, prostate-specific antigen.
3.1% to 8.9%) had csPCa when systematic biopsies were applied despite a negative MRI but on the cost of 14.2% (95% CI 5.9% to 30.2%) detected with insignificant PCa.

Overall, MRI studies indicate that 20%-50% of men with initial negative TRUS biopsies harbour csPCa defined as GS 3+4 or higher. Our review underlines the marked difference between a histological definition of csPCa at re-biopsy and csPCa defined as lethal disease in men with initial negative systematic TRUS biopsies. Recent studies have found that men with negative mpMRI of the prostate hold little risk of harbouring csPCa. It can be speculated whether in the future, negative mpMRI will hold the same prognostic information as negative TRUS biopsies. However, mpMRI may miss some potentially csPCa as in the case of TRUS biopsies.20-29

**LIMITATIONS**

Only a few studies have investigated the risk of PCSM in men with initial negative biopsies which is the most important limitation of this systematic review. We fully acknowledge the limitation of searching only two databases as well. Second, the included studies to a large extent lacked information on pre-biopsy PSA or other prognostic parameters which is important if these data should be translated into clinical decisions. The lack of data also impaired the possibility to perform a meta-analysis which could have been beneficial for the review. Lastly, the short follow-up in all studies is an overall limitation that entails a careful interpretation of the results. Small aggressive tumours missed by TRUS biopsies may evolve into a lethal disease after a long time. Thus, length of follow-up is essential for evaluating the risk of PCSM.

**Results in context**

The results presented emerge from patients that may not resemble contemporary patients. The diagnostic strategy has changed thus it should be debated if the estimates from the included cohorts are representative in a modern context. Increasing the number of prostate biopsies and the introduction of image-guided biopsies have been demonstrated to increase the number of cancers diagnosed. Furthermore, more men are subjected to systematic or opportunistic PSA testing potentially lowering the threshold for diagnosis. These changes may reinforce that contemporary men with initial negative TRUS biopsies have an even lower risk of PCSM.

The optimal management of these men has spurred controversy, ranging from nothing to PSA follow-up to TRUS-guided re-biopsies and/or mpMRI. The present structured review adds to the discussion by demonstrating that initial negative systematic TRUS biopsies hold strong prognostic information which is amplified further by the addition of PSA.

The role of MRI in the follow-up in men with initial negative TRUS biopsies should be discussed. Currently, published papers on MRI and targeted biopsies compared with standard systematic TRUS biopsies conclude on the assumption that the cancers detected by targeted biopsies are of the same biological nature, but this may be far from the truth, as addressed by Vickers et al in a recent editorial.30 Our review underlines that few lethal PCa are missed at the initial TRUS biopsies and questions the definition of csPCa on targeted MRI-guided biopsies. No study has previously clarified the true effect of the MRI pathway in a randomised setting for men with initial negative TRUS biopsies comparing mpMRI and targeted biopsies versus systematic TRUS biopsies in the re-biopsy setting. Also, the clinical implication of csPCa detected with the MRI pathway needs to be addressed by studies with clinical endpoints such as PSA progression, metastases and PCSM.

**CONCLUSION**

Clinically significant PCa, defined as a lethal disease, is rarely missed in the initial systematic TRUS biopsies. In the continuing struggle to reduce overdiagnosis, it remains important to define the optimal candidate for re-biopsy when the initial biopsies are negative. The follow-up strategy and use of mpMRI in men with initial negative biopsies need further evaluation in randomised controlled trials.

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