Prevalence of prostate cancer in men with haematuria

a systematic review and meta-analysis

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Published in:
BJU International

DOI:
10.1111/bju.15950

Publication date:
2023

Document version:
Final published version

BJU Int 2023 doi:10.1111/bju.15950

BJUI
BJU International

Original Article

Prevalence of prostate cancer in men with haematuria: a systematic review and meta-analysis

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Objectives

To investigate the prevalence of prostate cancer in men attending evaluation for haematuria, as this could help healthcare providers to determine whether men with haematuria should have prostate examinations performed.

Methods

The study was performed according to a pre-specified protocol uploaded to the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022299383). A systematic search of MEDLINE, Ovid and Google Scholar was performed in December 2021. Two independent researchers evaluated all titles, available abstracts, and full texts. We included studies on adult men (aged ≥18 years) describing haematuria and prostate cancer.

Results

We screened 4252 titles and abstracts when available and assessed 350 studies in full text. In total, 65 studies were included and 42 was summarised in a meta-analysis. In total, 18 752 men with haematuria were included, and the pooled prevalence (95% confidence interval [CI]) of prostate cancer was 3.0% (2.0–4.1%). In men with macroscopic haematuria, the pooled prevalence (95% CI) of prostate cancer was 5.9% (2.9–9.9%; n = 265/5373). In men with microscopic haematuria, the pooled prevalence (95% CI) of prostate cancer was 1.4% (0.8–2.2%; n = 71/6642).

Conclusion

Our findings indicate that the prevalence of prostate cancer is considerable in men attending evaluation for haematuria. Therefore, digital rectal examination and prostate-specific antigen measurement should become a standard procedure for all men with haematuria, especially for men with macroscopic haematuria.

Keywords

prostate cancer, haematuria, microscopic haematuria, macroscopic haematuria, systematic review, meta-analysis, #PCSM, #ProstateCancer, #uroonc

Introduction

Around four per 1000 visits per year to GPs are individuals with haematuria, which is an abnormal number of red blood cells in the urine [1]. Understanding the importance of haematuria is central, as individuals with haematuria constitute about 5–10% of referrals to urology care [2]. Haematuria can be either macroscopic (macrohaematuria) or microscopic (microhaematuria) depending on whether the blood in the urine is visible to the naked eye or not, respectively [2,3]. Macrohaematuria often lead to healthcare consultation, but as microhaematuria is not visible, many patients are identified incidentally when urine analysis is performed for other reasons [4,5]. When encountering haematuria, diagnostic evaluation is recommended [2,4,6], as genitourinary malignancy is diagnosed in ~3% of patients with microhaematuria [4,7], and ~10% of patients with macrohaematuria [7]. When scrutinising the literature on the prevalence of cancer in individuals with haematuria, most studies focus on bladder, kidney, and upper urinary tract cancers [4,7], probably because guidelines on evaluation for haematuria focuses on identifying these [2,4,6]. Of interest, a recent epidemiological study indicates that prostate cancer is almost three-times as prevalent as kidney cancer in individuals with haematuria [8]. Although, the latter study was based on diagnosis codes the results suggest that prostate

cancer is a relevant differential diagnose in the diagnostic evaluation for causes of haematuria.

To the best of our knowledge no systematic reviews or meta-analysis has been performed on the prevalence of prostate cancer in men presenting with haematuria [9]. We hypothesised that prostate cancer is relevant to investigate for in men attending evaluation for haematuria. The purpose of this study was therefore to investigate the prevalence of prostate cancer in men attending evaluation for haematuria, as this would help healthcare providers to determine whether men with haematuria should have prostate examinations performed.

Methods

A pre-specified protocol for conducting this systematic review and meta-analysis was uploaded to the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022299383) on 20 December 2021 [10]. A systematic search of the databases MEDLINE (PubMed), Ovid (EMBASE) and Google Scholar was performed right after submitting the protocol to PROSPERO [11].

The search strategy (Appendix S1) was developed and refined by our team with assistance from a librarian at the University Library of Southern Denmark, Odense University Hospital, Denmark. To describe the information needed, we used the Condition, Context, Population (CoCoPop) model as follows; Co: prostate cancer, Co: individuals who are evaluated for macro- or microhaematuria, Pop: individuals with haematuria.

The systematic search was performed with no restrictions on publication time period and included terms related to prostate cancer and haematuria. All records identified by the database search were screened by title and abstract if available by both R.S.H. and J.B.B. Any discrepancies during the selection of titles and abstracts were discussed until consensus. Studies considered relevant were evaluated in full text according to the inclusion and exclusion criteria. All full-text records were evaluated by both R.S.H. and S.H.B. Any discrepancies during the selection of records were discussed until consensus. Handling of identified records and screening was performed using Covidence (Software for Systematic Review) [12]. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist was consulted for how to report results [13].

Inclusion criteria were studies on adult human individuals (aged ≥18 years) describing haematuria and prostate cancer. Original data from cohort studies (both prospective and retrospective), randomised controlled trials, observational studies and comparative observational studies were included. We excluded in vitro studies, animal studies, reviews, guidelines, letters that did not include original data, editorials that did not include original data, case reports, case series, poster abstracts and conference abstracts. Records in non-English language were excluded, unless relevant information on haematuria and prostate cancer could be extracted from the paper without any doubt. Studies using International Classification of Diseases (ICD) codes for haematuria or cancer were excluded. To avoid underestimating the prostate cancer prevalence, only studies describing the number of males with haematuria were included.

After the search and application of inclusion criteria, we ended up with two categories of studies: (A) studies clearly describing the proportion of men referred to hospital or private practice for evaluation of haematuria aetiology having prostate cancer, and (B) studies clearly describing haematuria as the presenting symptom leading to a prostate cancer diagnosis. Category B was not part of our a priori PROSPERO plan but was included for secondary analysis in support of primary results, as studies of category B enlighten the prostate cancer prevalence of men with haematuria. Thus, the studies were analysed in two separate categories and only category A studies were included in the meta-analysis.

From all studies included in the meta-analysis (category A), we extracted information regarding author, publication year, study design, inclusion and exclusion criteria, information needed to perform study quality assessment, study population, diagnostic approach (tests, methods, and setup), prostate cancer characteristics, and haematuria characteristics.

From category B studies, we extracted information regarding author, publication year, study design, inclusion and exclusion criteria, study population, age, how prostate cancer was diagnosed, Gleason sum score, and haematuria characteristics.

Quality Assessment

For all studies included in the meta-analysis, bias was assessed using the Study Quality Assessment Tools provided by National Heart, Lung and Blood Institute [14]. This tool addresses participation rate, recruitment of cohort, sample size justification, data analysis, timeframe, exposure information, outcome information, blinding, follow-up, and adjustment for confounding.

Bias was assessed by both R.S.H. and S.H.B., with regard to the purpose of this systematic review and meta-analysis. Each study was rated 'good', 'fair', or 'poor' according to the estimated risk of bias. After individual assessment, R.S.H. and S.H.B. discussed any rating disagreement until consensus was achieved.

Sensitivity analysis was performed for studies rated of 'good' quality.

Diagnostic Approach

For all studies included in the meta-analysis, we extracted information on all diagnostic tests (e.g., cystoscopy, digital rectal examination (DRE), prostate specific antigen (PSA), prostate biopsy) performed on the population of each study [15]. We had no restrictions on which diagnostic tests the study population had to undergo for being included in this review. As a DRE and PSA test are the initial tests recommended for the detection of prostate cancer [15], and are often used to decide whether to proceed with prostate biopsy or imaging, we performed a sensitivity analysis of studies that described performing these tests. In this sub-analysis, we also included studies performing physical examination by a trained urologist, as we believe a DRE would be performed in men when examined by a trained urologist for haematuria.

Moreover, haematuria is one of the major reasons for referral to urology care, why many departments have established fast tracks for diagnostic evaluation with use of a standard test package for individuals with haematuria [6]. Therefore, sensitivity analysis was performed for studies reporting results from haematuria fast tracks.

Prostate Cancer Characteristics

To address the association between haematuria occurrence and prostate cancer characteristics, we extracted all available information on the prostate cancers identified, including tumor, node, metastasis (TNM) stage, Gleason sum score, histopathological type, PSA, cancer burden and size. If the included study did not report any of the above mentioned parameters, the cases were still included.

Haematuria Characteristics

To determine if there was a difference in prostate cancer prevalence between men with macro- or microhaematuria, we stratified haematuria into microhaematuria, macrohaematuria and 'any' haematuria. The definition of macro- and microhaematuria was according to the included studies. If the study did not clearly report the number of men with macrohaematuria or microhaematuria the haematuria episode was classified as 'any'. If the study reported haematuria, but no definition of haematuria was provided, the information was still included, but assessed as 'any' haematuria.

Statistical Analyses

The results are presented as numbers and proportions. We expected that the included studies were heterogeneous with a high level of variance, and therefore we used a random-effects model for calculation of prostate cancer prevalence's among men with haematuria [16]. We transformed the included prevalence proportions using a double arcsine model and calculated an overall mean prevalence (95% CIs), which was depicted in Forest plots [16]. I^2 was calculated to determine statistical heterogeneity [17,18]. Funnel plots were used to depict publication bias [19]. The statistical analyses were performed in MetaXL (EpiGear International, Sunrise Beach, Qld, Australia).

Results

The process of identification, screening and inclusion of studies is shown in Fig. 1. In total, 65 studies were included in this review [20–84] (Table S1), and divided in two categories; (A) studies describing clearly how many of men referred to hospital or private practice for evaluation of haematuria aetiology had prostate cancer (n = 42) [20–61], and (B) studies clearly describing haematuria as a presenting symptom leading to a prostate cancer diagnosis (n = 23) [62–84]. The 42 studies describing evaluation of haematuria were included in a meta-analysis [20–61]. All of the 42 studies [20–61] were cohort studies, enabling direct comparison. Prostate cancer prevalence's are given in Table 1.

Study Quality

For the 42 studies [20–61], quality was 'good' in eight [20,21,24–26,36,53,57], 'fair' in 22 [23,27,29,31–33,37,38,40,41,43,47,49,51,52,54–56,58–61] and 'poor' in 12 studies [22,28,30,34,35,39,42,44–46,48,50]. As studies rated of 'good' quality were deemed to have low bias, we wanted to investigate the prostate cancer prevalence specifically for these studies [20,21,24–26,36,53,57].

Prevalence of Prostate Cancer in Men Attending Evaluation for Haematuria

From the 42 studies included in the meta-analysis [20–61], the pooled prevalence (95% CI) of prostate cancer was 3.0% (2.0–4.1%; Fig. 2). We found an asymmetric funnel plot indicating low publication bias, with an I^2 of 93% indicating considerable heterogeneity between the 42 studies (Appendix S2) [20–61].

Diagnostic Approach for Prostate Cancer

Almost all included studies reported performing either cystoscopy or imaging, or both, but as a DRE and PSA test are the initial clinical tests for the evaluation of prostate cancer, we enumerated the prostate cancer prevalence for studies that clearly described performing a DRE or PSA test on all included men (n = 11) [21–24,26,29,32,33,38,44,58]. In these 11 studies, the pooled prevalence (95% CI) of prostate cancer was 3.1% (1.9–4.5%; Fig. 3), with I^2 on 76% indicating heterogeneity between the 11 studies (Appendix S2). Of these 11 studies, three described performing histopathological

Fig. 1 PRISMA flow diagram of the exclusion and inclusion process of records and studies [89].

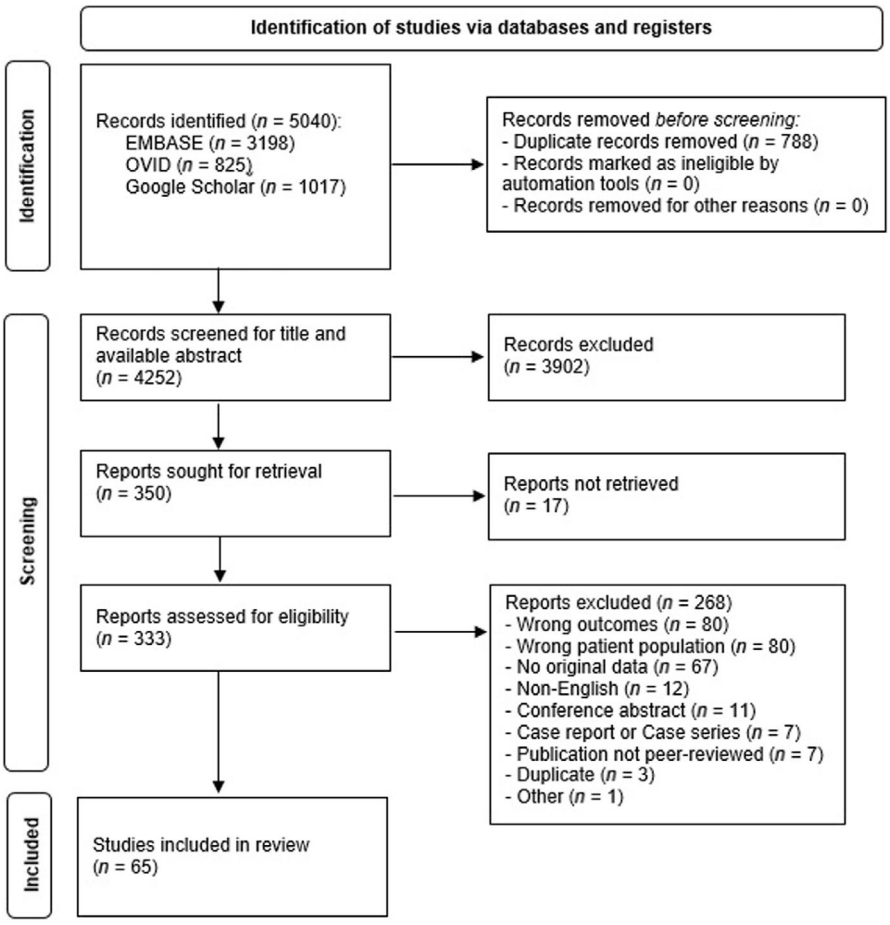


Table 1 Prostate cancer prevalence for studies included in the meta-analysis and stratified in studies rated of 'good, quality, performed a DRE, PSA test or physical examination by a trained urologist, attending a haematuria clinic and histopathologically confirmed prostate cancer.

Study stratification (number of studies included)	Prostate cancer prevalence, % (95% CI) *n* = prostate cancer cases/men with haematuria		
	Overall	Macrohaematuria	Microhaematuria
All included (*n* = 42)	3.0 (2.0–4.1) *n* = 505/18752	5.9 (2.9–9.9) *n* = 263/5373	1.4 (0.8–2.2) *n* = 71/6642
Studies rated of 'good' quality (*n* = 8)	2.5 (1.1–4.3) *n* = 140/6104	2.1 (0.2–5.5) *n* = 66/3376	1.0 (0.3–2.1) *n* = 16/1905
DRE, PSA test or physical examination by a trained urologist (*n* = 11)	3.1 (1.9–4.5) *n* = 117/4053	3.6 (1.3–6.8) *n* = 55/2060	1.5 (0.7–2.5) *n* = 10/741
Haematuria clinics (*n* = 12)	2.4 (1.5–3.5) *n* = 181/7979	2.9 (1.1–5.4) *n* = 98/4164	0.9 (0.2–1.9) *n* = 13/1722
Histopathologically confirmed prostate cancer (*n* = 13)	2.4 (1.3–3.7) *n* = 147/7247	4.7 (2.7–7.3) *n* = 56/1072	0.4 (0.2–0.6) *n* = 15/3983

We anticipated that the included studies would be heterogeneous and that is why the above mentioned prostate cancer prevalence was calculated using a random-effects model. Forest plots and funnel plots are depicted in Appendix S2.

verification of the cancer [26,29,38], while one study diagnosed prostate cancer clinically and histopathologically [33]. In the three studies with histopathological verification of the cancer, the pooled prevalence (95% CI) of prostate cancer was 2.5% (0.6–5.5%) (*n* = 28/815 men with haematuria) [26,29,38].

Fig. 2 Forest plot of prostate cancer prevalence in men attending evaluation for haematuria (n = 42).

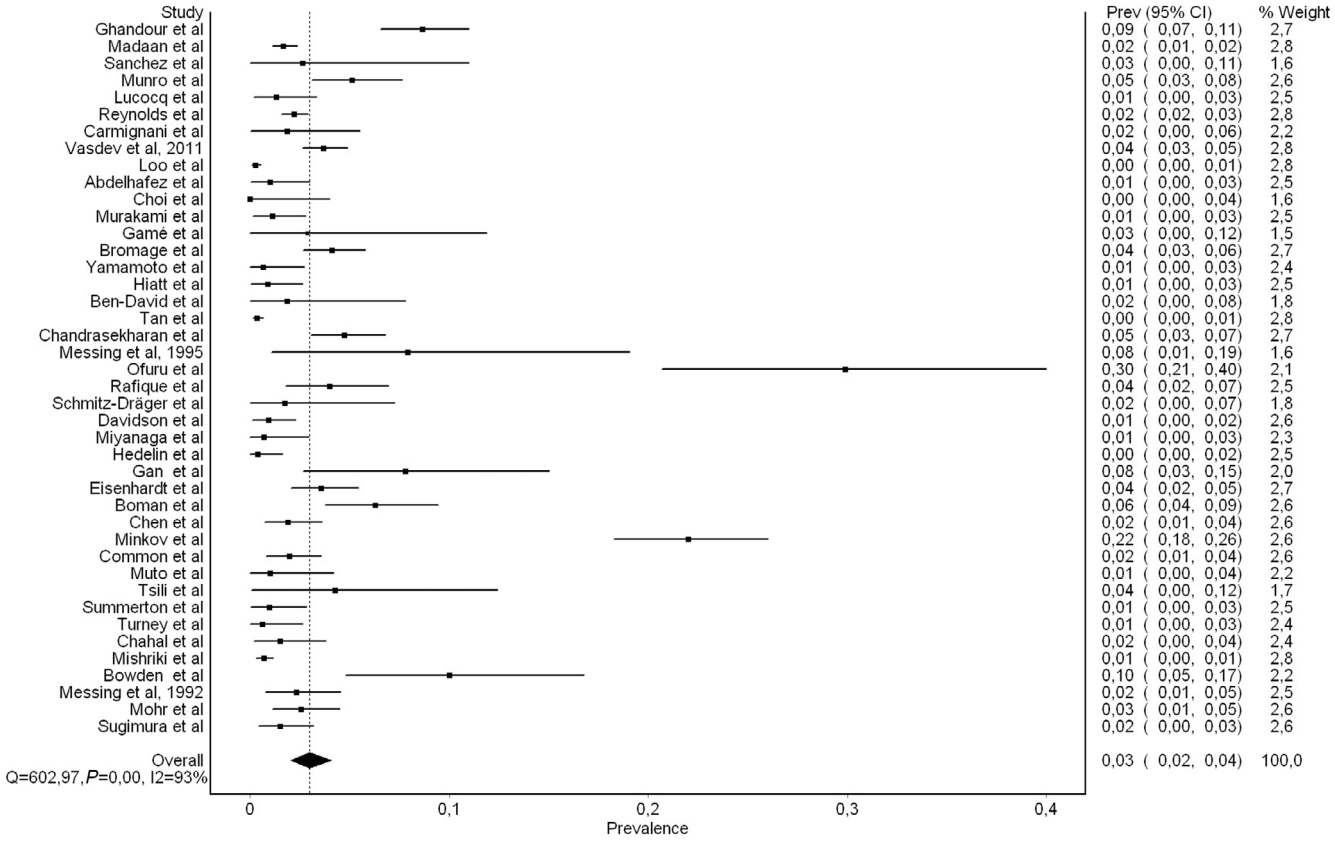
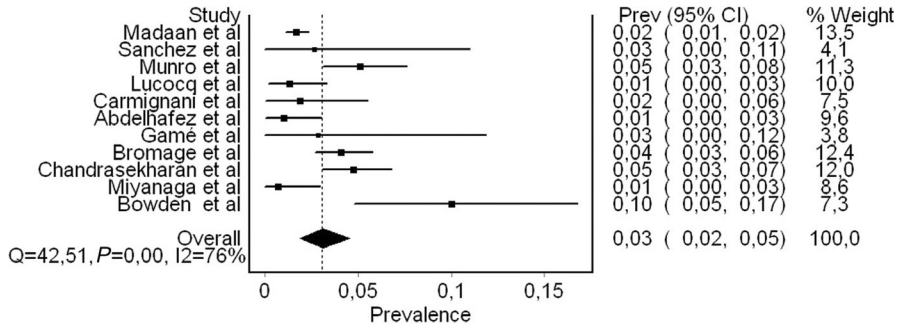


Fig. 3 Forest plot of prostate cancer prevalence in studies that reported performing a DRE, PSA test or physical examination by a trained urologist on all patients (n = 11).



Attending a Haematuria Clinic

To determine the significance of the organisation of haematuria diagnostic evaluation, we enumerated the prostate cancer prevalence for studies reporting results from specialised haematuria clinics (n = 12) [21,23,25–27,29,38,54–58]. In the remaining studies (n = 30), haematuria was handled in general urology departments, other hospital departments, or by GPs, and in some studies the setup was not described.

Prostate Cancer Characteristics

Of the 42 studies, prostate cancer was histopathologically verified in 13 [25–29,36,38,41,45,46,49,51,53], and in one study, some cases were histopathological verified and some clinically verified [33]. The rest of studies provided no information on how the prostate cancer was diagnosed.

Of the 505 identified prostate cancers, TNM stage was provided for 27 cases (T4, two; T3, 10; T2, six; T1, nine)

[29,33,39,45], with TNM not described in 478 cases. Moreover, Gleason sum score was ≤6 in 17 cases, and ≥7 in eight [29,33,46], with Gleason sum score not described in 480. Histopathology was provided for 50 of the 505 identified prostate cancers, and all were adenocarcinomas [26,27,39,51]. The PSA level was described for 61 of the 505 identified prostate cancers, and all had elevated PSA [23,40,46,57]. No study described tumour burden or cancer size.

Haematuria as a Presenting Symptom for Prostate Cancer

Our systematic search identified 23 studies clearly describing the presenting symptom leading to a prostate cancer diagnosis and reported haematuria (studies included in category B) [62–84]. In these 23 studies, the pooled prevalence (95% CI) of men with haematuria as a presenting symptom of prostate cancer was 19.5% (14.7–24.8%; n = 627/3886 men with prostate cancer). Three studies reported macrohaematuria and found that 36.4% (12.2–64.3%; n = 31/87 men with prostate cancer) reported macrohaematuria as the presenting symptom [69,78,79].

Discussion

To determine the prevalence of prostate cancer in men attending diagnostic evaluation for haematuria we performed a meta-analysis on 42 studies. We found a pooled prostate cancer prevalence (95% CI) of 3.0% (2.0–4.1%). Although we investigated prostate cancer prevalence in men with haematuria, it is clearly important to be aware of all cancers associated with both macro- and microhaematuria to determine which tests to perform. Previous studies on the correlation between haematuria and urogenital cancer have shown a significant difference in cancer prevalence between individuals with macro- and microhaematuria [85,86]. A meta-analysis on the diagnostic value of macrohaematuria for urogenital cancer found a pooled positive predictive value of macrohaematuria for urological cancer to be 22% [85], with most cancers (255/317) found to be bladder cancer. Another meta-analysis on 19 193 patients with microhaematuria found a pooled bladder cancer prevalence of 3.2% and 0.3% for kidney cancer [86]. We found a prostate cancer prevalence of 5.9% in men with macrohaematuria and 1.4% in men with microhaematuria. The difference in cancer prevalence is probably due to pathogenic factors, with a lower pathological stage in individuals with microhaematuria, equal to previous findings in individuals with upper tract carcinoma [87]. Another explanation could be that individuals with macrohaematuria often are more extensively investigated [6]. Our findings indicate that prostate cancer is less prevalent than bladder cancer in both individuals with macro- and microhaematuria, but more prevalent than kidney cancer in individuals with microhaematuria [85,86]. Therefore, guidelines on evaluation of haematuria, both macro- and microhaematuria, should consider also including diagnostics tests for prostate cancer.

Study Quality

Of studies included in the meta-analysis, 71% (n = 30) were rated good or fair for quality, which we deem acceptable for reporting results. However, when interpreting the data of this meta-analysis one should be cautious, as 29% of the included studies were of poor quality. The pooled prostate cancer prevalence (3.0%) seems a little higher than the findings of the eight studies rated as 'good' quality (2.5%), indicating that the pooled findings of the meta-analysis may be overestimated.

Diagnostic Approach

The pooled prostate cancer prevalence (3.0%) was equal to the findings of the 11 studies that reported performing a DRE, PSA test or physical examination by a trained urologist on all patients (3.1%). Some studies reported performing a DRE or PSA test on their population, but it was not clear whether these tests were performed on the whole population of men, why these were not summarised to avoid introducing bias. Moreover, some studies probably performed a DRE on their population, but did not report it specifically as it can be thought as part of a general physical examination.

Attending a Haematuria Clinic

In the Nordic countries it is recommended to establish fast-track haematuria clinics, especially for the evaluation of macrohaematuria [6]. The prostate cancer prevalence in patients examined in a haematuria clinic (2.4%) seems lower than the pooled findings of this study (3.0%), probably due to the fact that these clinics' main focus is on bladder cancer diagnostics. Of the 12 studies reporting data from haematuria clinics (7979 men with haematuria), only six studies reported performing a DRE, PSA test or physical examination by a trained urologist on all included (2970 men with haematuria) [21,23,26,29,38,58]. Interestingly, the pooled prostate cancer prevalence (95% CI) of these six studies was 3.5% (1.7–5.9%) [21,23,26,29,38,58], indicating that performing a DRE and PSA test should be considered standard tests for all men attending a haematuria clinic.

Prostate Cancer Characteristics

In theory, advanced prostate cancers are more prone to impact the urethra leading to haematuria, than early prostate cancer stages, as they often develop in the peripheral zone [29,33]. The number of studies describing prostate cancer characteristics was too few, and included too few cases, to

determine if there was a correlation between haematuria and prostate cancer TNM stage, differentiation, histopathological type, or size. Further studies are needed to determine which prostate cancers present with haematuria.

Only 13 of the 42 studies reported that the prostate cancer was histopathologically verified [25–29,36,38,41,45,46,49,51,53]. The reason for this is probably because many of the included studies had urogenital cancer in general as the objective. Moreover, the reason for this could also be due to non-strict guidelines for evaluation of prostate cancer in men with haematuria [15]. The prostate cancer prevalence appears lower in these 13 studies compared to the pooled findings (2.4% vs 3.0%). This could indicate that some of the studies without information of how prostate cancer was diagnosed are causing an overestimation of the true prostate cancer prevalence. A prospective study performing tests for prostate cancer in all men with haematuria and taking biopsies when indicated [88] would be important for determination of a 'true' prostate cancer prevalence.

Haematuria and Prostate Cancer

Surprisingly, the pooled prostate cancer prevalence was much lower (3.0%) in studies describing prostate cancer in men undergoing evaluation of haematuria [20–61], than in studies reporting haematuria as a presenting symptom leading to prostate cancer diagnosis (19.5%) [62–84]. This is probably due to multiple factors. In many of the 23 studies, haematuria was not a sole symptom leading to diagnosis, and some of the studies were based on a retrospective questionnaire increasing recall bias. Moreover, we only included studies describing haematuria as a presenting symptom leading to prostate cancer diagnosis, thus our findings could be overestimated, as studies with no mention of haematuria were not included. Finally, it could also be due to a selection bias, as large or advanced prostate cancers would probably be diagnosed before a haematuria diagnostic evaluation.

Strength and Limitations

From our perspective, the strengths of this meta-analysis and systematic review are the comprehensive literature search and inclusion of a large number of men with haematuria, increasing the statistical power. Moreover, the included studies were acceptably distributed in the funnel plot, indicating a low publication bias. Furthermore, we performed sensitivity analysis to determine the robustness of our estimates and found an overall robust estimate.

Our analysis also has limitations. We found an I^2 of 93% indicating that the included studies were rather heterogeneous, and therefore the pooled findings of this study have an increased risk of bias. Additionally, too few studies provided information for subgroup analysis. Subgroup studies on cancer characteristics (TNM stage, Gleason sum score, histopathological type etc.) or age would be relevant to consider in future studies, to determine whether advanced prostate cancers are more prevalent in individuals with haematuria than early stage cancers and if age impacts the prevalence.

Moreover, we only included studies that clearly described how many men were investigated, to prevent underestimating the true prostate cancer prevalence, by accidentally including females in the analysis. However, this could impair comparison with other studies on urogenital cancer in individuals with haematuria, as these also include females. Furthermore, many of the included studies, had bladder cancer as the objective, potentially reducing the number of identified prostate cancers. However, when stratifying the cohort in studies performing tests for prostate cancer detection, we found the prostate cancer prevalence equal to the pooled findings.

Conclusion

In conclusion, our findings indicate that the prevalence of prostate cancer is 3.0% in men attending evaluation for haematuria. Therefore, a DRE and PSA testing should become standard procedures in all men with haematuria, especially in men with macrohaematuria.

Acknowledgements

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved the submission.

Funding

This work was supported by the following funds: Digitaliseringsstyrelsen signaturprojekt "Bedre diagnosticering af prostatacancer" [English: Better diagnostics of prostate cancer]. PhD scholarship, University of Southern Denmark. PhD stipend, Region of Southern Denmark.

Disclosure of Interests

All authors declare that they have no disclosure of interests.

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Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PROSPERO, International Prospective Register of Systematic Reviews.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Search strategy.

Appendix S2 Forest plots and funnel plots of the included studies.

Table S1. Characteristics of included studies.